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TETRAMETHYL BISPHENOL F

(CAS #5384-21-4)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

Assessment Date: December 4, 2020

Expiration Date: December 4, 2025

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GreenScreen® Executive Summary for Tetramethyl Bisphenol F (CAS #5384-21-4)

Tetramethyl bisphenol F is used as an alternative monomer to bisphenol A in the synthesis of polymeric epoxy resins used as coatings for beverage and food containers. It is non-reactive and non-flammable, is not volatile, and is slightly soluble in water. Tetramethyl bisphenol F and bisphenol A each incorporate a 4,4'-methylenediphenol polymer chain functionality, and when properly cured, such polymers serve as flexible barriers in metal food contact applications that is able to protect food for extended durations under extreme conditions.

Due to incomplete data for human health and environmental hazard endpoints, ToxServices used modeling as well as read-across to fill the data gaps for tetramethyl bisphenol F. ToxServices did not utilize hazard data from surrogates presented in the REACH dossier for tetramethyl bisphenol F due to low chemical structural similarity determined via Tanimoto coefficients and different configuration of aromatic ring constituents that the available research indicate is critical for endocrine activity. Rather, ToxServices used data for 4,4'-bisphenol F (4,4'-BPF, CAS #620-92-8), tetramethyl bisphenol A (CAS #5613-46-7), and bisphenol A (BPA, CAS #80-05-7) as they have sufficient structural similarity to the target chemical and have similar configurations of aromatic ring constituents. Specifically, data for all three chemicals are used to address data gaps or add to the weight of evidence for developmental toxicity, reproductive toxicity, and endocrine activity and data for 4,4'-BPF and tetramethyl bisphenol A were used to address a data gap for skin sensitization in addition to modeling.

In terms of human health hazards, tetramethyl bisphenol F has moderate concerns for developmental toxicity (based on surrogate data: decreased anogenital distance and increased nipple retention in male pups following prenatal exposed to tetramethyl bisphenol A), and endocrine activity, based on equivocal anti-androgenic activity for the target chemical *in vivo*. Tetramethyl bisphenol F also has moderate concerns for single dose neurotoxicity as an acute oral toxicity study in rats indicate that tetramethyl bisphenol F may induce transient narcotic effects upon single oral exposure at a high dose.

In terms of environmental hazards, tetramethyl bisphenol F is predicted to have very high acute and chronic aquatic toxicities in fish, aquatic invertebrates, and algae. It is predicted to be persistent in its expected major environmental compartment (soil), but is predicted to have a very low bioaccumulation potential based on modeled data with the Arnot-Gobas method.

Tetramethyl bisphenol F was assigned a **GreenScreen Benchmark™ Score of 2** ("Use but Search for Safer Substitutes"). This score is based on the following hazard score combinations:

- Benchmark 2c
  - High persistence-P + Very High Ecotoxicity (acute aquatic toxicity-AA, chronic aquatic toxicity-CA)
  - High P + Moderate Group I Human Health Hazard (developmental toxicity-D, endocrine activity-E)
  - High P + Moderate Group II Human Health Hazard (single dose neurotoxicity-Ns)
- Benchmark 2e
  - Moderate Group I Human Health Hazard (D, E)
- Benchmark 2f
  - Very High Ecotoxicity (AA, CA)

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GreenScreen® Hazard Summary Table for Tetramethyl Bisphenol F

Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	Rx	F
						single	repeat*	single	repeat*										
L	**L**	*L*	*M*	*M*	**L**	**L**	**L**	*M*	**L**	**L**	*L*	**L**	**L**	*vH*	*vH*	*H*	*vL*	**L**	**L**

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect lower confidence in the hazard classification while hazard levels in **BOLD** font reflect higher confidence in the hazard classification. Group II Human Health endpoints differ from Group II* Human Health endpoints in that they have four hazard scores (i.e., vH, H, M, and L) instead of three (i.e., H, M, and L), and are based on single exposures instead of repeated exposures. Group II* Human Health endpoints are indicated by an * after the name of the hazard endpoint or after "repeat" for repeated exposure sub-endpoints. Please see Appendix A for a glossary of hazard acronyms.

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GreenScreen® Chemical Assessment for Tetramethyl Bisphenol F (CAS #5384-21-4)

Method Version: GreenScreen® Version 1.4
Assessment Type[1]: Certified
Assessor Type: Licensed GreenScreen® Profiler

GreenScreen® Assessment (v.1.4) Prepared By:
Name: Zach Guerrette, Ph.D., D.A.B.T.
Title: Senior Toxicologist
Organization: ToxServices LLC
Date: November 5, 2020

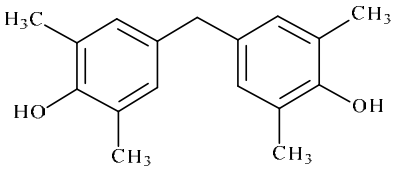
Quality Control Performed By:
Name: Bingxuan Wang, Ph.D., D.A.B.T.
Title: Senior Toxicologist
Organization: ToxServices LLC
Date: December 4, 2020

Expiration Date: December 4, 2025[2]

Chemical Name: Tetramethyl Bisphenol F

CAS Number: 5384-21-4

Chemical Structure(s):



Also called:
4,4'-Methylenebis(2,6-dimethylphenol); 4,4'-Methylenedi-2,6-xylenol; Phenol, 4,4'-methylenebis[2,6-dimethyl-; 4-[(4-hydroxy-3,5-dimethylphenyl)methyl]-2,6-dimethylphenol; Bis(4-hydroxy-3,5-dimethylphenyl)methane; Bis(3,5-dimethyl-4-hydroxyphenyl)methane; Phenol, 4,4'-methylenebis(2,6-dimethyl-; 4,4'-Dihydroxy-3,3',5,5'-tetramethyldiphenylmethane; 4,6-xylenol; 2,6-Xylenol, 4,4'-methylenedi-; 4,6-dimethylphenol); EC 226-378-9; 4,4'-Methylenebis[2,6-xylenol]; 4,3',5,5'-tetramethyl diphenylmethane; Phenol,4'-methylenebis[2,6-dimethyl-; 4,4\'-Methylenebis(2,6-dimethyl phenol); 2,2',6,6'-Tetramethyl-4,4'-methylenediphenol; 3,5,5'-Tetramethyl-4,4'-dihydroxy diphenylmethane; 3,3,5,5-Tetramethyl-4,4-dihydroxy-diphenylmethane; 3,3',5,5'-Tetramethyl-4,4'-dihydroxydiphenyl methane; 4-(4-hydroxy-3,5-dimethylbenzyl)-2,6-dimethylphenol (ChemIDplus 2020, PubChem 2020)

Suitable surrogates or moieties of chemicals used in this assessment (CAS #'s):
ToxServices identified limited data for tetramethyl bisphenol F. In order to address the data gaps, ToxServices used the U.S. EPA's Analog Identification Methodology (AIM) software and ChemIDplus's structural similarity search function (>80% similarity search function) to identify potential surrogates, but ToxServices identified no surrogates with sufficient data to address the data gaps using these approaches.

The authors of the REACH registration dossier for tetramethyl bisphenol F used data for 2,3,5-trimethylphenol (CAS #697-82-5) and 2,6-dimethylphenol (CAS #576-26-1) to address the skin

[1] GreenScreen® reports are either "UNACCREDITED" (by unaccredited person), "AUTHORIZED" (by Authorized GreenScreen® Practitioner), or "CERTIFIED" (by Licensed GreenScreen® Profiler or equivalent).
[2] Assessments expire five years from the date of completion starting from January 1, 2019. An assessment expires three years from the date of completion if completed before January 1, 2019 (CPA 2018a).

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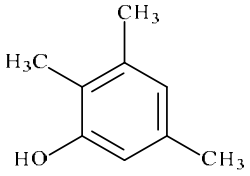
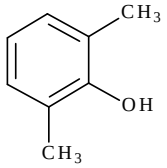
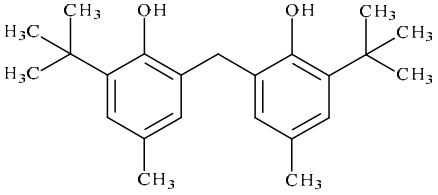
sensitization data gap and data for 2,2'-methylenebis(4-methyl-6-tert-butylphenol) (CAS #119-47-1) to address reproduction and developmental toxicity data gaps. The structures of these chemicals are presented below.



2,3,5-Trimethylphenol (CAS #697-82-5)



2,6-Dimethylphenol (CAS #576-26-1)



2,2'-Methylenebis(4-methyl-6-tert-butylphenol) (CAS #119-47-1).

ToxServices disagrees with the selection of these chemicals as surrogates to address the data gaps for tetramethyl bisphenol F. In terms of chemical structural similarity, ToxServices calculated maximum common substructure (MCS) Tanimoto structural similarity coefficients of 0.3810, 0.4737, and 0.6296 for tetramethyl bisphenol F and 2,3,5-trimethylphenol, 2,6-dimethylphenol, and 2,2'-methylenebis(4-methyl-6-tert-butylphenol), respectively, using the ChemMine similarity workbench.[3] These values are below ToxServices' internal standard for sufficient Tanimoto structural similarity of 0.7.

Additionally, the endocrine activity of bisphenol compounds is dependent on the substituent positions on the aromatic rings. Kitamura et al. (2005) demonstrated that the 4-hydroxyl aromatic ring constituent confers greater estrogenic activity than the 3- and 2-hydroxyl aromatic ring constituents, and anti-androgenic activity is limited to bisphenols with the 4-hydroxyl aromatic ring constituent. As 2,2'-methylenebis(4-methyl-6-tert-butylphenol) only contains 2-hydroxyl aromatic ring constituents, ToxServices did not consider it to be a suitable surrogate to assess the reproductive or developmental toxicity of tetramethyl bisphenol F.

To identify suitable surrogates, ToxServices used the "Find Similar Structures" function of PubChem to identify chemicals with fingerprint Tanimoto coefficients > 80% and with 4,4'-methylenebis and/or 2,6-dimethylphenol chemical groups. This strategy identified 2,2-bis(4-hydroxy-3,5-dimethylphenyl) propane (aka tetramethyl bisphenol A) (CAS #5613-46-7) and 4,4'-methylenediphenol (aka 4,4'-BPF) (CAS #620-92-8) as chemicals with data available to address the data gaps for tetramethyl bisphenol F. Using the ChemMine similarity workbench, ToxServices identified MCS sufficient Tanimoto coefficients of 0.7895 for tetramethyl bisphenol F and bisphenol F and 0.9048 for tetramethyl bisphenol F and tetramethyl bisphenol A. The structures for these chemicals are presented below.

[3] https://chemminetools.ucr.edu/similarity/

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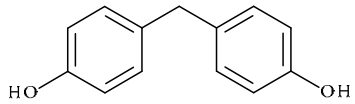
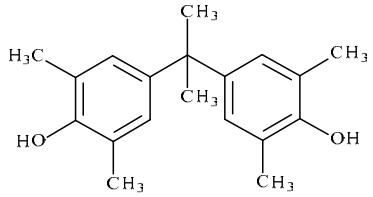
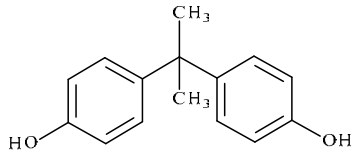


Surrogate: 4,4'-BPF (CAS #620-92-8)



Surrogate: Tetramethyl bisphenol A (CAS #5613-46-7)

Based on sufficient structural similarity to tetramethyl bisphenol F (i.e., Tanimoto coefficients > 0.7), ToxServices used data for 4,4'-BPF and tetramethyl bisphenol A to address data gaps for tetramethyl bisphenol F. Although all three chemicals are bisphenol A alternatives (BPA, CAS #80-05-7), available data indicate that 4,4'-BPF and tetramethyl bisphenol A have similar or greater endocrine activity than BPA (Kitamura et al. 2005, Eladak et al. 2015, Rochester and Bolden 2015). Therefore, ToxServices also used BPA as a surrogate for reproductive toxicity, developmental toxicity, and endocrine activity endpoints.



Surrogate: BPA (CAS #80-05-7)

BPA has a fingerprint Tanimoto score of ≥ 80% to < 90% with tetramethyl bisphenol F as identified by PubChem, and ToxServices identified a MCS Tanimoto coefficient of 0.7143 for tetramethyl bisphenol F and BPA using ChemMine.

Identify Applications/Functional Uses:
Monomer in the synthesis of polymeric epoxy resins (Maffini and Canatsey 2020).

Known Impurities[4]:
No information is available. The screen is performed on the theoretical pure substance.

GreenScreen® Summary Rating for Tetramethyl Bisphenol F[5,6 7,8]: Tetramethyl bisphenol F was assigned a **GreenScreen Benchmark™ Score of 2** ("Use but Search for Safer Substitutes") (CPA 2018b). This score is based on the following hazard score combinations:

[4] Impurities of the chemical will be assessed at the product level instead of in this GreenScreen®.
[5] For inorganic chemicals with low human and ecotoxicity across all hazard endpoints and low bioaccumulation potential, persistence alone will not be deemed problematic. Inorganic chemicals that are only persistent will be evaluated under the criteria for Benchmark 4.
[6] See Appendix A for a glossary of hazard endpoint acronyms.
[7] For inorganic chemicals only, see GreenScreen® Guidance v1.4 Section 12 (Inorganic Chemical Assessment Procedure).
[8] For Systemic Toxicity and Neurotoxicity, repeated exposure data are preferred. Lack of single exposure data is not a Data Gap when repeated exposure data are available. In that case, lack of single exposure data may be represented as NA instead of DG. See GreenScreen® Guidance v1.4 Annex 2.

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- Benchmark 2c
  - High persistence-P + Very High Ecotoxicity (acute aquatic toxicity-AA, chronic aquatic toxicity-CA)
  - High P + Moderate Group I Human Health Hazard (developmental toxicity-D, endocrine activity-E)
  - High P + Moderate Group II Human Health Hazard (single dose neurotoxicity-Ns)
- Benchmark 2e
  - Moderate Group I Human Health Hazard (D, E)
- Benchmark 2f
  - Very High Ecotoxicity (AA, CA)

Figure 1: GreenScreen® Hazard Summary Table for Tetramethyl Bisphenol F

Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	Rx	F
						single	repeat*	single	repeat*										
L	**L**	*L*	*M*	*M*	**L**	**L**	**L**	*M*	**L**	**L**	*L*	**L**	**L**	*vH*	*vH*	*H*	*vL*	**L**	**L**

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect lower confidence in the hazard classification while hazard levels in **BOLD** font reflect higher confidence in the hazard classification. Group II Human Health endpoints differ from Group II* Human Health endpoints in that they have four hazard scores (i.e., vH, H, M, and L) instead of three (i.e., H, M, and L), and are based on single exposures instead of repeated exposures. Group II* Human Health endpoints are indicated by an * after the name of the hazard endpoint or after "repeat" for repeated exposure sub-endpoints. Please see Appendix A for a glossary of hazard acronyms.

Environmental Transformation Products

ToxServices did not identify transformation products for tetramethyl bisphenol F. Therefore, ToxServices used OECD QSAR Toolbox (OECD 2020) to predict the hydrolysis products of tetramethyl bisphenol F under acidic, neutral, and basic conditions. No hydrolysis products were identified using this approach. Therefore, ToxServices did not modify the Benchmark Score for tetramethyl bisphenol F based on transformations products.

Introduction

Tetramethyl bisphenol F is used as an alternative monomer to bisphenol A in the synthesis of polymeric epoxy resins used as coatings of beverage and food containers (Maffini and Canatsey 2020). Both tetramethyl bisphenol F and bisphenol A incorporate a 4,4'-methylenediphenol polymer chain functionality, and, when properly cured, such polymers serve as flexible barriers in metal food contact applications that is able to protect food for extended durations under extreme conditions (Soto et al. 2017). ToxServices assessed tetramethyl bisphenol F against GreenScreen® Version 1.4 (CPA 2018b) following procedures outlined in ToxServices' SOPs (GreenScreen® Hazard Assessment) (ToxServices 2020).

U.S. EPA Safer Choice Program's Safer Chemical Ingredients List (SCIL)

The SCIL is a list of chemicals that meet the Safer Choice standard (U.S. EPA 2020) and can be ccessed at: http://www2.epa.gov/saferchoice/safer-ingredients. Chemicals on the SCIL have been assessed for compliance with the Safer Choice Standard and Criteria for Safer Chemical Ingredients (U.S. EPA 2015).

Tetramethyl bisphenol F is not listed on the U.S. EPA SCIL.

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GreenScreen® List Translator Screening Results

The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to identify GreenScreen Benchmark™ 1 chemicals (CPA 2018b). Pharos (Pharos 2020) is an online list-searching tool that is used to screen chemicals against all of the lists in the List Translator electronically. ToxServices also checks the U.S. Department of Transportation (U.S. DOT) lists (U.S. DOT 2008a,b),[9] which are not considered GreenScreen® Specified Lists but are additional information sources, in conjunction with the Pharos query. The output indicates benchmark or possible benchmark scores for each human health and environmental endpoint. The output for tetramethyl bisphenol F can be found in Appendix C.

- Tetramethyl bisphenol F is an LT-UNK chemical when screened using Pharos, and therefore a full GreenScreen® is required.
- Tetramethyl bisphenol F is not listed on the U.S. DOT list.
- Tetramethyl bisphenol F is not on any GreenScreen®-specified lists for multiple endpoints.

Hazard Statement and Occupational Control

Tetramethyl bisphenol F does not have a harmonized EU GHS classification. The authors of the REACH dossier classified it as a GHS Category 1 acute aquatic toxicant (H400) and a GHS Category 1 chronic aquatic toxicant (H410) (ECHA 2020a). A majority of EU notifiers self-classified tetramethyl bisphenol F as a GHS Category 2 skin irritant (H315), GHS Category 2 eye irritant (H319), GHS Category 3 specific target organ toxicant following single exposure (H335), GHS Category 1 acute aquatic toxicant (H400) and GHS Category 1 chronic aquatic toxicant (H410) (ECHA 2020b).

Table 1: H Statements for Tetramethyl Bisphenol F (CAS #5384-21-4) (ECHA 2020a,b)

H Statement	H Statement Details
H315	Causes skin irritation
H319	Causes serious eye irritation
H335	May cause respiratory irritation
H400	Very toxic to aquatic life
H410	Very toxic to aquatic life with long lasting effects

Table 2: Occupational Exposure Limits and Recommended Personal Protective Equipment for Tetramethyl Bisphenol F (CAS #5384-21-4)

Personal Protective Equipment (PPE)	Reference	Occupational Exposure Limits (OEL)	Reference
Safety glasses, gloves, protective clothing, respiratory for nuisance exposures	TCI 2018, Sigma-Aldrich 2019	None established	TCI 2018, Sigma-Aldrich 2019

Physicochemical Properties of Tetramethyl Bisphenol F

Tetramethyl bisphenol F is an amorphous, colorless solid under standard temperature and pressure. It has a low vapor pressure (1.92×10^{-8} mm Hg), indicating that it exists mostly in the solid phase. It is slightly soluble in water (100 mg/L), and is predicted to be more soluble in octanol than in water (log $K_{ow} = 3.75$).

[9] DOT lists are not required lists for GreenScreen® List Translator v1.4. They are reference lists only.

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Table 3: Physical and Chemical Properties of Tetramethyl Bisphenol F (CAS #5384-21-4)		
Property	**Value**	**Reference**
Molecular formula	C_{17}-H_{20}-O_2	ChemIDplus 2020
SMILES Notation	Cc1cc(Cc2cc(C)c(O)c(C)c2)cc(C)c1O	ChemIDplus 2020
Molecular weight	256.343 g/mol	ChemIDplus 2020
Physical state	Solid	ECHA 2020a
Appearance	Amorphous, colorless	ECHA 2020a
Melting point	170-175°C (OECD 102)	ECHA 2020a
Boiling point	> 240°C (OECD 103)	ECHA 2020a
Vapor pressure	0.00000256 Pa (1.92×10^{-8} mm Hg) at 25°C (estimated)	ECHA 2020a
Water solubility	100 mg/L at 25°C	ECHA 2020a
Dissociation constant	pKa = 0.1676×10^{-12} at 25°C	ECHA 2020a
Density/specific gravity	0.744 g/cm^3 at 25°C	ECHA 2020a
Partition coefficient	Log K_{ow} = 3.75 (estimated) Log K_{ow} = 5.24 (estimated)	ECHA 2020a U.S. EPA 2017a

Toxicokinetics

ToxServices identified no toxicokinetics data for tetramethyl bisphenol F or for the surrogate tetramethyl bisphenol A. Based on the results of the repeated oral dose toxicity tests performed with these chemicals (ECHA 2020a,c, Maffini and Canatsey 2020), tetramethyl bisphenol F is assumed to be orally bioavailable. ToxServices predicts that tetramethyl bisphenol F will have similar toxicokinetics as 4,4'-BPF as discussed below.

Absorption

- Cabaton et al. 2006
  - *Surrogate: 4,4'-BPF (CAS #620-92-8):* Pregnant and non-pregnant Sprague-Dawley rats were administered single gavages of ^{3}H-radiolabeled 4,4'-BPF at 7 or 100 mg/kg and kept in metabolic cages for 96 hours. Pregnant animals were dosed on gestation day 17. During the course of the study, 15-20% of the administered dose was detected in the feces and approximately 8-10% of the dose was still located in the gastrointestinal tract after 96 hours, suggesting at least 70% of the dose was absorbed via the gastrointestinal tract following single gavage doses.

Distribution

- Cabaton et al. 2006
  - *Surrogate: 4,4'-BPF (CAS #620-92-8):* Pregnant and non-pregnant Sprague-Dawley rats were administered single gavages of ^{3}H-radiolabeled 4,4'-BPF at 7 or 100 mg/kg and kept in metabolic cages for 96 hours. Pregnant animals were dosed on gestation day 17. After 96 hours, radioactivity was detected in all tissues, with the highest radioactivity (0.5% of the dose) detected in the liver. Approximately 8-10% of the dose was still located in the gastrointestinal tract. Pregnant animals had detectable radioactivity in the range of 0.9-1.3% of the administered dose in the uterus, amniotic fluid, placenta, and fetus.

Metabolism

- Cabaton et al. 2006
  - *Surrogate: 4,4'-BPF (CAS #620-92-8):* In pregnant and non-pregnant Sprague-Dawley rats were administered single gavages of ^{3}H-radiolabeled 4,4'-BPF at 7 or 100 mg/kg and

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monitored for 96 hours, the dominant urinary metabolite is the sulfate conjugate of 4,4'-BPF, indicating that 4,4'-BPF undergoes extensive Phase II metabolism.

- Cabaton et al. 2008
  - *Surrogate: 4,4'-BPF (CAS #620-92-8):* Rat and human liver subcellular fractions were incubated with 4,4'-BPF and the resulting metabolites were identified via high-performance liquid chromatography (HPLC) and mass spectrometry (MS) or nuclear magnetic resonance (NMR). 4,4'-BPF is oxidized to hydroxylated metabolites via cytochrome P450-mediated reactions and conjugated with glucuronide and sulfate.

Excretion/Elimination

- Cabaton et al. 2006
  - *Surrogate: 4,4'-BPF (CAS #620-92-8):* Pregnant and non-pregnant Sprague-Dawley rats were administered single gavages of ^{3}H-radiolabeled 4,4'-BPF at 7 or 100 mg/kg and kept in metabolic cages for 96 hours. Pregnant animals were dosed on gestation day 17. During the course of the study, 43-54% and 15-20% of the administered dose was detected in the urine and feces, respectively. Sulfatase treatment and analysis via high-performance liquid chromatography identified the sulfate conjugate of 4,4'-BPF as the dominant urinary metabolite, representing more than 50% of the urinary radioactivity. Over a six-hour period, 46% of the distributed radioactivity was eliminated via bile, suggesting that 4,4'-BPF and/or its metabolites exhibit enterohepatic cycling.

Hazard Classification Summary

Group I Human Health Effects (Group I Human)

Carcinogenicity (C) Score (H, M, or L): *L*

Tetramethyl bisphenol F was assigned a score of Low for carcinogenicity based on the lack of structural alerts and the negative predictions for carcinogenic potential provided by VEGA, Danish (Q)SAR and OncoLogic models. Additionally, the European Union (EU) risk assessment authors concluded that the surrogate BPA was not carcinogenic in experimental animals. GreenScreen® criteria classify chemicals as a Low hazard for carcinogenicity when adequate negative data are available and they are not GHS classified (CPA 2018b). The confidence in the score is low as it is based on modeling and a weaker surrogate.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- Toxtree 2018
  - Tetramethyl bisphenol F does not contain structural alerts for genotoxic or non-genotoxic carcinogenicity (Appendix D).
- VEGA 2019
  - The CAESAR model predicts tetramethyl bisphenol F is a carcinogen with low reliability because the compound is outside of the model's applicability domain (global applicability domain (AD) index = 0) (Appendix E).
  - The ISS model predicts tetramethyl bisphenol F is a non-carcinogen with moderate reliability because the compound could be outside of the model's applicability domain (global AD index = 0.654) (Appendix E).
  - The IRFMN/Antares model predicts tetramethyl bisphenol F is a possible non-carcinogen with good reliability because the compound is inside of the model's applicability domain

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(global AD index = 0.955) (Appendix E).
    - The IRFMN/ISSCAN-CGX model predicts tetramethyl bisphenol F is a possible non-carcinogen with moderate reliability because the compound could be outside of the model's applicability domain (global AD index = 0.72) (Appendix E).
    - The IRFMN oral classification model predicts tetramethyl bisphenol F is a carcinogen with moderate reliability because the compound could be outside of the model's applicability domain (global AD index = 0.651) (Appendix E).
    - The IRFMN inhalation classification model predicts tetramethyl bisphenol F is a carcinogen with moderate reliability because the compound could be outside of the model's applicability domain (global AD index = 0.651) (Appendix E).
    - In summary, two models have predictions with sufficient reliability (global AD index > 0.70) (Gad 2016), and both of those models predict that tetramethyl bisphenol F is a non-carcinogen.
- DTU 2020
    - Tetramethyl bisphenol F is in the applicability domains of four of seven Case Ultra carcinogenicity models and is predicted to be non-carcinogenic in female rats, male mice, female mice, and mice. It was inside of the applicability domain of four of seven Leadscope models and is predicted to be non-carcinogenic mice and rodents and carcinogenic in male mice and female mice. It is inside of the applicability models for the CASE Ultra liver specific cancer model and is predicted to be negative for liver carcinogenicity in rats and mice (Appendix F).
- U.S. EPA 2013
    - The OncoLogic computer program, a structure-activity relationship program developed by the United States Environmental Protection Agency, was used to evaluate the carcinogenic potential of tetramethyl bisphenol F. Tetramethyl bisphenol F was evaluated as a phenol and phenolic compound in OncoLogic. As the program could not generate the biphenyl structure, ToxServices used the structure for 2,4,6-trimethylphenol (CAS #527-60-6) to represent tetramethyl bisphenol F. Phenols and phenolic compounds are not considered to have carcinogenic potential, with the following exceptions: polyhydric phenolics capable of being oxidized to reactive simple or conjugated quinones; phenolics capable of being oxidized to reactive quinoneimine or quinonemethide intermediates; phenolics with structural similarity to estrogenic/androgenic compounds; and phenolics containing linear tricyclic ring structure with hydroxy groups at both the 1- and 8- positions or all the peri positions on one side. As tetramethyl bisphenol F does not contain these structural features, OncoLogic predicts tetramethyl bisphenol F to have a low carcinogenic concern (Appendix G).
- EU 2010
    - *Surrogate: BPA (CAS #80-05-7):* Based on all available data the EU concluded that BPA is not carcinogenic in the risk assessment report, although there are some effects observed in the mammary gland, which currently are of unknown significance to human health. A dietary carcinogenicity study was performed in F344 rats and $B6C3F_1$ mice. Slight increases in leukemia in male and female rats and mammary gland fibroadenomas in male rats were reported. However, these increases were not statistically significant. Male rats also had a small increase in benign Leydig cell tumors which was within the historical controls. The authors reported a small increase in lymphomas in male mice; this increase was not dose-related or statistically significant. No change in tumor incidence was reported in female mice. Based on this study the EU determined that BPA does not have carcinogenic potential.

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Mutagenicity/Genotoxicity (M) Score (H, M, or L): L

Tetramethyl bisphenol F was assigned a score of Low for mutagenicity/genotoxicity based on negative results for mutagenicity and clastogenicity in *in vitro* assays. GreenScreen® criteria classify chemicals as a Low hazard for mutagenicity/genotoxicity when negative data are available for both gene mutations and chromosome aberrations, and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on measured data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2020a
  - *In vitro*: Negative results for mutagenicity were obtained in a non-GLP-compliant mammalian cell gene mutation assay conducted according to OECD Guideline 476. Chinese hamster ovary (CHO) cells were exposed to tetramethyl bisphenol F (as 4,4'-methylenedi-2,6-xylenol, purity not specified) in ethanol at ≤ 100 µM with exogenous metabolic activation (S9 liver mix from Aroclor 1254-induced male Sprague-Dawley rats). N-Ethyl-N-nitrosourea served as the positive control. Tetramethyl bisphenol F treatment did not increase the mutation frequency in the presence of metabolic activation. The vehicle, untreated negative, and positive controls were valid (Klimisch 1, reliable without restriction).
  - *In vitro*: Negative results for mutagenicity were obtained in a non-GLP-compliant mammalian cell gene mutation assay conducted according to OECD Guideline 476. CHO cells were exposed to tetramethyl bisphenol F (as 4,4'-methylenedi-2,6-xylenol, purity not specified) in ethanol at ≤ 100 µM without exogenous metabolic activation. Ethylnitrosurea served as the positive control. Tetramethyl bisphenol F treatment did not increase the mutation frequency in the absence of metabolic activation. The vehicle, untreated negative, and positive controls were valid (Klimisch 1, reliable without restriction).
  - *In vitro*: Negative results for clastogenicity were obtained in a mammalian chromosome aberration assay conducted in a manner similar to OECD Guideline 473 (GLP status not specified). CHL / IU cells were exposed to tetramethyl bisphenol F (as 4,4'-methylenedi-2,6-xylenol, purity not specified) in acetone at ≤ 0.008 mg/mL for continuous treatment and ≤ 0.003 mg/mL without and ≤ 0.3 mg/mL with exogenous metabolic activation (unspecified S9 mix). Cyclophosphamide, mitomycin C, and 1-methyl-3-nitro-1-nitrosoguanidine, 3,4-benzo[a]pyrene served as positive controls. Tetramethyl bisphenol F treatment did not increase the frequency of chromosome aberrations in the presence or absence of metabolic activation. The vehicle and positive controls were valid (Klimisch 2, reliable with restrictions).

Reproductive Toxicity (R) Score (H, M, or L): *L*

Tetramethyl bisphenol F was assigned a score of Low for reproductive toxicity based on the lack of adverse effects on reproductive organs in repeated oral toxicity studies and the lack of reproductive toxicity produced by the surrogate tetramethyl bisphenol A in an OECD Guideline 422 study. GreenScreen® criteria classify chemicals as a Low hazard for reproductive toxicity when adequate negative data are available and they are not GHS classified (CPA 2018b). The confidence in the score is low as no reproductive toxicity data were identified for the target chemical and the data for the surrogate were obtained from a screening test that evaluates fewer endpoints than a full one- or two-generation reproductive toxicity test.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.

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  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2020c
  - *Surrogate: Tetramethyl bisphenol A (CAS #5613-46-7)*: A GLP-compliant combined repeated dose toxicity study with the reproduction / developmental toxicity screening test conducted according to OECD Guideline 422 was performed with Crl:CD (SD) rats (12/sex/group) administered gavage doses of tetramethyl bisphenol A (as 4,4'-(1-methylethylidene)-bis(2,6-dimethylphenol, 99.74% purity) in corn oil at 10, 100, or 1,000 mg/kg/day. Females were dosed for two weeks prior to mating, during the two-week mating period, during gestation and through lactation day 21 (57-63 doses). Males were dosed for two weeks prior to mating and during the two-week mating period, up to 28 days total. Parental animals were evaluated for mortality, clinical signs of toxicity, body weight and body weight gains, sperm parameters (motility, morphology, testes weight, and testicular spermatid count and sperm production rate), reproductive organ weights, gross pathology, and histopathology, and reproductive indices (male mating, male fertility, male copulation, female mating, female fertility, and female conception). Treatment did not affect survival of parental animals, but did induce clinical signs of toxicity which included clear and red material around the mouth and/or nose 1-2 hours after dosing in the mid and high dose groups throughout the treatment period. Mid and high dose males exhibited decreased mean body weight gains throughout the treatment period (statistical significance not specified) and, as a result, mean body weights were 4.2% and 5.1% lower, respectively, than the control group on day 27. Treated males exhibited decreased mean food consumption during the first week of treatment. Mid and high dose females exhibited decreased mean body weight gains (statistically significant in the high dose group) and mean food consumption during the premating phase, but were not sufficient to statistically affect pre-mating body weights. Treatment did not affect female body weight gains or food consumption during the gestation; although the mid dose group mean body weights were statistically significantly less than the control group mean on gestation day 7 and 20, the authors concluded this effect was not treatment-related as the high dose group did not exhibit statistically significant decreases in body weights at these time points. During the lactation period, mid and high dose group females exhibited statistically significant decreases in mean body weights on lactation day 1 (control, low, mid, and high dose group mean body weights: 306, 308, 283, and 287, unit not specified, most likely gram), but a dose response pattern was not identified and the mid and high dose females exhibited a statistically significantly higher body weight gain over the lactation period (postnatal days 1-21). At necropsy, treatment did not impact gross pathological findings, histopathological findings, or organ weights for reproductive organs. Treatment did not produce adverse effects on sperm measures or reproductive indices. Based on the lack of adverse effects on reproductive organs and parameters, the authors identified a reproductive NOAEL of 1,000 mg/kg/day, the highest dose tested (Klimisch 1, reliable without restriction).
- Ullah et al. 2019
  - *Surrogate: 4,4'-BPF (CAS #620-92-8)*: Male Sprague-Dawley rats (7/group) were administered oral doses of 4,4'-BPF (99% purity) at 0 (saline), 1, 5, 25, 50, or 100 mg/kg/day for 28 days. At the end of the exposure period, the animals were euthanized and the left testis and left epididymis were weighed and processed for antioxidant enzymes while the right testis and epididymis were fixed for histopathological evaluation. 4,4'-BPF treatment did not alter body weight gain or testis weights but did increase the level of reactive oxygen species (ROS) and lipid peroxidation at doses as low as 50 mg/kg/day and decreased the total protein content, superoxide dismutase (SOD) activity, and catalase

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(CAT) activity at doses as low as 5 mg/kg/day. 4,4'-BPF treatment statistically significantly decreased the epithelial height in the right testis at 50 and 100 mg/kg/day. Upon histopathological evaluation, treatment thinned the testicular epithelium and reduced the number of secondary spermatocytes, and higher doses (not defined) decreased the number of seminiferous tubules and contained few elongated spermatids in the lumen (statistics not provided).

- ECHA 2020d
  - *Surrogate: BPA (CAS #80-05-7):* BPA has a harmonized EU GHS classification; it is classified as a Category 1B reproductive toxicant (H360F – may damage fertility).
- ECHA 2014
  - *Surrogate: BPA (CAS #80-05-7):* A large number of studies are available on the effects of BPA on reproduction and prenatal development, some of which performed according to internationally-accepted guidelines and GLP-compliant. These studies were conducted in rats and mice. Female and male reproductive toxicity after oral exposure occurred with an overall NOAEL of 50 mg/kg/day and 5 mg/kg/day, respectively. In male animals a reduction of the sperm production after an exposure of adults to BPA for 5 weeks was established. In female animals, the following effects were reported: increased occurrence of ovarian cysts; early onset of puberty after prenatal and postnatal exposure; effects on the hypothalamic-pituitary-gonadal axis after in utero or early postnatal exposure resulting in changes in sex hormone levels and the expression of these hormones receptors. Moreover, in female animals, effects related to exposure in adulthood (e.g. number of implantation sites, histological changes in the uterine wall, morphology of the genital tract, etc.) were also observed. Based on these findings, the Committee for Risk Assessment (RAC) agreed with the proposed harmonized classification of Repro 1B toxicant for BPA.
- Based on the weight of evidence, a Low was assigned for this endpoint. Although the surrogate tetramethyl bisphenol A did not produce adverse effects on reproductive outcomes in rats, the study was a screening test that lacks full evaluation of reproductive outcomes performed in a full one- or two-generation test. The surrogate 4,4'-BPF produced adverse effects on spermatogenesis in male rats following a 28-day exposure period at doses of 50 mg/kg/day and above. However similar effects were not observed in the OECD Guideline 422 study with the surrogate tetramethyl bisphenol A that also examined sperm parameters and testicular histopathology, at much higher doses (up to 1,000 mg/kg/day), or for tetramethyl bisphenol F in 28-day and 90-day repeated dose studies (see details in repeated exposure systemic toxicity section below). The surrogate BPA is a classified as a GHS Category 1B reproductive toxicant by the EU. However, available repeated dose toxicity data suggest that tetramethyl bisphenol F is not as reproductively toxic, if at all, than the surrogates 4,4'-BPF and BPA. Therefore, due to the lack of adverse effects on reproductive organs by tetramethyl bisphenol F in the 28- and 90-day repeated oral dose toxicity studies, the lack of reproductive toxicity produced by tetramethyl bisphenol A in an OECD Guideline 422 study, and the greater structural similarity to tetramethyl bisphenol A than 4,4'-BPF and BPA (MCS Tanimoto coefficients of 0.9048 for tetramethyl bisphenol F and tetramethyl bisphenol A compared to 0.7143 for tetramethyl bisphenol F and BPA and 0.7895 for tetramethyl bisphenol F and 4,4'-BPF), ToxServices assigned a Low score for this endpoint.

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Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): *M*
Tetramethyl bisphenol F was assigned a score of Moderate for developmental toxicity based on the male-specific developmental toxicity (decreased anogenital distance and nipple retention) produced by the surrogate tetramethyl bisphenol A. GreenScreen® criteria classify chemicals as a Moderate hazard for developmental toxicity when there is limited or marginal evidence of developmental toxicity in animals (CPA 2018b). The confidence in the score is low as tetramethyl bisphenol F has lower endocrine activities than the surrogates and it is not clear that tetramethyl bisphenol F has sufficient anti-androgenic activity to produce the same effects as tetramethyl bisphenol A.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2020c
  - *Surrogate: Tetramethyl bisphenol A (CAS #5613-46-7)*: A GLP-compliant combined repeated dose toxicity study with the reproduction / developmental toxicity screening test conducted according to OECD Guideline 422 was performed with Crl:CD (SD) rats (12/sex/group) administered gavage doses of tetramethyl bisphenol A (as 4,4'-(1-methylethylidene)-bis(2,6-dimethylphenol, 99.74% purity) in corn oil at 10, 100, or 1,000 mg/kg/day. Females were dosed for two weeks prior to mating, during the two-week mating period, during gestation and through lactation day 21 (57-63 doses). The offspring were evaluated for sex ratio, weight on postnatal days 1, 4, 7, 14, and 21, number live and stillborn at birth, incidence of external malformations, anogenital distance, nipple retention (males only), and survival. Treatment did not affect the mean number of pups born, sex ratio, live litter size, offspring body weight or body weight gains, organ weights, gross pathological findings, or postnatal survival. Tetramethyl bisphenol A decreased the anogenital distance in mid and high dose male and female offspring; the mean anogenital distances in the control, low, mid, and high dose groups were 4.30, 4.26, 4.05, and 3.92 mm in males, respectively, and 2.24, 2.21, 2.06, and 2.08 mm for females, respectively. The anogenital distance relative to the cube root of pup body weight was also statistically significantly decreased in mid and high dose group males, but only statistically significantly decreased in mid dose females. Tetramethyl bisphenol A increased the proportion of male offspring with thoracic nipples in the high dose group on day 12 (21.2% compared to 0% in the control group) and on day 13 (20.5% compared to 0% in the control group). Treatment did not affect mean ages or body weights at attainment of preputial separation or vaginal patency. The authors identified a developmental toxicity NOAEL/LOAEL of 10/100 mg/kg/day based on effects on anogenital distance and nipple retention (Klimisch 1, reliable without restriction).
- NTP-CERHR 2008
  - *Surrogate: BPA (CAS #80-05-7):* The NTP-CERHR monograph stated that there was clear evidence of adverse developmental effects on survival and growth at high doses of BPA, based on reduced survival in fetuses or newborns (≥500 mg/kg/day), reduced fetal or birth weight or growth of offspring early in life (≥ 300 mg/kg/day), and delayed puberty in female rats (≥ 50 mg/kg/day) and male rats and mice (≥ 50 mg/kg/day). In the case of low dose developmental toxicity, the NTP concluded that there was limited evidence of adverse effects based on various neural and behavior alterations (≥10μg/kg/day), lesions in the prostate (10 μg/kg/day) and mammary glands (2.5–1,000 μg/kg/day), altered prostate gland and urinary tract development (10 μg/kg/day), and early onset of puberty (24 and 200 μg/kg/day).
- In summary, altered development of male pups was detected following prenatal exposure to the

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surrogate tetramethyl bisphenol A. This included decreased anogenital distance and nipple retention at up to postnatal day 13. The surrogate BPA also produced adverse effects on development, including changes to the reproductive organs, sexual development, and behavior. The NTP concluded that BPA produces clear evidence of adverse developmental effects. These effects, however, appear to be endocrine disruption-mediated. As demonstrated below in endocrine activity section, BPA and tetramethyl bisphenol A are known endocrine disruptors, while tetramethyl bisphenol F has marginal or equivocal evidence of endocrine activity *in vivo*, specifically anti-androgenic activity. Therefore, the surrogates may be overly conservative. Due to the lack of developmental toxicity data for tetramethyl bisphenol F and the greater structural similarity to tetramethyl bisphenol A than BPA (MCS Tanimoto coefficients of 0.9048 for tetramethyl bisphenol F and tetramethyl bisphenol A compared to 0.7143 for tetramethyl bisphenol F and BPA), ToxServices conservatively assigned a Moderate score for this endpoint based on tetramethyl bisphenol A effects on male pup development.

Endocrine Activity (E) Score (H, M, or L): *M*

Tetramethyl bisphenol F was assigned a score of Moderate for endocrine activity based on equivocal/marginal anti-androgenic effects measured in a Hershberger assay and a pubertal assay. GreenScreen® criteria classify chemicals as a Moderate hazard for endocrine activity when there is evidence of endocrine activity (CPA 2018b). The confidence in the score is low as the findings are either marginally statistically significant or are of equivocal biological significance.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2020a
  - *Oral*: A GLP-compliant repeated dose toxicity test conducted according to OECD Guideline 407 was performed with Sprague-Dawley rats (6/sex/group) administered gavage doses of tetramethyl bisphenol F (as 4,4'-methylenebis (2,6 dimethylphenol (4,4'-methylenedi-2,6-xylenol), 0.47% impurities) in propylene glycol 400 at 250, 500, or 1,000 mg/kg/day for 28 days. No treatment related effects were identified on organ weights or histopathology for the thyroid, seminal vesicles, or testes (see the repeated dose systemic toxicity section below for a full discussion of this study) (Klimisch 1, reliable without restriction).
- Maffini and Canatsey 2020
  - In a U.S. EPA Test Guideline OCSPP 890.1200 assay, tetramethyl bisphenol F (> 98% purity) produced up to 19.4% CYP19 aromatase activity inhibition of human CYP19 + P450 reductase Supersomes at up to 10^{-4} M. According to the guideline, chemicals that produce at least 50% inhibition are considered aromatase inhibitors. In contrast, the positive control formestane (4-hydroxyandrostenedione) produced ≥ 99% inhibition at 10^{-5} M.
  - In a GLP-compliant, *in vitro* steroidogenesis assay conducted according to OECD Guideline 456, H295R human adrenocortical carcinoma cells were exposed to tetramethyl bisphenol F (> 98% purity) at 100 pM–100 µM in dimethyl sulfoxide (DMSO). Forskolin and Prochloraz were used as the inducer (positive control) and inhibitor (negative control), respectively. Tetramethyl bisphenol F concentrations ≥ 30 µM produced viabilities less than 80% and 10 µM produced less than 80% cell viability in one of three runs. Tetramethyl bisphenol F treatment statistically significantly increased the mean testosterone levels in one of three tests at ≥ 1 µM, and statistically significantly increased the mean estradiol levels in two of three tests at 10 µM. The negative and positive controls performed as expected.
  - In a GLP-compliant, OECD Guideline 441 Hershberger assay was performed with castrated

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male Sprague Dawley Crl:CD (SD) rats (6/group) administered gavage doses of tetramethyl bisphenol F (> 98% purity) at 100, 300, or 1,000 mg/kg/day for 10 consecutive days. Flutamide served as the positive control. Androgenic effects and anti-androgenic effects were investigated in two phases of the study. The animals were evaluated for body weight and organ weights [seminal vesicles, ventral prostate, Levator ani/bulbocavernosus muscle (LABC), Cowper's gland, and glans penis]. Treatment did not affect these parameters in the low and mid dose males. High dose males exhibited statistically significant decreases in seminal vesicle weights (351 mg vs. 445 mg in controls, 21% decrease) and LABC weights (492.9 mg vs. 575 mg in controls, 14.3% decrease). Treatment did not decrease the other organ weights and/or the organ weight changes did not exhibit dose-related trends. Flutamide treatment statistically significantly decreased all of the male organ weights. The OECD guideline[10] defines a chemical as an androgen antagonist when reductions are detected in the weights of all five male reproductive organs and statistically significant reductions are detected for at least two of the organs. The authors concluded that tetramethyl bisphenol F treatment produced equivocal anti-androgenic activity as treatment only reduced the weights of 2/5 organs evaluated only at the high dose group, not meeting the OECD criteria for positive androgen antagonist, and no androgenic activity under the tested conditions.

  - *Oral*: A subchronic repeated oral dose toxicity test conducted according to OECD Guideline 408 was performed with Sprague-Dawley rats (10/sex/group) provided diets containing tetramethyl bisphenol F (> 98% purity) at doses equivalent to 100, 300, 750 (females only) or 1,000 mg/kg/day (males only) for 90 days. Additional groups of 5 animals/sex/group were provided the high dose and then maintained for an additional 28 days on the basal diet (recovery group). The animals were evaluated for organ weights (included thyroid, testes, and epididymides), gross pathology, and histopathology (included thyroid, testes, epididymides, prostate, seminal vesicles, ovaries, cervix, uterus, vagina, mammary glands). Treatment did not affect the organ weights or pathological findings for the reproductive or endocrine-related organs (see the repeated dose systemic toxicity section below for a full discussion of this study).

- Soto et al. 2017
  - An OECD Guideline 455 estrogen receptor transactivation assay was performed with variant of human breast cancer estrogen-responsive MCF7 cells containing the luciferase gene under transactivational control of the ER (VM7Luc4E2) exposed to tetramethyl bisphenol F (99.63% purity) at ≤ 100 µg/mL. Tetramethyl bisphenol F treatment was cytotoxic at ≥ 10 µg/mL, but did not increase luciferase activation in the estrogen agonist or antagonist assays at up to 100 µg/mL.
  - A GLP-compliant, U.S. EPA OPPTS 890.1600 uterotrophic assay was performed with immature female Sprague-Dawley rats (6/group) administered gavage doses of tetramethyl bisphenol F (99.63% purity) in corn oil at 100, 300, or 1,000 mg/kg/day on postnatal days 19-21. 17α-Ethynylestradiol (EE) served as the positive control. Tetramethyl bisphenol F treatment did not increase mean wet or blotted absolute or relative uterine weights, while EE treatment statistically significantly increased the absolute uterine weights. Additionally, tetramethyl bisphenol F treatment did not produce histopathological changes in the mammary glands, while 5/6 animals treated with EE exhibited mild hyperplasia of the glandular epithelium.
  - A GLP-compliant pubertal assay conducted according to U.S. EPA OPPTS 890.1450/890.1500 was performed with juvenile male and female Sprague-Dawley rats

[10] https://www.oecd-ilibrary.org/environment/test-no-441-hershberger-bioassay-in-rats_9789264076334-en

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(15/sex/group) administered gavage doses of tetramethyl bisphenol F (99.63% purity) in corn oil at 200 or 600 mg/kg/day on postnatal days 22-42 (males) or 23-53 (females). The females were evaluated for vaginal opening and estrous cyclicity, males were evaluated for preputial separation, and animals of both sexes were evaluated for reproductive organ weights and pathology. Tetramethyl bisphenol F treatment did not impact vaginal opening, vaginal cytology, estrous cyclicity, or reproductive organ weights or histopathology in females of either group. Low dose males did not exhibit statistically significant changes to preputial separation, while high dose males exhibited a delay in preputial separation (48.7 days vs. 47.3 days in the control group) but this difference was not statistically significant ($p = 0.05$) per the U.S. EPA guideline which considers statistically significant differences to occur when p-values are less than 0.05. Treatment did not produce effects on male reproductive organ weights or histopathology.

Szafran et al. 2017

- Tetramethyl bisphenol F treatment did not induce significant estrogen receptor alpha DNA binding in a PRL-HeLa cell line at ≤ 5 µM. Higher concentrations induced significant cytotoxicity. However, tetramethyl bisphenol F potentially antagonized estradiol activity in PRL-HeLa cells based on decreased gene expression profiles.

- ANSES 2017
  - French Agency for Food, Enviornmental and Occupational Health and Safety (ANSES) esvaluated available *in vitro* and *in vivo* endocrine data on tetramethyl bisphenol F and concluded that the chemical did not show activation effect with estrogen receptor, androgen receptor, aryl hydrocarbon receptor (AhR), no estrogenic effect in a uterotrophic test in rodents, and no aromatase inhibition activity *in vitro*. However, Danish QSAR database predicted tetramethyl bisphenol F to be an androgen antagonist using Leadscope and SciQSAR models.
- Ullah et al. 2019
  - *Surrogate: 4,4'-BPF (CAS #620-92-8)*: Male Sprague-Dawley rats (7/group) were administered oral doses of 4,4'-BPF (99% purity) at 0 (saline), 1, 5, 25, 50, or 100 mg/kg/day for 28 days. At the end of the exposure period, serum samples and the testes were collected for the assessment of hormone levels. 4,4'-BPF treatment at ≥ 25 mg/kg/day statistically significantly reduced plasma testosterone, luteinizing hormone (LH), and follicle stimulating hormone (FSH) levels and intra-testicular testosterone levels.
- Siracusa et al. 2018.
  - *Surrogate: 4,4'- BPF (CAS #620-92-8)*: A recent review concluded that "4,4'-BPF exposure may alter steroidogenesis both *in vitro* and *in vivo*, but its effects on the reproductive organs, oogenesis, spermatogenesis, and embryonic development remain inconclusive."
- Kitamura et al. 2005
  - *Surrogates: 4,4'-BPF (CAS #620-92-8), BPA (CAS #80-05-7), and tetramethyl bisphenol A (CAS #5613-46-7)*: In a MCF-7 estrogen luciferase reporter assay evaluating estrogenic activity of bisphenols and related chemicals 4,4'-BPF and tetramethyl bisphenol A produced EC_{50} values of 1.0 and 0.73 µM, respectively, compared to an EC_{50} of 0.63 µM for BPA, indicating that 4,4'-BPF and tetramethyl bisphenol A produce estrogenic activity that is within an order of magnitude of BPA's estrogenic activity.
  - *Surrogates: 4,4'-BPF (CAS #620-92-8), BPA (CAS #80-05-7), and tetramethyl bisphenol A (CAS #5613-46-7)*: In the 17-β-estradiol (E2) assay in MCF-7 cells evaluating anti-estrogenic activity, tetramethyl bisphenol A inhibited the activity of E2 at 10^{-5} M, the highest concentration tested, but neither 4,4'-BPF nor BPA inhibited the activity of E2 at up to 10^{-5} M. This result suggests that tetramethyl bisphenol F may have anti-estrogenic

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activity based on the presence of the 3,5-methyl groups not present in 4,4'-BPF.
  - *Surrogate: 4,4'-BPF (CAS #620-92-8) and BPA (CAS #80-05-7):* Using an ARE-luciferase reporter assay with NIH3T3 cells, the authors did not identify androgenic activity for 4,4'-BPF at up to 10^{-4} M, similar to BPA.
  - *Surrogates: 4,4'-BPF (CAS #620-92-8), BPA (CAS #80-05-7), and tetramethyl bisphenol A (CAS #5613-46-7)*: In a dihydrotestosterone anti-androgenic activity assay using NIH3T3 cells transfected with an AR responsive luciferase reporter gene, 4,4'-BPF and tetramethyl bisphenol A produced IC_{50} values of 12 and 0.29 µM, respectively, compared to an IC_{50} of 4.3 µM for BPA. *Based on the increased anti-androgenic activity of tetramethyl bisphenol A relative to BPA, tetramethyl bisphenol F may have a greater anti-androgenic activity than 4,4'-BPF.*
  - *Surrogates: 4,4'-BPF (CAS #620-92-8), BPA (CAS #80-05-7), and tetramethyl bisphenol A (CAS #5613-46-7)*: In an assay evaluating thyroid hormone-dependent production of growth hormone in GH3 cells, 4,4'-BPF did not induce growth of the cells, similar to BPA. Tetramethyl bisphenol A weakly induced growth hormone release under the conditions of this assay but was cytotoxic at 10^{-4} M.
- ChemSec 2020
  - *Surrogate: 4,4'-BPF (CAS #620-92-8)*: Bisphenol F is listed in the SIN (Substitute It Now!) List based on having endocrine disrupting properties: "Bisphenol F has shown to be estrogenic in *in vitro* studies and there is also some evidence of anti-androgenicity. *In vivo* studies have shown uterine growth in rodents and altered weight of testes and cowper´s gland." No further details were provided.
- HSDB 2013
  - *Surrogate: 4,4'-BPF (CAS #620-92-8)*: The estrogenic activity of some bisphenol A congeners (BPA, BPB, NP, and 4,4'-BPF) was tested using MCF-7 breast carcinoma cells, and murine bone marrow dendritic cells. A proliferation ranking between the tested EDCs was established and 4,4'-BPF has the lowest estrogenic activity.
  - *Surrogate: 4,4'-BPF (CAS #620-92-8)*: The estrogenic activity of various bisphenol A congeners (BPA, BPAF, BPAP, and 4,4'-BPF) was tested in a recombinant gene yeast assay. EC_{50} values of 6.81×10^{-6} mol/L, 7.44×10^{-7} mol/L, 1.43×10^{-5} mol/L, and 7.52×10^{-6} mol/L were reported for BPA, BPAF, BPAP, and 4,4'-BPF, respectively. Based on the EC_{50} values 4,4'-BPF has a moderate estrogenic activity.
  - *Surrogate: 4,4'-BPF (CAS #620-92-8)*: The estrogenic activity of 13 Bisphenol-A –related chemicals including 4,4'-BPF was tested in three *in vitro* bioassays; the yeast two-hybrid system, a fluorescence polarization system and E-screen; in the presence and absence of a post-mitochondrial metabolizing system (S9 mix). 4,4'-BPF showed estrogenic activity in the three assays with the activity being enhanced in the presence of S9 mix. In addition, the estrogenic activity in the E-screen occurred at concentration level that is 10 times lower than those of the other two assays.
  - *Surrogate: 4,4'-BPF (CAS #620-92-8)*: Bisphenol F was reported to be estrogenic in an *in vitro* bioassay in MCF7 human breast cancer cells.
  - *Surrogate: 4,4'-BPF (CAS #620-92-8)*: The endocrine activities of 4,4'-BPF and its metabolites were tested using the HepG2 human cell line. 4,4'-BPF increased the luciferase activity in HepG2 cells transiently transfected with a concentration dependent pattern. Its metabolite, DHB, also induced a positive response but at higher concentrations. Using MDA-kb2 cell line stably transfected with pMMTV-neo-Luc, only 4,4'-BPF was anti-androgenic at the highest concentration (10^{-5}M). 4,4'-BPF was the most toxic compound in terms of genotoxicity and endocrine activities compared to its free metabolites, DHB and

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BPF-OH.

- OEHHA 2012
  - *Surrogate: 4,4'-BPF (CAS #620-92-8)*: There is *in vitro* evidence of endocrine disrupting activity for bisphenol F.
  - *Surrogate: 4,4'-BPF (CAS #620-92-8)*: Bisphenol F is estrogenic based on an *in vivo* uterotrophic assay.
- SCENIHR 2015
  - *Surrogate: 4,4'-BPF (CAS #620-92-8)*: 4,4'-BPF has estrogenic effect based on the results of *in vivo* and *in vitro* assays. Moreover, anti-androgenic activity of 4,4'-BPF has also been observed in several human recombinant cell lines carrying hAR.
  - *Surrogate: 4,4'-BPF (CAS #620-92-8)*: One study also showed that 4,4'-BPF interacts with and disrupts thyroid hormone receptor signaling.
- Rochester and Bolden 2015
  - *Surrogate: 4,4'-BPF (CAS #620-92-8)*: The estrogenic activity of 4,4'-BPF was studied in 19 *in vitro* assays and 5 *in vivo* assays. The nineteen *in vitro* studies showed estrogenic, androgenic, and other physiological/biochemical effect, and four of the five *in vivo* studies showed that 4,4'-BPF exposure was estrogenic, androgenic and thyroidogenic.
  - *Surrogate: 4,4'-BPF (CAS #620-92-8)*: In a 28-day repeated dose toxicity study conducted according to OECD Guideline 407 using rats, oral exposure to 4,4'-BPF increased thyroid weight and altered thyroid hormone concentrations, as well as caused changes to hematological parameters and enzyme expression. Increased weight of the testes in treated animals was also reported. In addition, liver toxicity was noted as characterized by changes on clinical biochemical parameters and liver weight but without histopathological changes. The study authors identified a LOAEL of 20 mg/kg/day based on decreases in body weight, serum total cholesterol, glucose, and albumin in the female rats.
  - *Surrogates: 4,4'-BPF (CAS #620-92-8)*: A Hershberger assay with 4,4'-BPF showed a cumulative effect of 4,4'-BPF when co-administered with testosterone propionate that increased Cowper's gland weigh, indicative of anti-androgenic effects.
  - *Surrogates: 4,4'-BPF (CAS #620-92-8)*: 4,4'-BPF exposure also induced uterine growth in rats as shown in two studies, indicating estrogenic activity.
  - *Surrogates: 4,4'-BPF (CAS #620-92-8)*: The authors of the report examined the physiological effects and endocrine activities of the BPA substitutes BPS and 4,4'-BPF and compared the hormonal potency of BPS and 4,4'-BPF to BPA. Based on all the available data for these compounds, they concluded that BPS and 4,4'-BPF are as hormonally active as BPA, and have endocrine disrupting effects.
- In summary, tetramethyl bisphenol F does not inhibit aromatase (which converts testosterone to estradiol), weakly induced steroidogenesis in human adrenocortical carcinoma cells, was equivocally anti-androgenic in a Hershberger assay, was not estrogenic in an estrogen receptor transactivation assay or uterotrophic assay, and marginally significantly delayed preputial separation in male pups in a pubertal assay (indicating either estrogenic or anti-androgenic effects). *In vitro*, the surrogates 4,4'-BPF, BPA, and tetramethyl bisphenol A were estrogenic and anti-androgenic, and the surrogate tetramethyl bisphenol A may have anti-estrogenic and thyroid activity. The surrogate bisphenol F is included in the SIN screening lists warrants a Moderate or High score. Evidence from *in vitro* and *in vivo* studies indicates that bisphenol F has estrogenic effects. Moreover, anti-androgenic activity of 4,4'-BPF has also been observed in several human recombinant cell lines carrying hAR. One study also showed that 4,4'-BPF interacts with and disrupts thyroid hormone receptor signaling. Other animal studies with 4,4'-BPF showed changes in uterine growth in rodents and altered weight of testes and Cowper´s gland. Although limited details

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were provided for these studies, they indicate that the surrogate 4,4'-BPF is an endocrine disruptor and reproductive toxicant.

In contrast to the surrogates, tetramethyl bisphenol F demonstrated no estrogenic activity *in vitro* or *in vivo*, and did not affect weight or histopathology of thyroid and reproductive organs in GLP-compliant 28-day and 90-day toxicity studies (see ECHA 2020a and Maffini and Canatsey 2020; similar studies with 4,4'-BPF demonstrated clear thyroid effects by affecting thyroid hormone levels and thyroid weight (Ullah et al. 2019, Rochester and Bolden 2015)). While there are some *in vitro* data suggesting that the methyl substituents may increase the anti-androgen effects and hence tetramethyl bisphenol F may have higher anti-androgen effects than the surrogate bisphenol F, and a Hershberger assay on surrogate bisphenol F demonstrated clear anti-androgenic effect, the *in vivo* Hershberger assay and a pubertal assay on tetramethyl bisphenol F only demonstrated marginal or equivocal anti-androgenic effects. Further, while tetramethyl bisphenol F demonstrated weak steroidogenesis *in vitro,* there is no *in vivo* evidence of disrupted steroidogenesis in 28-day and 90-day repeated dose toxicity studies. Collectively, these data suggest that while tetramethyl bisphenol F may have equivocal anti-androgenic effects, its overall endocrine activity (if any) is less than the surrogates selected in this report. Therefore, ToxServices assigned a Moderate score for this endpoint.

Group II and II* Human Health Effects (Group II and II* Human)

Note: Group II and Group II* endpoints are distinguished in the v 1.4 Benchmark system (the asterisk indicates repeated exposure). For Systemic Toxicity and Neurotoxicity, Group II and II* are considered sub-endpoints. See GreenScreen® Guidance v1.4, Annex 2 for more details.

Acute Mammalian Toxicity (AT) (Group II) Score (vH, H, M, or L): L

Tetramethyl bisphenol F was assigned a score of Low for acute toxicity based on oral and dermal LD_{50} values > 2,000 mg/kg. GreenScreen® criteria classify chemicals as a Low hazard for acute toxicity when oral and dermal LD_{50} values > 2,000 mg/kg (CPA 2018b). The confidence in the score is high as it is based on measured data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2020a
  - *Oral*: LD_{50} (female Wistar rats) = 5,000 mg/kg (GLP-compliant, OECD Guideline 423) (Klimisch 1, reliable without restriction)
  - *Oral*: LD_{50} (female Wistar rats) > 2,000 mg/kg (non-GLP-compliant, OECD Guideline 423) (Klimisch 2, reliable with restrictions)
  - *Dermal*: LD_{50} (Wistar rats) > 2,000 mg/kg (GLP-compliant, OECD Guideline 402) (Klimisch 1, reliable without restriction)
  - *Dermal*: LD_{50} (Wistar rats) > 2,000 mg/kg (non-GLP-compliant, OECD Guideline 402) (Klimisch 2, reliable with restrictions)

Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST-single) (Group II) Score (vH, H, M, or L): L

Tetramethyl bisphenol F was assigned a score of Low for systemic toxicity (single dose) based on ToxServices not classifying it as a specific target organ toxicant following single exposures under GHS criteria. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (single dose) when adequate and negative data and no GHS classification are available (CPA 2018b). The confidence

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in the score is high as it is based on reliable measured data on the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2020b
  - A majority of EU notifiers (38/44, 86.4%) self-classified tetramethyl bisphenol F as a GHS Category 3 specific target organ toxicant following single exposures for respiratory irritation (H335).
- ECHA 2020a
  - *Oral*: In the GLP-compliant, OECD Guideline 423 acute oral toxicity test that identified an oral LD_{50} of 5,000 mg/kg in female Wistar rats, no non-behavioral clinical signs of toxicity were noted with treatment (see single dose neurotoxicity for a discussion of the behavioral clinical signs of toxicity). Tetramethyl bisphenol F treatment did not affect body weight gain or gross pathological findings (Klimisch 1, reliable without restriction).
  - *Oral*: In the non-GLP-compliant, OECD Guideline 423 acute oral toxicity test that identified an oral LD_{50} > 2,000 mg/k in female Wistar rats, treatment did not produce clinical signs of toxicity, effects on body weight, or alterations to gross pathological findings (Klimisch 2, reliable with restrictions).
  - *Dermal*: In the GLP-compliant, OECD Guideline 402 study that identified a dermal LD_{50} > 2,000 mg/kg in Wistar rats, treatment did not produce clinical signs of toxicity, changes to body weights, or alterations to gross pathological findings (Klimisch 1, reliable without restriction)**.**
  - *Dermal*: In the non-GLP-compliant, OECD Guideline 402 study that identified a dermal LD_{50} > 2,000 mg/kg in Wistar rats, treatment did not produce clinical signs of toxicity, changes to body weights, or alterations to gross pathological findings (Klimisch 2, reliable with restrictions)**.**
- Based on the lack of treatment-related effects on gross pathological findings in acute toxicity studies, ToxServices did not classify tetramethyl bisphenol F as a specific target organ toxicant following single exposures under GHS criteria (UN 2019).

Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST-repeat) (Group II*) Score (H, M, or L): L

Tetramethyl bisphenol F was assigned a score of Low for systemic toxicity (repeated dose) based on ToxServices not classifying it as a specific target organ toxicant following repeated doses under GHS criteria. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (repeated dose) when adequate and negative data and no GHS classification are available (CPA 2018b). The confidence in the score is high as it is based on reliable measured data on the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2020a
  - *Oral*: A GLP-compliant repeated dose toxicity test conducted according to OECD Guideline 407 was performed with Sprague-Dawley rats (6/sex/group) administered gavage doses of tetramethyl bisphenol F (as 4,4'-methylenebis (2,6 dimethylphenol (4,4'-methylenedi-2,6-xylenol), 0.47% impurities) in propylene glycol 400 at 250, 500, or 1,000 mg/kg/day for 28 days. The animals were evaluated for clinical signs of toxicity, body weight, food consumption, ophthalmoscopy, hematology, clinical chemistry, gross pathology, organ weights, and histopathology (included the thyroid, seminal vesicles, and

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testes). Tetramethyl bisphenol F treatment did not produce statistically significant and/or dose-related effects on these parameters. Therefore, the authors identified a systemic toxicity NOAEL of 1,000 mg/kg/day, the highest dose tested (Klimisch 1, reliable without restriction).

- As the exposure duration was less than 90 days, ToxServices adjusted the GHS oral guidance values of 10 and 100 mg/kg/day for 90-day studies (UN 2019) by a factor of three (28 days is approximately one third of 90 days) to 30 and 300 mg/kg/day, respectively. Since the NOAEL of 1,000 mg/kg/day is greater than the adjusted GHS guidance value of 300 mg/kg/day, ToxServices did not classify tetramethyl bisphenol F as a specific target organ toxicant following repeated doses under GHS criteria.

- Maffini and Canatsey 2020
  - *Oral*: A subchronic repeated oral dose toxicity test conducted according to OECD Guideline 408 was performed with Sprague-Dawley rats (10/sex/group) provided diets containing tetramethyl bisphenol F (> 98% purity) at doses equivalent to 100, 300, 750 (females only) or 1,000 mg/kg/day (males only) for 90 days. Additional groups of 5 animals/sex/group were provided the high dose and then maintained for an additional 28 days on the basal diet (recovery group). The animals were evaluated for body weights, food consumption, clinical signs of toxicity, ophthalmology, clinical chemistry, hematology, urinalysis, organ weights (included thyroid, testes, and epididymides), gross pathology, and histopathology (included thyroid, testes, epididymides, prostate, seminal vesicles, ovaries, cervix, uterus, vagina, mammary glands). Tetramethyl bisphenol F treatment did not affect clinical signs of toxicity, body weight, food consumption, ophthalmology, or gross pathology. At the end of the exposure period, tetramethyl bisphenol F treatment decreased serum creatinine in high dose males and females in all treatment groups, increased cholesterol in mid and high dose females and in males of all dose groups, increased total serum proteins in high dose males and females, increased serum albumin levels in high dose levels, increased serum globulin levels in high dose males and females, decreased hemoglobin levels in high dose females, increased red cell distribution width in high dose females, and increased activated partial thromboplastin time in mid and high dose males and low and high dose females. Treatment-related organ weights identified at the end of the exposure period included increased relative heart weights in high dose females, increased absolute kidney weights in high dose males and females, increased relative kidney weights in high dose males and mid and high dose females, and increased absolute and relative liver weights in males and females in all treatment groups. Histopathological changes related to tetramethyl bisphenol F treatment identified at the end of the exposure period (statistical significance not provided) included an increased incidences of minimal to mild hepatocellular hypertrophy in males in all treatment groups and in mid and high dose females, increased incidences of mild renal tubular dilatation in males in all treatment groups and increased incidence of minimal to mild renal tubular dilation in high dose females, increased incidence of minimal to mild renal tubular hypertrophy in males of all high dose groups and high dose females, increased incidence of minimal to mild thymus epithelial proliferation in females in all dose groups, and increased incidence of minimal to mild follicular cysts in high dose females. At the end of the recovery period, statistically significant changes to clinical chemistry and hematology parameters included decreased serum creatinine, alanine aminotransferase activity, and alkaline phosphatase activity and increased fibrinogen levels in high dose males, and decreased phosphorus, aspartate aminotransferase activity, alkaline phosphatase activity, and mean platelet volume and increased cholesterol esters in high dose females. Tetramethyl

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bisphenol F treatment increased absolute and relative (to brain weight) kidney weights and absolute and relative (to brain weight) liver weights in high dose males at the end of the recovery period. At the end of the recovery period, no treatment-related histopathological changes were identified in males or females. Based on the reversibility of the histopathological changes, the authors identified a systemic toxicity NOAEL of 750 and 1,000 mg/kg/day in females and males, respectively.

- Since the NOAEL of 750 mg/kg/day is greater than the GHS guidance value of 100 mg/kg/day for 90-day oral studies, ToxServices did not classify tetramethyl bisphenol F as a specific target organ toxicant following repeated doses under GHS criteria.

Neurotoxicity (single dose, N-single) (Group II) Score (vH, H, M, or L): *M*
Tetramethyl bisphenol F was assigned a score of Moderate for neurotoxicity (single dose) based on ToxServices classifying it as a Category 3 specific target organ toxicant following single exposures for narcotic effects under GHS criteria. GreenScreen® criteria classify chemicals as a Moderate hazard for neurotoxicity (single dose) when they are classified as GHS Category 3 specific target organ toxicant following single exposures for narcotic effects (CPA 2018b). The confidence in the score is low due to the inconsistent effects identified in the acute oral toxicity tests and the lack of mechanistic data for the lethargy and ataxia.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2020a
  - *Oral*: In the GLP-compliant, OECD Guideline 423 acute oral toxicity test that identified an oral LD_{50} of 5,000 mg/kg in female Wistar rats, no clinical signs of toxicity were noted at 300 mg/kg. At 2,000 mg/kg, all six animals exhibited mild to severe lethargy and mild to moderate ataxia (impaired balance or coordination) at up to six hours after dosing (Klimisch 1, reliable without restriction).
  - *Oral*: In the non-GLP-compliant, OECD Guideline 423 acute oral toxicity test that identified an oral LD_{50} > 2,000 mg/k in female Wistar rats, treatment did not produce behavioral clinical signs of toxicity or changes to the shape or size of the brain (Klimisch 2, reliable with restrictions).
- In summary, reversible narcotic effects (lethargy and ataxia) were detected in one of two acute oral toxicity tests. As it is not clear whether the narcotic effects are neurological in nature or a manifestation of discomfort following dosing with the target chemical, ToxServices conservatively classified tetramethyl bisphenol F as a Category 3 specific target organ toxicant following single exposures for narcotic effects under GHS criteria (UN 2019).

Neurotoxicity (repeated dose, N-repeated) (Group II*) Score (H, M, or L): L
Tetramethyl bisphenol F was assigned a score of Low for neurotoxicity (repeated dose) based on ToxServices not classifying it as a specific target organ toxicant following repeated doses for neurotoxicity under GHS criteria. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (repeated dose) when adequate and negative data and no GHS classification are available (CPA 2018b). The confidence in the score is high as it is based on reliable measured data on the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.

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- Maffini and Canatsey 2020
    - *Oral*: The previously described subchronic repeated oral dose toxicity test conducted according to OECD Guideline 408 was performed with Sprague-Dawley rats (10/sex/group) provided diets containing tetramethyl bisphenol F (> 98% purity) at doses equivalent to 100, 300, 750 (females only) or 1,000 mg/kg/day (males only) for 90 days. Additional groups of 5 animals/sex/group were provided the high dose and then maintained for an additional 28 days on the basal diet (recovery group). The animals were evaluated in a functional observational battery (FOB), and were assessed for stimulus response, grip strength, and locomotor activity. Tetramethyl bisphenol F treatment did not affect these parameters. Therefore, ToxServices identified a neurotoxicity NOAEL of 750 mg/kg/day, the highest dose in females, for this study.
        - Since the NOAEL of 750 mg/kg/day is greater than the GHS guidance value of 100 mg/kg/day for 90-day oral studies, ToxServices did not classify tetramethyl bisphenol F as a specific target organ toxicant following repeated doses for neurotoxicity under GHS criteria.

Skin Sensitization (SnS) (Group II*) Score (H, M, or L): L

Tetramethyl bisphenol F was assigned a score of Low for skin sensitization based on modeling indicating a lack of structural alerts and a negative read-across prediction for skin sensitization, and negative results for the surrogates 4,4'-BPF and tetramethyl bisphenol A in guinea pigs. GreenScreen® criteria classify chemicals as a Low hazard for skin sensitization when adequate and negative data and no GHS classification (CPA 2018b). The confidence in the score is high as it is based in part on measured data from a high quality study (GLP-compliant, internationally-accepted guideline) on a strong surrogate.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2020c
    - *Surrogate: Tetramethyl bisphenol A (CAS #5613-46-7)*: A GLP-compliant guinea pig maximization test conducted according to OECD Guideline 406/EU Method B.6/EPA OPPTS 870.2600 was performed with Hartley guinea pigs (3-5/sex in control groups, 10/sex in treatment groups) administered dermal doses of tetramethyl bisphenol A (as 4,4'-(1-methylethylidene)-bis(2,6-dimethylphenol), 99.74% purity). The induction doses were administered as intradermal injections of 0.1 mL Freund's complete adjuvant (FCA) in distilled water (1:1), 1% tetramethyl bisphenol A in mineral oil, and 1% tetramethyl bisphenol A in FCA in distilled water (1:1). Seven days later, the topical induction dose was applied as 25% tetramethyl bisphenol A in petrolatum under occlusive dressing for 48 hours. The challenge dose was applied 15 days after the topical induction dose as 25% tetramethyl bisphenol A in petrolatum under occlusive dressing for 24 hours. The application sites were evaluated 24 and 48 hours later. The tetramethyl bisphenol A treatment and negative control treatment did not induce positive dermal reactions. The positive control, dinitrochlorobenzene, induced positive dermal reactions in 6/6 animals. Therefore, the authors concluded that tetramethyl bisphenol A was not sensitizing to the skin under the tested condition.
- Bruze 1986
    - *Surrogate: 4,4'-BPF (CAS #620-92-8)*: 4,4'-BPF [as 4,4(1)-dihydroxydiphenyl methane (4,4(1)-HPM)] and 2,4'-bisphenol F (CAS #2467-03-0) [as 2,4(1)-dihydroxydiphenyl methane (2,4(1)-HPM)] were not sensitizing in a guinea pig maximization test. In contrast,

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2,2'-bisphenol F (CAS #2467-02-9) [as 2,2(1)-dihydroxydiphenyl methane (2,2(1)-HPM)] was sensitizing under the conditions of the test. No further details were available.

- Bruze and Zimerson 1985
  - *Surrogate: 4,4'-BPF (CAS #620-92-8)*: A patch test was performed with 16 patients with contact allergies towards phenol-formaldehyde resins to determine reactivity towards the three isomers of bisphenol F, which may be generated during production of phenol-formaldehyde resins. Nine patients reacted towards at least one BPF isomer, three patients reacted simultaneously towards 4,4'-BPF and 2,4'-BPF, and all patients reacted towards 2,4'-BPF. Additionally, possible cross-reactivity was identified for 4,4'-BPF and diethylstilbestrol in two patients.
- Payne and Walsh 1994
  - Tetramethyl bisphenol F contains none of the known structural alerts for skin sensitization as identified by Payne and Walsh (Appendix H).
- OECD 2020
  - Tetramethyl bisphenol F is not predicted to be a skin sensitizer based on the results of four of the five nearest neighbors when the category is defined as "Phenols (skin irritation/corrosion inclusion rules by BfR)" (Appendix I).
- Toxtree 2018
  - Tetramethyl bisphenol F does not contain structural alerts for skin sensitization (Appendix J).
- VEGA 2019
  - The CAESAR model predicts tetramethyl bisphenol F is a sensitizer with low reliability because the compound is outside of the model's applicability domain (global AD index = 0.379) (Appendix K).
  - The IRGMN/JRC model predicts tetramethyl bisphenol F is a sensitizer with low reliability because the compound is outside of the model's applicability domain (0.379) (Appendix K).
  - As tetramethyl bisphenol F was outside of the applicability domain, ToxServices did not include the results of the VEGA models in the weight of evidence.
- In summary, ToxServices concludes that tetramethyl bisphenol F is not likely to be a skin sensitizer. Although the surrogate 4,4'-BPF produced positive results for skin sensitization in a patch test, the results may be due to cross reactivity with other BPF isomers and it was negative for sensitization in a guinea pig maximization test. The surrogate tetramethyl bisphenol A was also negative for skin sensitization in a guinea pig maximization test. Finally, tetramethyl bisphenol F does not contain structural alerts for skin sensitization and read-across with OECD QSAR Toolbox indicates that it is not likely be a skin sensitizer.

Respiratory Sensitization (SnR) (Group II*) Score (H, M, or L): *L*

Tetramethyl bisphenol F was assigned a score of Low for respiratory sensitization based on the lack of dermal sensitization potential according to the ECHA guidance (2017). GreenScreen® criteria classify chemicals as a Low hazard for respiratory sensitization when they are not GHS classified (CPA 2018b). Confidence in the score is low as this evaluation does not include non-immunologic mechanisms of respiratory sensitization, and no specific data are available for respiratory sensitization.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- OECD 2020
  - Tetramethyl bisphenol F does not contain any structural alerts for respiratory sensitization (Appendix L).

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- Based on the weight of evidence and guidance from ECHA regarding assessment of respiratory sensitization potential, a score of Low was assigned. The guidance from ECHA states that the mechanisms leading to respiratory sensitization are essentially similar to those leading to skin sensitization (ECHA 2017). ECHA recommended that if a chemical is not a dermal sensitizer based on high quality data, it is unlikely to be a respiratory sensitizer. ECHA also noted that this rationale does not cover respiratory hypersensitivity caused by non-immunological mechanisms, for which human experience is the main evidence of activity (ECHA 2017). As the surrogates were not sensitizing to the skin (see skin sensitization section above), a literature search did not find any human evidence of respiratory sensitization by tetramethyl bisphenol F, and as tetramethyl bisphenol F does not contain any structural alerts for respiratory sensitization (OECD 2020), tetramethyl bisphenol F is not expected to be a respiratory sensitizer.

Skin Irritation/Corrosivity (IrS) (Group II) Score (vH, H, M, or L): L

Tetramethyl bisphenol F was assigned a score of Low for skin irritation/corrosivity based on the lack of dermal irritation detected in rabbit studies. GreenScreen® criteria classify chemicals as a Low hazard for skin irritation/corrosivity when adequate and negative data and no GHS classification are available (CPA 2018b). The confidence in the score is high as it is based on reliable measured data on the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2020b
  - A majority of EU notifiers (39/44, 88.6%) self-classified tetramethyl bisphenol F as a GHS Category 2 skin irritant (H315).
- ECHA 2020a
  - A GLP-compliant skin irritation test conducted according to OECD Guideline 404 was performed with female New Zealand White rabbits (three total) administered topical applications of 0.5 g tetramethyl bisphenol F (as 4, 4'-methylenedi-2, 6-xylenol, 99.79% purity) in 0.5 mL distilled water to clipped skin under occlusive dressing for four hours. An observation period of 72 hours followed the exposure period. At 24, 48, and 72 hours, the mean erythema and edema scores were both zero. Therefore, the authors concluded that tetramethyl bisphenol F was not irritating to the skin under the tested conditions (Klimisch 1, reliable without restriction).
  - A non-GLP-compliant skin irritation test conducted according to OECD Guideline 404 was performed with female New Zealand White rabbits (three total) administered topical applications of 0.5 g undiluted tetramethyl bisphenol F (as 4, 4'- methylenedi-2, 6-xylenol, purity not specified) to clipped skin under occlusive dressing for four hours. An observation period of 14 days followed the exposure period. The mean primary dermal irritation index (PDII) was 0/8 at three minutes, 4, 24, 48, and 72 hours, and 14 days. Therefore, the authors concluded that tetramethyl bisphenol F was not irritating to the skin under the tested conditions (Klimisch 2, reliable with restrictions).
- Although a majority of EU notifiers self-classified tetramethyl bisphenol F as a GHS Category 2 skin irritant, the available data indicate that it is not irritating to the skin of rabbits. Therefore, ToxServices did not classify tetramethyl bisphenol F as a skin irritant under GHS criteria (UN 2019).

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Eye Irritation/Corrosivity (IrE) (Group II) Score (vH, H, M, or L): L
Tetramethyl bisphenol F was assigned a score of Low for eye irritation/corrosivity based on the lack of dermal irritation detected in rabbit studies. GreenScreen® criteria classify chemicals as a Low hazard for eye irritation/corrosivity when adequate and negative data and no GHS classification are available (CPA 2018b). The confidence in the score is high as it is based on reliable measured data on the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2020b
  - A majority of EU notifiers (39/44, 88.6%) self-classified tetramethyl bisphenol F as a GHS Category 2 eye irritant (H319).
- ECHA 2020a
  - A GLP-compliant ocular irritation test conducted according to OECD Guideline 405 was performed with female New Zealand White rabbits (three total) administered ocular instillations of 100 mg undiluted tetramethyl bisphenol F (as 4, 4'-methylenedi-2, 6-xylenol, 99.79% purity). The eyes were rinsed with normal saline 24 hours after instillation. At 24, 48, and 72 hours, the mean corneal opacity score was 0/4, the mean iris score was 0/2, the mean conjunctival score was 0/3, and the mean chemosis score was 0/4. Therefore, the authors concluded that tetramethyl bisphenol F is not irritating to the eyes under the tested conditions (Klimisch 1, reliable without restriction).
  - A non-GLP-compliant ocular irritant test conducted according to OECD Guideline 405 was performed with female New Zealand White rabbits (three total) administered ocular instillations of 0.1 g undiluted tetramethyl bisphenol F (as 4, 4'-methylenedi-2, 6-xylenol, purity not specified). The eyes were not washed. At 72 hours, the mean overall irritation score was zero. As no evidence of ocular irritation was detected at 1, 24, 48, or 72 hours after instillation, the authors concluded that tetramethyl bisphenol F is not irritating to the eyes under the tested conditions (Klimisch 2, reliable with restrictions).
- Although a majority of EU notifiers self-classified tetramethyl bisphenol F as a GHS Category 2 eye irritant, the available data indicate that it is not irritating to the eyes of rabbits. Therefore, ToxServices did not classify tetramethyl bisphenol F as an eye irritant under GHS criteria (UN 2019).

Ecotoxicity (Ecotox)

Acute Aquatic Toxicity (AA) Score (vH, H, M, or L): *vH*
Tetramethyl bisphenol F was assigned a score of Very High for acute aquatic toxicity based on predicted acute aquatic toxicity values as low as 0.16 mg/L. GreenScreen® criteria classify chemicals as a Very High hazard for acute aquatic toxicity when acute aquatic toxicity values are no greater than 1 mg/L (CPA 2018b). The confidence in the score is low as it is based on modeled data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2020a
  - 72-hour EC_{30} (*Chlorella vulgaris*, microalgae) = 18.05 mg/L based on growth rate (non-GLP-compliant, OECD Guideline 201) (Klimisch 1, reliable without restriction).
  - The REACH dossier authors classified tetramethyl bisphenol F as a GHS Category 1 acute aquatic toxicant (H400).

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- ECHA 2020b
  - A majority of EU notifiers (43/44, 97.7%) self-classified tetramethyl bisphenol F as a GHS Category 1 acute aquatic toxicant (H400).
- ANSES 2017
  - ANSES discounted the aquatic toxicity studies on surrogates presented in the REACH dossier for tetramethyl bisphenol F due to the differences in physicochemical properties and structures. Based on predicted (OECD Toolbox, Danish EPA model, and ECOSAR) ecotoxicity data, consisted of 0.3 – 0.72 mg/L for fish 96h EC_{50}, 0.16 mg/L for *Ceriodaphnia dubia* 48h LC_{50}, and 0.023 mg/L for green algae (*Scenedesmus subspicatus*) EC_{50}, ANSES concluded that tetramethyl bisphenol F is potentially toxic to the aquatic environment (i.e., T).
- U.S. EPA 2017b
  - Tetramethyl bisphenol F belongs to the Phenols, Poly ECOSAR chemical class. The most conservative predicted acute E/LC_{50} values are 0.16 mg/L in fish (96h), 0.35 mg/L in daphnia (48h) (log K_{ow} of 5.24 exceeded the log K_{ow} limit of 5 for daphnia), and 0.43 mg/L in green algae (96h) (Appendix M).
- ECHA 2020c
  - *Surrogate: Tetramethyl bisphenol A (CAS #5613-46-7)*: 96-hour LC_{50} (*Pimephales promelas*, fathead minnow) > 0.76 mg/L (measured) (GLP-compliant, OECD Guideline 203/EPA OPPTS 850.1075) (Klimisch 1, reliable without restriction).
  - *Surrogate: Tetramethyl bisphenol A (CAS #5613-46-7)*: 48-hour mobility EC_{50} (*Daphnia magna*) = 3.1 mg/L (measured) (GLP-compliant, OECD Guideline 202/EU Method C.2) (Klimisch 1, reliable without restriction).
  - *Surrogate: Tetramethyl bisphenol A (CAS #5613-46-7)*: 72-hour EC_{50} (*Pseudokirchneriella subcapitata*, algae) = 0.37 mg/L (biomass), 0.67 mg/L (growth rate) (both measured time-weighted averages) (OECD Guideline 201/EU Method C.3) (Klimisch 1, reliable without restriction).
- In summary, measured acute aquatic toxicity data for the strong surrogate tetramethyl bisphenol A indicate that algae is more sensitive than daphnia (only the lower-bound toxicity value was identified in fish so it is not possible to determine if algae are significantly more sensitive than fish). While the measured algal value for tetramethyl bisphenol F is larger than the value for the surrogate, the result may reflect differences in species sensitivity as tetramethyl bisphenol F was tested with *C. vulgaris* while tetramethyl bisphenol A was tested in *P. subcapitata*. It should be noted that OECD Guideline 301 is most commonly performed with *P. subcapitata* and *Desmodesmus subspicatus*.[11]

  Differences between the measured and modeled algal toxicity data for tetramethyl bisphenol F may also reflect species differences depending on the data used to generate the model. Additionally, the available value for tetramethyl bisphenol F is an EC_{30}, which is bigger than EC_{50} values, and GHS and GreenScreen® classifications as well as modeled data are EC_{50} values. As the weight of evidence indicates that tetramethyl bisphenol F is expected to be very toxic to fish and algae based on modeling, supported by experimental data on the surrogate tetramethyl bisphenol A in algae with a standard test species. ToxServices assigned a Very High hazard score for this endpoint.

[11] https://search.oecd.org/env/test-no-201-alga-growth-inhibition-test-9789264069923-en.htm

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Chronic Aquatic Toxicity (CA) Score (vH, H, M, or L): *vH*

Tetramethyl bisphenol F was assigned a score of Very High for chronic aquatic toxicity based on predicted chronic aquatic toxicity values as low as 0.05 mg/L. GreenScreen® criteria classify chemicals as a Very High hazard for chronic aquatic toxicity when chronic aquatic toxicity values are no greater than 0.1 mg/L (CPA 2018b). The confidence in the score is low as it is based on modeling.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2020a
  - The REACH dossier authors classified tetramethyl bisphenol F as a GHS Category 1 chronic aquatic toxicant (H410).
- U.S. EPA 2017b
  - Tetramethyl bisphenol F belongs to the Phenols, Poly ECOSAR chemical class. The most conservative predicted chronic values (ChVs) are 0.05 mg/L in fish, 0.11 mg/L in daphnia, and 0.09 mg/L in green algae (Appendix M).
- ECHA 2020c
  - *Surrogate: Tetramethyl bisphenol A (CAS #5613-46-7)*: 72-hour NOEC (*P. subcapitata*, algae) = 0.15 mg/L (biomass and growth rate) (both measured time-weighted averages) (OECD Guideline 201/EU Method C.3) (Klimisch 1, reliable without restriction).
- In summary, measured data for the strong surrogate tetramethyl bisphenol A indicate that it exhibits high hazard (NOECs > 0.1 and ≤ 1.0 mg/L) towards algae following chronic exposures. As the predicted chronic aquatic toxicity values for fish and algae exposed to the target chemical tetramethyl bisphenol F are both < 0.1 mg/L and ToxServices identified no measured chronic aquatic toxicity values for tetramethyl bisphenol A, ToxServices assigned a Very High hazard score for this endpoint.

Environmental Fate (Fate)

Persistence (P) Score (vH, H, M, L, or vL): *H*

Tetramethyl bisphenol F was assigned a score of High for persistence based on an estimated half-life of 75 days in soil, its predicted dominant environmental compartment. GreenScreen® criteria classify chemicals as a High hazard for persistence when soil is the dominant environmental compartment and the half-life in soil is greater than 60 to 180 days (CPA 2018b). The confidence in the score is low as it is based on modeling.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ANSES 2017
  - ANSES concluded that tetramethyl bisphenol F may be persistent (P) or very persistent (vP) based on modeled biodegradation rates, environmental distribution and half-lives using OECD Toolbox, EPI Suite™, and Danish QSAR database.
- U.S. EPA 2017a
  - The BIOWIN modeling Ready Biodegradable Predictor indicates that tetramethyl bisphenol F is not expected to be readily biodegradable. Fugacity modeling (MCI method) predicts 61.7% will partition to soil with a half-life of 1,800 hours (75 days), 32.5% will partition to sediment with a half-life of 8,100 hours (337.5 days), and 5.87% will partition to water with a half-life of 900 hours (37.5 days) (Appendix N).

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- ECHA 2020c
    - *Surrogate: Tetramethyl bisphenol A (CAS #5613-46-7):* A GLP-compliant ready biodegradability test conducted according to OECD Guideline 301 B/EU Method C.4-C (CO_2 evolution test) was performed with activated domestic sludge (adaptation not specified) exposed to tetramethyl bisphenol A (as 4,4'-(1-methylethylidene)-bis(2,6-dimethylphenol), 98.7% purity) at 10 mg carbon/L for 28 days. At the end of the exposure period, tetramethyl bisphenol A degraded 4.1% and the authors concluded that it was not readily biodegradable under the tested conditions (Klimisch 1, reliable without restriction).
- The Level III Fugacity Model predicts tetramethyl bisphenol F will mainly partition to soil. In the absence of measured data on the target chemical, it is ToxServices internal policy to assign the hazard score for persistence based on the dominant environmental compartment(s) identified via fugacity modeling (ToxServices 2020). Therefore, ToxServices assigned a High score for this endpoint based on the fugacity modeling. This result is supported by the measured data for the surrogate tetramethyl bisphenol A which indicate it is not readily biodegradable.

Bioaccumulation (B) Score (vH, H, M, L, or vL): *vL*
Tetramethyl bisphenol F was assigned a score of Very Low for bioaccumulation based on an estimated BCF of 32.59 (Arnot-Gobas model for the upper trophic level) and experimental BCFs of 20 – 67 for the surrogate BPA. While the regression based model of EPI Suite™ predicted a higher BCF of 1,340 L/kg wet-wt that corresponds to a High score, ToxServices prefers the results from the Arnot-Gobas model as it incorporates metabolism into the modeling. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when BCF values are between no greater than 100 (CPA 2018b). The confidence in the score is low due to the uncertainty regarding the bioaccumulation potential voiced by ANSES.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2020a
    - Tetramethyl bisphenol F has an estimated log K_{ow} of 3.75 using OPERA v1.02.
- ANSES 2017
    - ANSES stated that the bioaccumulation potential of tetramethyl bisphenol F was unclear due to the inconsistencies between the modeled low K_{ow} of 5.21 by EPI Suite™ and the log K_{ow} of 1.21 presented in the REACH registration dossier, which leads to different modeled bioaccumulation potential. ANSES requested that a robust log K_{ow} be generated in order to reliably predict bioaccumulation.
- U.S. EPA 2017a
    - Tetramethyl bisphenol F has a modeled log K_{ow} of 5.24.
    - BCFBAF predicts a BCF of 1,340 L/kg wet-wt using the regression based model based on a modeled log K_{ow} of 5.24, and a BCF of 32.59 using the Arnot-Gobas model for the upper trophic level, taking metabolism into consideration (Appendix N).
- ECHA 2020
    - *Surrogate: BPA (CAS #80-05-7):* A bioaccumulation study was performed with carp (*Cyprinus carpio*) exposed to BPA (purity not specified) at nominal concentrations of 15 or 150 µg/L for 42 days. The concentrations were analytically verified. At the end of the exposure period, the whole body BCFs were 20-67 and 5.1-13.3 for the 15 and 150 µg/L solutions, respectively.
- In summary, ToxServices did not identify measured BCF/BAF values for tetramethyl bisphenol F or the surrogate tetramethyl bisphenol A or 4,4'-BPF. Modeling indicates that tetramethyl bisphenol F

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has a BCF of 32.59 which is the same order of magnitude as the measured BCFs of ≤ 67 for the surrogate BPA.

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): L
Tetramethyl bisphenol F was assigned a score of Low for reactivity based on ToxServices not classifying it as a reactive chemical under GHS criteria. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when no GHS classification is available (CPA 2018b). The confidence in the score was high as it is based in part on measured oxidizing properties data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2020a
  - Tetramethyl bisphenol F does not contain functional groups associated with explosive properties.
  - Tetramethyl bisphenol F does not have oxidizing properties when exposed to potassium permanganate.
- TCI 2018
  - Tetramethyl bisphenol F has an instability/physical hazards rating of zero from NFPA ("Normally stable, even under fire exposure conditions, and is not reactive with water") and HMIS ("Materials that are normally stable, even under fire conditions, and will not react with water, polymerize, decompose, condense, or self-react. Non-explosives").
- Based on the above data, ToxServices did not classify tetramethyl bisphenol F as a reactive chemical under GHS criteria (UN 2019).

Flammability (F) Score (vH, H, M, or L): L
Tetramethyl bisphenol F was assigned a score of Low for flammability based on ToxServices not classifying it as a flammable solid under GHS criteria. GreenScreen® criteria classify chemicals as a Low hazard for flammability when no GHS classification is available (CPA 2018b). The confidence in the score was high as it is based on reliable measured data on the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2020a
  - Tetramethyl bisphenol F has a flash point of 121.6°C as identified in a non-GLP-compliant closed cup test.
  - Tetramethyl bisphenol F has a flash point of 131.5°C as identified in a non-GLP-compliant open cup test.
  - Tetramethyl bisphenol F did not catch fire when exposed to air at 25°C in a non-GLP-compliant auto-flammability test.
  - Tetramethyl bisphenol F ignited only when a flame of 950°C was brought in contact with it.

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- TCI 2018
    - Tetramethyl bisphenol F has a flammability hazards rating of zero from NFPA (“Materials that will not burn under typical fire conditions (e.g. Carbon tetrachloride), including intrinsically noncombustible materials such as concrete, stone, and sand. Materials that will not burn in air when exposed to a temperature of 820°C (1,500°F) for a period of 5 minutes”) and HMIS (“Materials that will not burn”).
- Based on the above information, ToxServices did not classify tetramethyl bisphenol F as a flammable solid under GHS criteria (UN 2019).

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Use of New Approach Methodologies (NAMs)[12] in the Assessment

Table 4: Summary of NAMs Used in the GreenScreen® Assessment		
Endpoint	**NAMs Data Available and Evaluated? (Y/N)**	**Types of NAMs Data (*in silico* modeling/*in vitro* biological profiling/frameworks)**
Carcinogenicity	Y	*In silico* modeling: VEGA/Toxtree/OncoLogic/OECD Toolbox/Danish QSAR
Mutagenicity	Y	*In vitro* data: *in vitro* gene mutation assay/*in vitro* chromosome aberration assay
Reproductive toxicity	N	Not applicable
Developmental toxicity	N	Not applicable
Endocrine activity	Y	*In vitro* receptor binding/activation assays
Acute mammalian toxicity	N	Not applicable
Single exposure systemic toxicity	N	Not applicable
Repeated exposure systemic toxicity	N	Not applicable
Single exposure neurotoxicity	N	Not applicable
Repeated exposure neurotoxicity	N	Not applicable
Skin sensitization	Y	*In silico* modeling: Toxtree and VEGA/Toxtree/OECD Toolbox/Payne and Walsh (1994) QSAR
Respiratory sensitization	Y	*In silico* modeling: OECD Toolbox structural alerts
Skin irritation	N	Not applicable
Eye irritation	N	Not applicable
Acute aquatic toxicity	Y	*In silico* modeling: ECOSAR
Chronic aquatic toxicity	Y	*In silico* modeling: ECOSAR
Persistence	Y	*In silico* modeling: EPI Suite™
Bioaccumulation	Y	*In silico* modeling: EPI Suite™

[12] NAMs refers to any non-animal technology, methodology, approach, or combination thereof that inform chemical hazard and risk assessments. NAMs include *in silico*/computational tools, *in vitro* biological profiling (e.g., cell cultures, 2,3-D organotypic culture systems, genomics/transcriptomics, organs on a chip), and frameworks (i.e., adverse outcome pathways (AOPs), defined approaches (DA), integrated approaches to testing and assessment (IATA).

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APPENDIX A: Hazard Classification Acronyms
(in alphabetical order)

(AA) Acute Aquatic Toxicity

(AT) Acute Mammalian Toxicity

(B) Bioaccumulation

(C) Carcinogenicity

(CA) Chronic Aquatic Toxicity

(D) Developmental Toxicity

(E) Endocrine Activity

(F) Flammability

(IrE) Eye Irritation/Corrosivity

(IrS) Skin Irritation/Corrosivity

(M) Mutagenicity and Genotoxicity

(N) Neurotoxicity

(P) Persistence

(R) Reproductive Toxicity

(Rx) Reactivity

(SnS) Sensitization- Skin

(SnR) Sensitization- Respiratory

(ST) Systemic/Organ Toxicity

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APPENDIX B: Results of Automated GreenScreen® Score Calculation for Tetramethyl Bisphenol F (CAS #5384-21-4)

TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING

GreenScreen® Score Inspector

Table 1: Hazard Table

			Group I Human					Group II and II* Human								Ecotox		Fate		Physical	
			Carcinogenicity	Mutagenicity/Genotoxicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability
Table 2: Chemical Details									S	R *	S	R *	*	*								
Inorganic Chemical?	**Chemical Name**	**CAS#**	**C**	**M**	**R**	**D**	**E**	**AT**	**STs**	**STr**	**Ns**	**Nr**	**SNS***	**SNR***	**IrS**	**IrE**	**AA**	**CA**	**P**	**B**	**Rx**	**F**
No	**Tetramethyl Bisphenol F**	**5384-21-4**	*L*	**L**	*L*	*M*	*M*	**L**	**L**	**L**	*M*	**L**	**L**	*L*	**L**	**L**	*vH*	*vH*	*H*	*vL*	**L**	**L**

Table 3: Hazard Summary Table

Benchmark	a	b	c	d	e	f	g
1	No	No	No	No	No		
2	No	No	Yes	No	Yes	Yes	No
3	STOP						
4	STOP						

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
Tetramethyl Bisphenol F	2

Note: Chemical has not undergone a data gap assessment. Not a Final GreenScreen™ Score

Table 6

Chemical Name	Final GreenScreen® Benchmark Score
Tetramethyl Bisphenol F	2

After Data gap Assessment
Note: No Data gap Assessment Done if Preliminary GS Benchmark Score is 1.

Table 5: Data Gap Assessment Table

Datagap Criteria	a	b	c	d	e	f	g	h	i	j	bm4	End Result
1												
2	Yes	Yes	Yes	Yes	Yes							2
3												
4												

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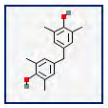
APPENDIX C: Pharos Output for Tetramethyl Bisphenol F (CAS #5384-21-4)



5384-21-4

Phenol, 4,4'-methylenebis[2,6-dimethyl-

ALSO CALLED 2,2',6,6'-Tetramethyl-4,4'-methylenediphenol, 2,6-Xylenol, 4,4'-methylenedi-, 3,3,5,5-Tetramethyl-4,...

View all synonyms (22)

Share Profile

Hazards | Properties | Functional Uses | Resources

Pharos Hazards View

Download Lists

ENDPOINT	HAZARD LEVEL	HAZARD LIST	HAZARD DESCRIPTION	OTHER LISTS
Restricted list	Potential Concern	EU - PACT-RMOA Substances	Substances selected for RMOA or hazard assessment	
Eye irritation	Potential Concern	EU - Manufacturer REACH hazard submissions	H319 - Causes serious eye irritation (unverified)	
Skin irritation	Potential Concern	EU - Manufacturer REACH hazard submissions	H315 - Causes skin irritation (unverified)	
Skin sensitize	Potential Concern	DK-EPA - Danish Advisory List	Skin Sens. 1 - May cause an allergic skin reaction (modeled)	
Organ toxicant	Potential Concern	EU - Manufacturer REACH hazard submissions	H335 - May cause respiratory irritation (unverified)	
Acute aquatic	Potential Concern	DK-EPA - Danish Advisory List	Aquatic Acute1 - Very toxic to aquatic life (modeled)	+2
	Potential Concern	DK-EPA - Danish Advisory List	Aquatic Chronic1 - Very toxic to aquatic life with long lasting effects (modeled)	
	Potential Concern	EU - Manufacturer REACH hazard submissions	H400 - Very toxic to aquatic life (unverified)	

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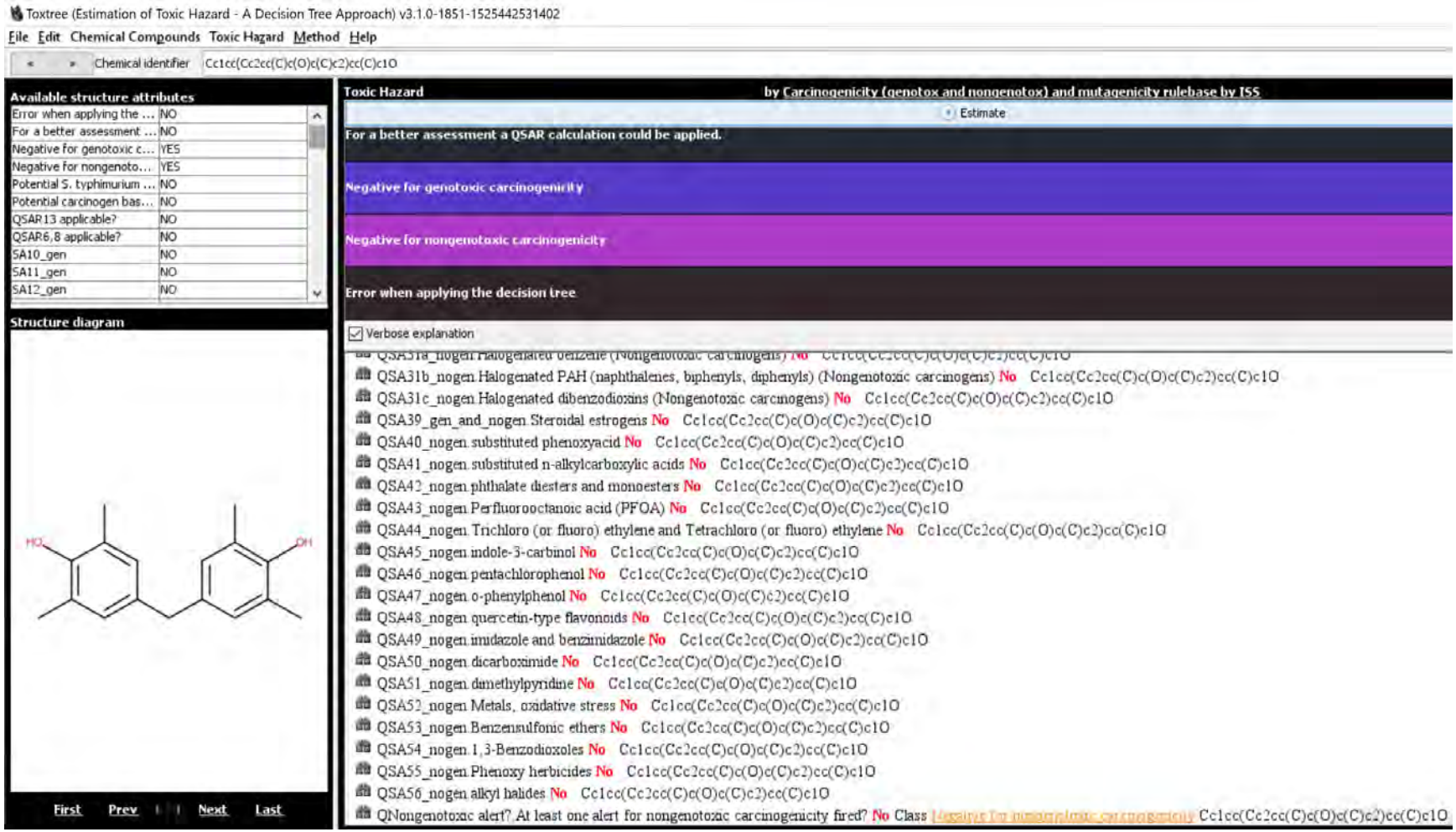
APPENDIX D: Toxtree Carcinogenicity Results for Tetramethyl Bisphenol F (CAS #5384-21-4)



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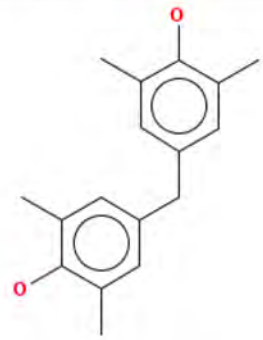
APPENDIX E: VEGA Carcinogenicity Results for Tetramethyl Bisphenol F (CAS #5384-21-4)

1. Prediction Summary

Prediction for compound Molecule 0



Prediction: Reliability:

Prediction is Carcinogen, but the result may be not reliable. A check of the information given in the following section should be done, paying particular attention to the following issues:
- similar molecules found in the training set have experimental values that disagree with the predicted value

Compound: Molecule 0
Compound SMILES: Oc1c(cc(cc1C)Cc2cc(c(O)c(c2)C)C)C
Experimental value: -
Predicted Carcinogen activity: Carcinogen
P(Carcinogen): 0.71
P(NON-Carcinogen): 0.29
Reliability: the predicted compound is outside the Applicability Domain of the model
Remarks:
none

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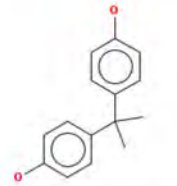
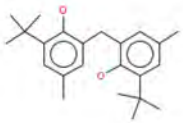
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 80-05-7
Dataset id: 100 (Training set)
SMILES: Oc1ccc(cc1)C(c2ccc(O)cc2)(C)C
Similarity: 0.927

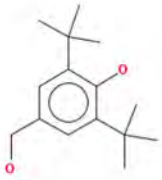
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #2

CAS: 119-47-1
Dataset id: 468 (Training set)
SMILES: Oc1c(cc(cc1C(C)(C)C)C)Cc2cc(cc(c2(O))C(C)(C)C)C
Similarity: 0.912

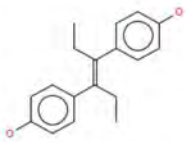
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #3

CAS: 88-26-6
Dataset id: 112 (Training set)
SMILES: Oc1c(cc(cc1C(C)(C)C)CO)C(C)(C)C
Similarity: 0.856

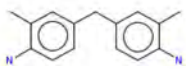
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #4

CAS: 56-53-1
Dataset id: 243 (Training set)
SMILES: Oc1ccc(cc1)C(=C(c2ccc(O)cc2)CC)CC
Similarity: 0.856

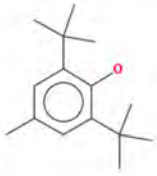
Experimental value: Carcinogen
Predicted value: Carcinogen



Compound #5

CAS: 838-88-0
Dataset id: 465 (Training set)
SMILES: Nc1ccc(cc1C)Cc2ccc(N)c(c2)C
Similarity: 0.843

Experimental value: Carcinogen
Predicted value: Carcinogen



Compound #6

CAS: 128-37-0
Dataset id: 116 (Training set)
SMILES: Oc1c(cc(cc1C(C)(C)C)C)C(C)(C)C
Similarity: 0.832

Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen

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3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0
Explanation: the predicted compound is outside the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.919
Explanation: strongly similar compounds with known experimental value in the training set have been found.

Accuracy of prediction for similar molecules
Accuracy index = 1
Explanation: accuracy of prediction for similar molecules found in the training set is good.

Concordance for similar molecules
Concordance index = 0
Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value.

Model's descriptors range check
Descriptors range check = True
Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set.

Atom Centered Fragments similarity check
ACF index = 1
Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Model class assignment reliability
Pos/Non-Pos difference = 0.419
Explanation: model class assignment is well defined.

Neural map neurons concordance
Neurons concordance = 1
Explanation: predicted value agrees with experimental values of training set compounds laying in the same neuron.

Symbols explanation:

The feature has a good assessment, model is reliable regarding this aspect.
The feature has a non optimal assessment, this aspect should be reviewed by an expert.
The feature has a bad assessment, model is not reliable regarding this aspect.

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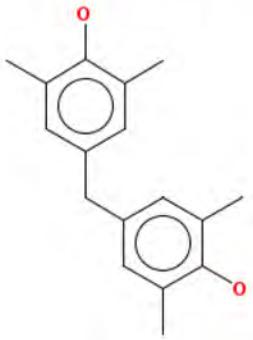
1. Prediction Summary

Prediction for compound Molecule 0



Prediction: Reliability:

Prediction is NON-Carcinogen, but the result shows some critical aspects, which require to be checked:
- accuracy of prediction for similar molecules found in the training set is not optimal
- some similar molecules found in the training set have experimental values that disagree with the predicted value

Compound: Molecule 0
Compound SMILES: Oc1c(cc(cc1C)Cc2cc(c(O)c(c2)C)C)C
Experimental value: -
Predicted Carcinogen activity: NON-Carcinogen
Structural alerts: -
Reliability: the predicted compound could be out of the Applicability Domain of the model
Remarks:
none

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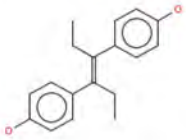
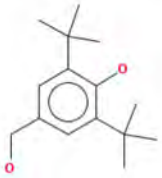
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 56-53-1
Dataset id: 5 (Training set)
SMILES: Oc1ccc(cc1)C(=C(c2ccc(O)cc2)CC)CC
Similarity: 0.856

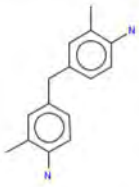
Experimental value: Carcinogen
Predicted value: NON-Carcinogen



Compound #2

CAS: 88-26-6
Dataset id: 811 (Training set)
SMILES: Oc1c(cc(cc1C(C)(C)C)CO)C(C)(C)C
Similarity: 0.856

Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen

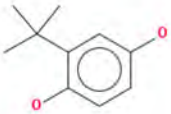


Compound #3

CAS: 838-88-0
Dataset id: 755 (Training set)
SMILES: Nc1ccc(cc1C)Cc2ccc(N)c(c2)C
Similarity: 0.843

Experimental value: Carcinogen
Predicted value: Carcinogen

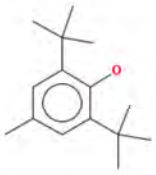
Alerts (not found in the target): SA28 Primary aromatic amine, hydroxyl amine and its derived esters (with restrictions)



Compound #4

CAS: 1948-33-0
Dataset id: 677 (Training set)
SMILES: Oc1ccc(O)c(c1)C(C)(C)C
Similarity: 0.834

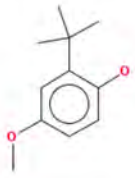
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #5

CAS: 128-37-0
Dataset id: 97 (Training set)
SMILES: Oc1c(cc(cc1C(C)(C)C)C)C(C)(C)C
Similarity: 0.832

Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #6

CAS: 25013-16-5
Dataset id: 367 (Training set)
SMILES: Oc1ccc(OC)cc1C(C)(C)C
Similarity: 0.816

Experimental value: Carcinogen
Predicted value: NON-Carcinogen

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3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.654
Explanation: the predicted compound could be out of the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.856
Explanation: strongly similar compounds with known experimental value in the training set have been found.

Accuracy of prediction for similar molecules
Accuracy index = 0.5
Explanation: accuracy of prediction for similar molecules found in the training set is not optimal.

Concordance for similar molecules
Concordance index = 0.5
Explanation: some similar molecules found in the training set have experimental values that disagree with the predicted value.

Atom Centered Fragments similarity check
ACF index = 1
Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

The feature has a good assessment, model is reliable regarding this aspect.

The feature has a non optimal assessment, this aspect should be reviewed by an expert.

The feature has a bad assessment, model is not reliable regarding this aspect.

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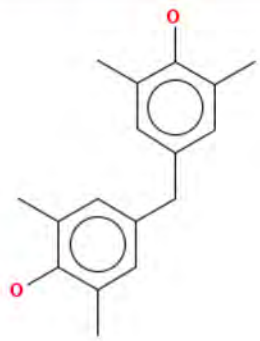
1. Prediction Summary

Prediction for compound Molecule 0



Prediction: Reliability:

Prediction is Possible NON-Carcinogen, the result appears reliable. Anyhow, you should check it through the evaluation of the information given in the following sections.

Compound: Molecule 0
Compound SMILES: Oc1c(cc(cc1C)Cc2cc(c(O)c(c2)C)C)C
Experimental value: -
Predicted Mutagen activity: Possible NON-Carcinogen
No. alerts for carcinogenicity: 0
Structural alerts: -
Reliability: the predicted compound is into the Applicability Domain of the model
Remarks:
none

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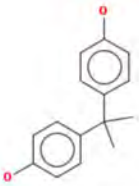
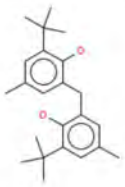
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: N.A.
Dataset id: 100 (Training set)
SMILES: Oc1ccc(cc1)C(c2ccc(O)cc2)(C)C
Similarity: 0.927

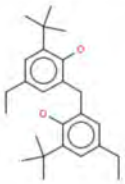
Experimental value: NON-Carcinogen
Predicted value: Possible NON-Carcinogen



Compound #2

CAS: N.A.
Dataset id: 467 (Training set)
SMILES: Oc1c(cc(cc1C(C)(C)C)C)Cc2cc(cc(c2(O))C(C)(C)C)C
Similarity: 0.912

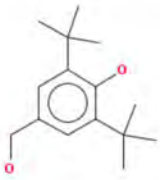
Experimental value: NON-Carcinogen
Predicted value: Possible NON-Carcinogen



Compound #3

CAS: N.A.
Dataset id: 822 (Training set)
SMILES: Oc1c(cc(cc1C(C)(C)C)CC)Cc2cc(cc(c2(O))C(C)(C)C)CC
Similarity: 0.898

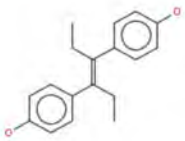
Experimental value: NON-Carcinogen
Predicted value: Possible NON-Carcinogen



Compound #4

CAS: N.A.
Dataset id: 112 (Training set)
SMILES: Oc1c(cc(cc1C(C)(C)C)CO)C(C)(C)C
Similarity: 0.856

Experimental value: NON-Carcinogen
Predicted value: Possible NON-Carcinogen

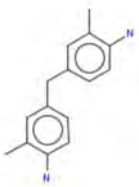


Compound #5

CAS: N.A.
Dataset id: 243 (Training set)
SMILES: Oc1ccc(cc1)C(=C(c2ccc(O)cc2)CC)CC
Similarity: 0.856

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): Carcinogenity alert no. 89



Compound #6

CAS: N.A.
Dataset id: 464 (Training set)
SMILES: Nc1ccc(cc1C)Cc2ccc(N)c(c2)C
Similarity: 0.843

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): Carcinogenity alert no. 27; Carcinogenity alert no. 28; Carcinogenity alert no. 29; Carcinogenity alert no. 31

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3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.955
Explanation: the predicted compound is into the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.912
Explanation: strongly similar compounds with known experimental value in the training set have been found.

Accuracy of prediction for similar molecules
Accuracy index = 1
Explanation: accuracy of prediction for similar molecules found in the training set is good.

Concordance for similar molecules
Concordance index = 1
Explanation: similar molecules found in the training set have experimental values that agree with the predicted value.

Atom Centered Fragments similarity check
ACF index = 1
Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

The feature has a good assessment, model is reliable regarding this aspect.
The feature has a non optimal assessment, this aspect should be reviewed by an expert.
The feature has a bad assessment, model is not reliable regarding this aspect.

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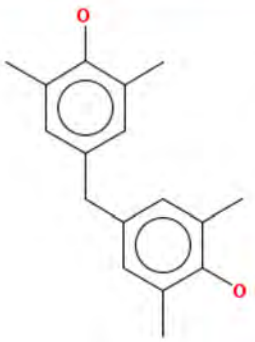
1. Prediction Summary

Prediction for compound Molecule 0



Prediction: Reliability:

Prediction is Possible NON-Carcinogen, but the result shows some critical aspects, which require to be checked:
- similar molecules found in the training set have experimental values that disagree with the predicted value

Compound: Molecule 0
Compound SMILES: Oc1c(cc(cc1C)Cc2cc(c(O)c(c2)C)C)C
Experimental value: -
Predicted Mutagen activity: Possible NON-Carcinogen
No. alerts for carcinogenicity: 0
Structural alerts: -
Reliability: the predicted compound could be out of the Applicability Domain of the model
Remarks:
none

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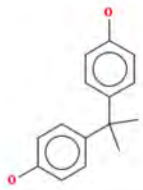
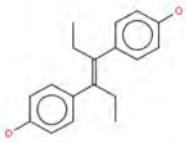
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 80-05-7
Dataset id: 960 (Training set)
SMILES: Oc1ccc(cc1)C(c2ccc(O)cc2)(C)C
Similarity: 0.927

Experimental value: NON-Carcinogen
Predicted value: Possible NON-Carcinogen

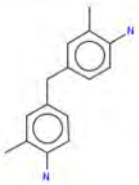


Compound #2

CAS: 56-53-1
Dataset id: 3 (Training set)
SMILES: Oc1ccc(cc1)C(=C(c2ccc(O)cc2)CC)CC
Similarity: 0.856

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): Carcinogenity alert no. 39

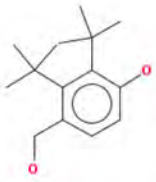


Compound #3

CAS: 838-88-0
Dataset id: 588 (Training set)
SMILES: Nc1ccc(cc1C)Cc2ccc(N)c(c2)C
Similarity: 0.843

Experimental value: Carcinogen
Predicted value: Carcinogen

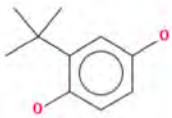
Alerts (not found in the target): Carcinogenity alert no. 6; Carcinogenity alert no. 41; Carcinogenity alert no. 42



Compound #4

CAS: 88-26-6
Dataset id: 740 (Training set)
SMILES: Oc1ccc(c(c1C(C)(C)C)C(C)(C)C)CO
Similarity: 0.843

Experimental value: NON-Carcinogen
Predicted value: Possible NON-Carcinogen



Compound #5

CAS: 1948-33-0
Dataset id: 692 (Training set)
SMILES: Oc1ccc(O)c(c1)C(C)(C)C
Similarity: 0.834

Experimental value: NON-Carcinogen
Predicted value: Possible NON-Carcinogen

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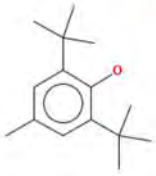
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #6

CAS: 128-37-0
Dataset id: 652 (Training set)
SMILES: Oc1c(cc(cc1C(C)(C)C)C)C(C)(C)C
Similarity: 0.832

Experimental value: NON-Carcinogen
Predicted value: Possible NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.72
Explanation: the predicted compound could be out of the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.869
Explanation: strongly similar compounds with known experimental value in the training set have been found.

Accuracy of prediction for similar molecules
Accuracy index = 1
Explanation: accuracy of prediction for similar molecules found in the training set is good.

Concordance for similar molecules
Concordance index = 0.356
Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value.

Atom Centered Fragments similarity check
ACF index = 1
Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

The feature has a good assessment, model is reliable regarding this aspect.
The feature has a non optimal assessment, this aspect should be reviewed by an expert.
The feature has a bad assessment, model is not reliable regarding this aspect.

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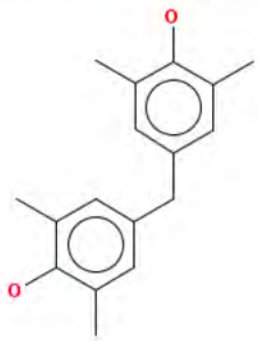
1. Prediction Summary

Prediction for compound Molecule 0



Prediction: Reliability:

Prediction is Carcinogen, but the result shows some critical aspects, which require to be checked:
- accuracy of prediction for similar molecules found in the training set is not adequate
- similar molecules found in the training set have experimental values that disagree with the predicted value

Compound: Molecule 0
Compound SMILES: Oc1c(cc(cc1C)Cc2cc(c(O)c(c2)C)C)C
Experimental value: -
Predicted Oral Carcinogenic class: Carcinogen
Reliability: the predicted compound could be out of the Applicability Domain of the model
Remarks:
none

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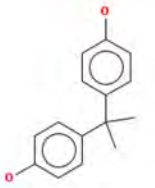
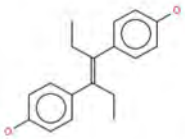
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 80-05-7
Dataset id: 354 (Training set)
SMILES: Oc1ccc(cc1)C(c2ccc(O)cc2)(C)C
Similarity: 0.927

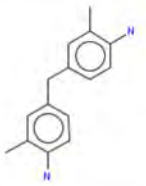
Experimental value: NON-Carcinogen
Predicted value: Carcinogen



Compound #2

CAS: 56-53-1
Dataset id: 117 (Training set)
SMILES: Oc1ccc(cc1)C(=C(c2ccc(O)cc2)CC)CC
Similarity: 0.856

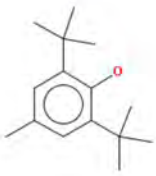
Experimental value: Carcinogen
Predicted value: Carcinogen



Compound #3

CAS: 838-88-0
Dataset id: 198 (Test set)
SMILES: Nc1ccc(cc1C)Cc2ccc(N)c(c2)C
Similarity: 0.843

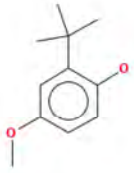
Experimental value: Carcinogen
Predicted value: Carcinogen



Compound #4

CAS: 128-37-0
Dataset id: 52 (Training set)
SMILES: Oc1c(cc(cc1C(C)(C)C)C)C(C)(C)C
Similarity: 0.832

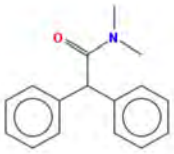
Experimental value: Carcinogen
Predicted value: Carcinogen



Compound #5

CAS: 25013-16-5
Dataset id: 51 (Test set)
SMILES: Oc1ccc(OC)cc1C(C)(C)C
Similarity: 0.816

Experimental value: Carcinogen
Predicted value: NON-Carcinogen



Compound #6

CAS: 957-51-7
Dataset id: 482 (Test set)
SMILES: O=C(N(C)C)C(c1ccccc1)c2ccccc2
Similarity: 0.807

Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen

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3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.651
Explanation: the predicted compound could be out of the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.887
Explanation: strongly similar compounds with known experimental value in the training set have been found.

Accuracy of prediction for similar molecules
Accuracy index = 0.477
Explanation: accuracy of prediction for similar molecules found in the training set is not adequate.

Concordance for similar molecules
Concordance index = 0.477
Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value.

Model's descriptors range check
Descriptors range check = True
Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set.

Atom Centered Fragments similarity check
ACF index = 1
Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

The feature has a good assessment, model is reliable regarding this aspect.
The feature has a non optimal assessment, this aspect should be reviewed by an expert.
The feature has a bad assessment, model is not reliable regarding this aspect.

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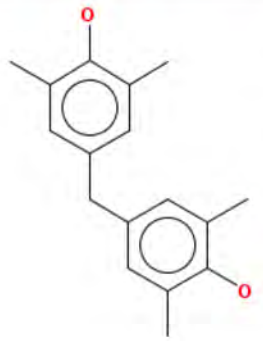
1. Prediction Summary

Prediction for compound Molecule 0



Prediction: Reliability:

Prediction is Carcinogen, but the result shows some critical aspects, which require to be checked:
- accuracy of prediction for similar molecules found in the training set is not adequate
- similar molecules found in the training set have experimental values that disagree with the predicted value

Compound: Molecule 0
Compound SMILES: Oc1c(cc(cc1C)Cc2cc(c(O)c(c2)C)C)C
Experimental value: -
Predicted Inhalation Carcinogenic class: Carcinogen
Reliability: the predicted compound could be out of the Applicability Domain of the model
Remarks:
none

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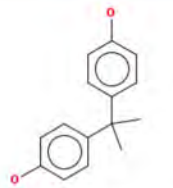
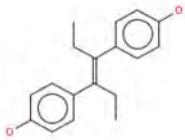
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 80-05-7
Dataset id: 306 (Training set)
SMILES: Oc1ccc(cc1)C(c2ccc(O)cc2)(C)C
Similarity: 0.927

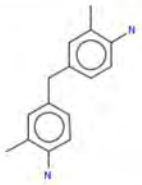
Experimental value: NON-Carcinogen
Predicted value: Carcinogen



Compound #2

CAS: 56-53-1
Dataset id: 97 (Training set)
SMILES: Oc1ccc(cc1)C(=C(c2ccc(O)cc2)CC)CC
Similarity: 0.856

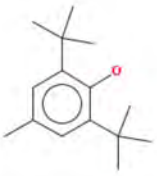
Experimental value: Carcinogen
Predicted value: Carcinogen



Compound #3

CAS: 838-88-0
Dataset id: 168 (Test set)
SMILES: Nc1ccc(cc1C)Cc2ccc(N)c(c2)C
Similarity: 0.843

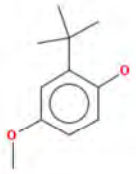
Experimental value: Carcinogen
Predicted value: Carcinogen



Compound #4

CAS: 128-37-0
Dataset id: 318 (Training set)
SMILES: Oc1c(cc(cc1C(C)(C)C)C)C(C)(C)C
Similarity: 0.832

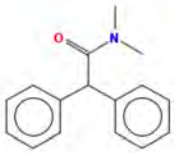
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #5

CAS: 25013-16-5
Dataset id: 44 (Training set)
SMILES: Oc1ccc(OC)cc1C(C)(C)C
Similarity: 0.816

Experimental value: Carcinogen
Predicted value: NON-Carcinogen



Compound #6

CAS: 957-51-7
Dataset id: 454 (Training set)
SMILES: O=C(N(C)C)C(c1ccccc1)c2ccccc2
Similarity: 0.807

Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen

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3.2 Applicability Domain:
Measured Applicability Domain Scores

⚠	**Global AD Index** AD index = 0.651 Explanation: the predicted compound could be out of the Applicability Domain of the model.
✓	**Similar molecules with known experimental value** Similarity index = 0.887 Explanation: strongly similar compounds with known experimental value in the training set have been found.
✗	**Accuracy of prediction for similar molecules** Accuracy index = 0.477 Explanation: accuracy of prediction for similar molecules found in the training set is not adequate.
✗	**Concordance for similar molecules** Concordance index = 0.477 Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value.
✓	**Model's descriptors range check** Descriptors range check = True Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set.
✓	**Atom Centered Fragments similarity check** ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

✓ The feature has a good assessment, model is reliable regarding this aspect.

⚠ The feature has a non optimal assessment, this aspect should be reviewed by an expert.

✗ The feature has a bad assessment, model is not reliable regarding this aspect.

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APPENDIX F: Danish (Q)SAR Carcinogenicity Results for Tetramethyl Bisphenol F (CAS #5384-21-4)

Carcinogenicity

	E Ultra	Leadscope
FDA RCA Cancer Male Rat	POS_OUT	INC_OUT
FDA RCA Cancer Female Rat	NEG_IN	NEG_OUT
FDA RCA Cancer Rat	POS_OUT	NEG_OUT
FDA RCA Cancer Male Mouse	NEG_IN	POS_IN
FDA RCA Cancer Female Mouse	NEG_IN	POS_IN
FDA RCA Cancer Mouse	NEG_IN	NEG_IN
FDA RCA Cancer Rodent	POS_OUT	NEG_IN

Commercial models from CASE Ultra and Leadscope

FDA RCA: Data from US Food and Drug Administration as part of Research Cooperation Agreement

Carcinogenicity (genotox and nongenotox) alerts by ISS, alerts in:	
- parent only	No alert found
Oncologic Primary Classification, alerts in:	
- parent only	Phenol Type Compounds

OECD QSAR Toolbox v.4.2 profilers

Profiler predictions are supporting information to be used together with the relevant QSAR predictions

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Liver Specific Cancer in Rat or Mouse		NEG_OUT	NEG_IN	POS_OUT	INC_OUT

DTU-developed models

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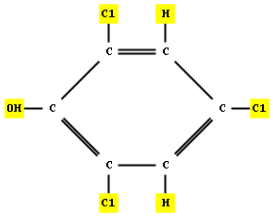
APPENDIX G: Oncologic Carcinogenicity Results for Tetramethyl Bisphenol F (CAS #5384-21-4)

OncoLogic Justification Report



SUMMARY :

CODE NUMBER : 5384214

SUBSTANCE ID :

The level of concern for this compound is LOW

JUSTIFICATION:

Phenolic compounds have generally not attracted much attention as carcinogens because (a) many phenolics are normal constituents of animal and plant tissues, (b) aromatic hydroxylation is often considered to be detoxifying in nature because of increased hydrophilicity, and (c) a large number of phenolics are inhibitors of carcinogenesis. However, at least several types of phenolics should be of concern as potential carcinogens or tumorigenesis promoters. These include (a) polyhydric phenolics capable of being oxidized to reactive simple or conjugated quinones, (b) phenolics capable of being oxidized to reactive quinoneimine or quinonemethide intermediates, (c) phenolics with structural similarity to estrogenic/androgenic compounds, and (d) phenolics containing linear tricyclic ring structure with hydroxy groups at both the 1- and 8-positions or all the peri positions on one side (e.g., 1,8,9-positions of anthracene).

Ring substitution with halogens may increase the activity depending on the number, position, and nature of the halogen. Ring substitution with bulky or hydrophilic groups tends to decrease activity. Phenolics which stimulate cell proliferation may contribute to carcinogenic activity. Some phenolics may have both carcinogenic and anticarcinogenic activity depending on the exposure scenario.

The baseline level of concern for an unsubstituted phenol is LOW.

The no alkyl or alkoxy groups with a total of two or three carbons are not expected to have a significant effect on the level of concern.

As a result of the combined substituent modifications, the level of concern remains LOW.
The final level of concern for this compound is LOW.

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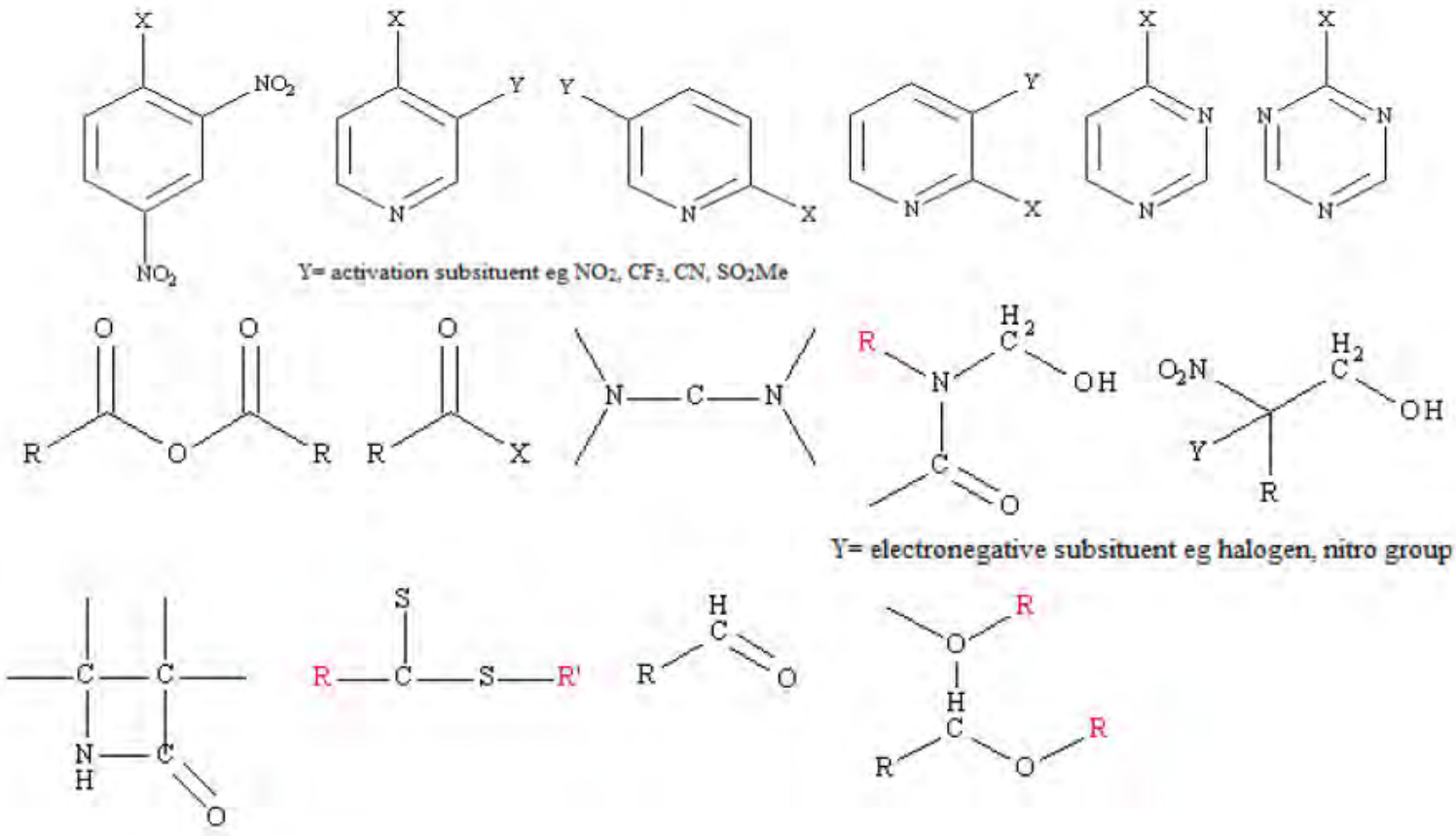
APPENDIX H: Known Structural Alerts for Skin Sensitization

Below are known structural alerts for skin sensitizers (Payne and Walsh 1994). Tetramethyl bisphenol F possesses none of the known structural alerts for skin sensitization.



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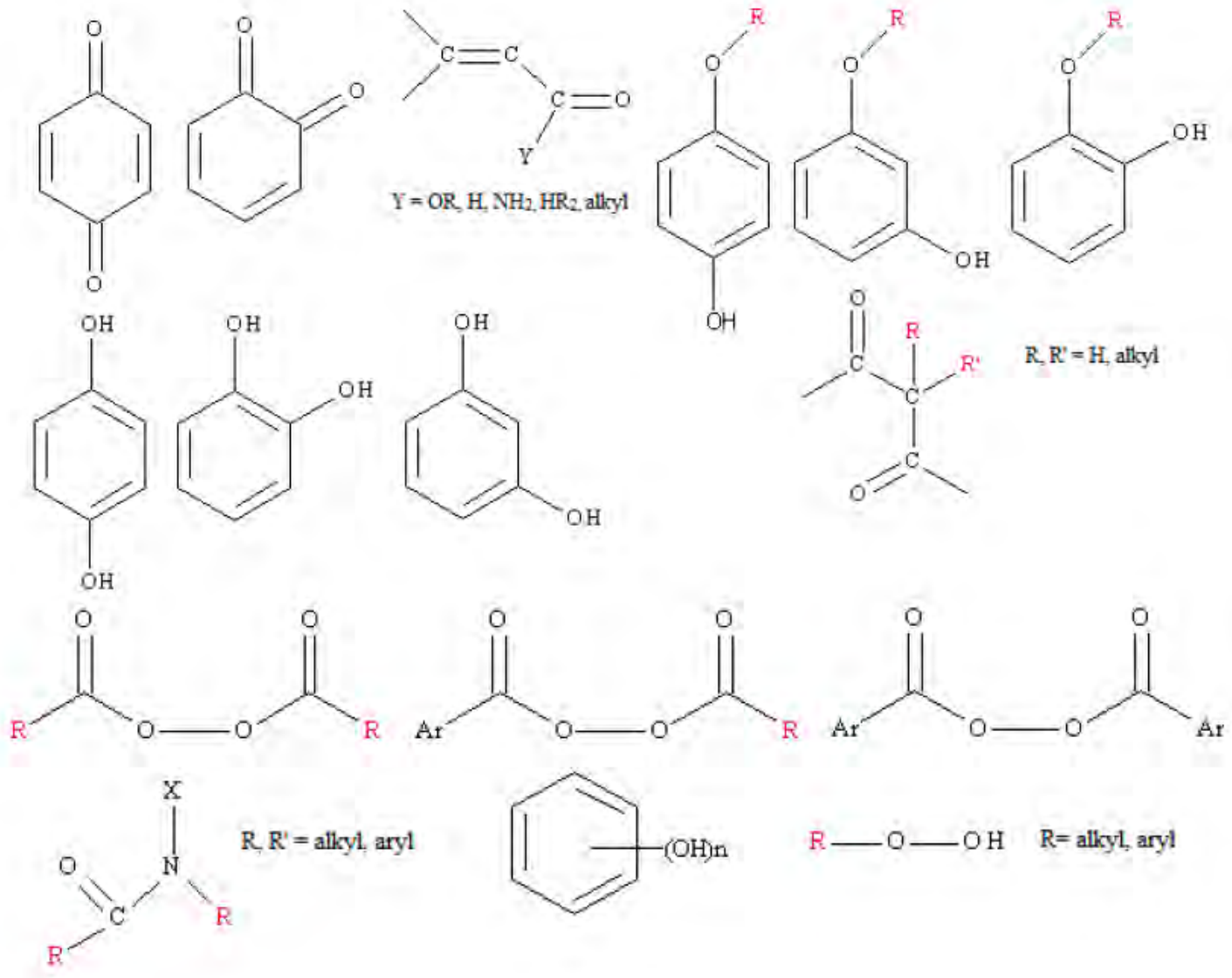

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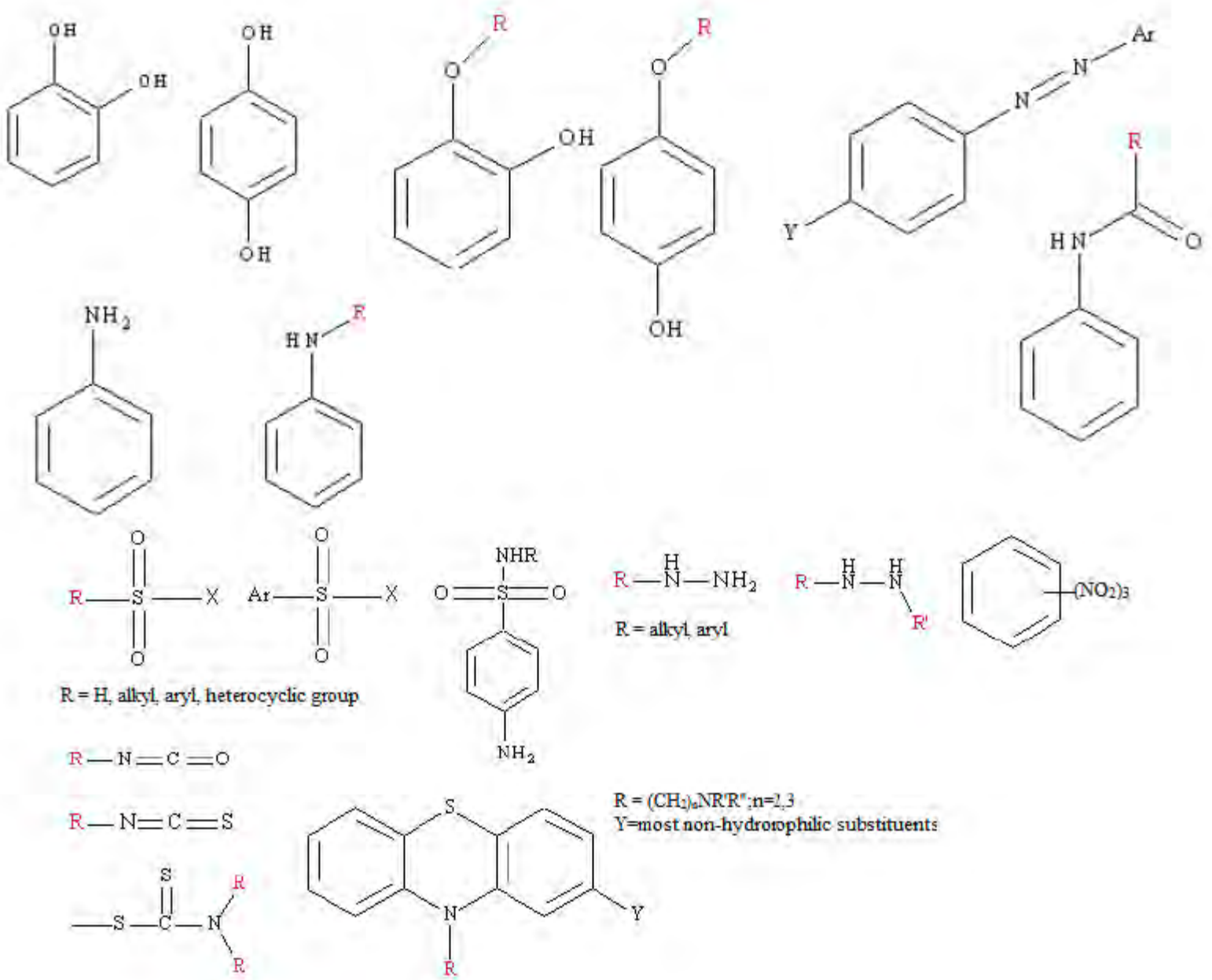

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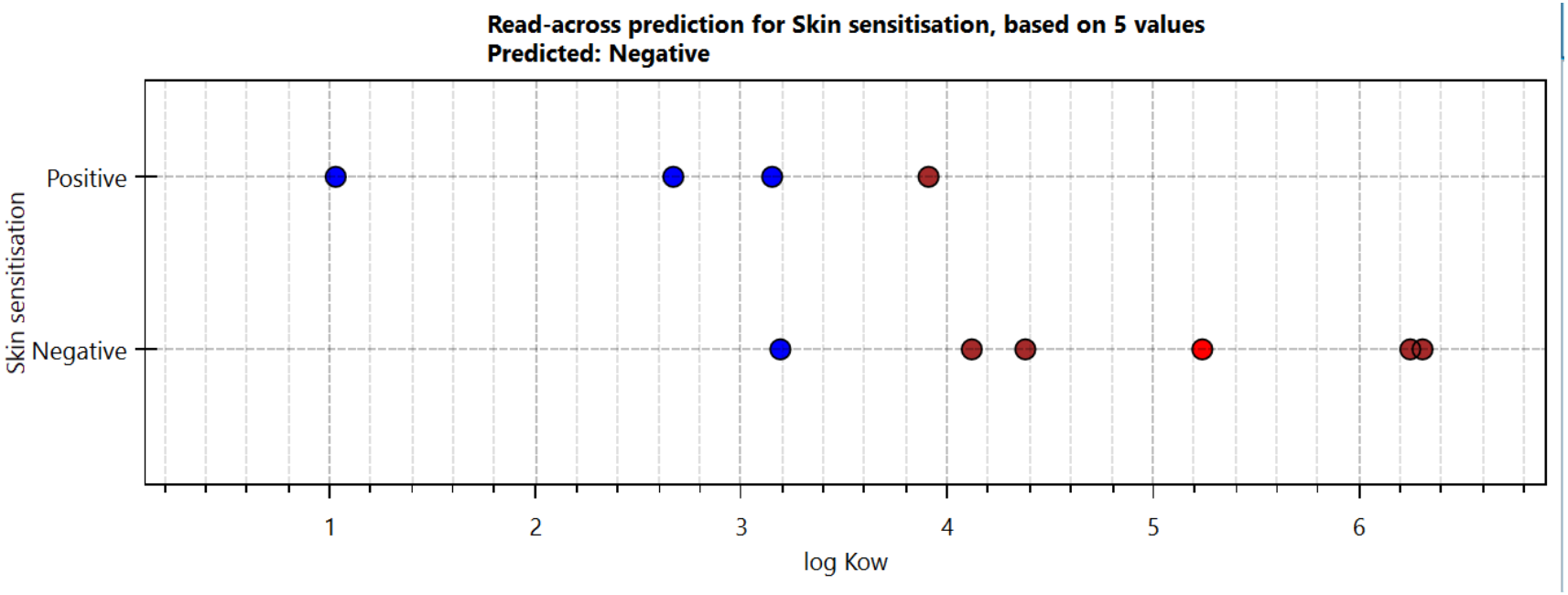
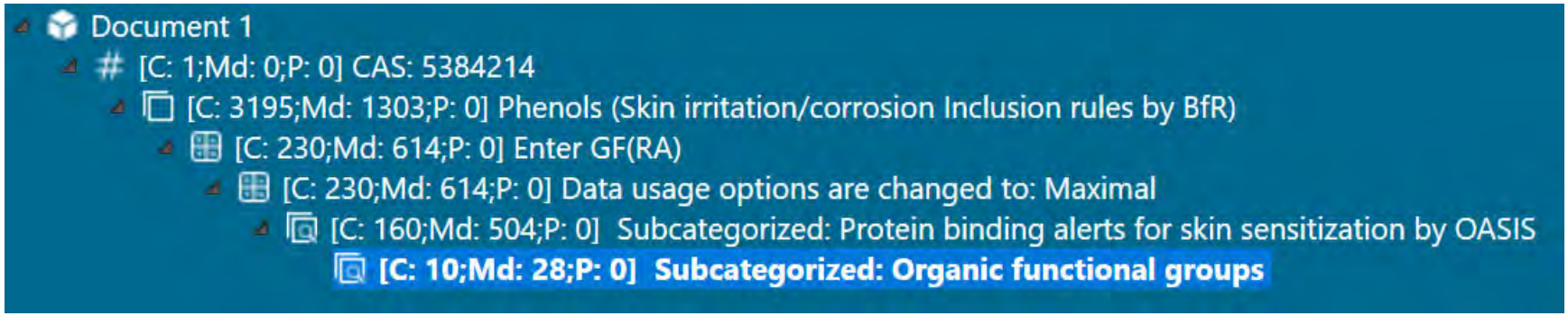
APPENDIX I: OECD Toolbox Skin Sensitization Results for Tetramethyl Bisphenol F (CAS #5384-21-4)





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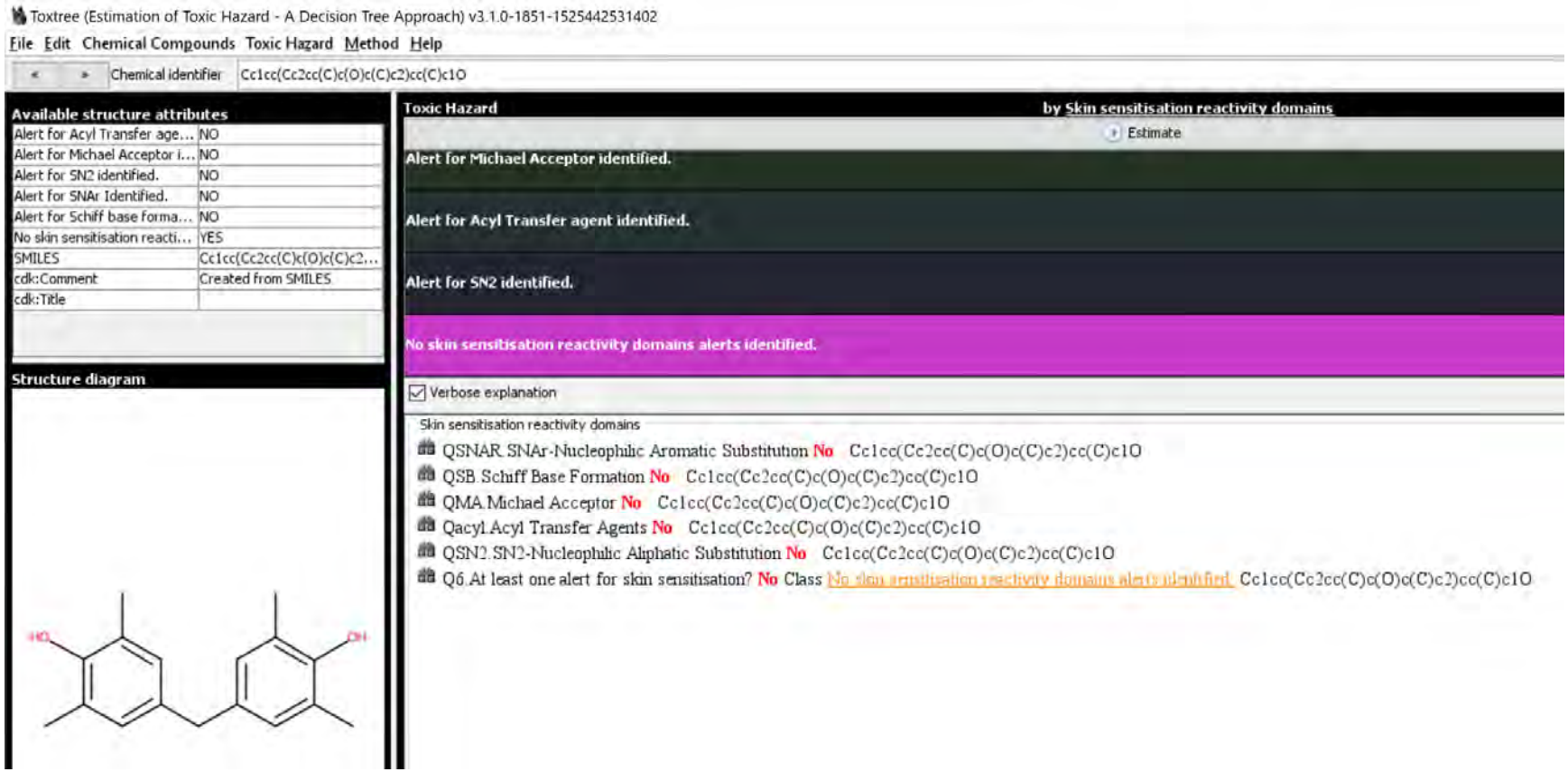
APPENDIX J: Toxtree Skin Sensitization Results for Tetramethyl Bisphenol F (CAS #5384-21-4)



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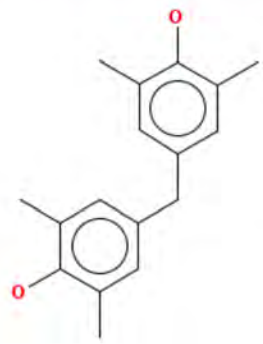
APPENDIX K: VEGA Skin Sensitization Results for Tetramethyl Bisphenol F (CAS #5384-21-4)

1. Prediction Summary

Prediction for compound Molecule 0



Prediction: Reliability:

Prediction is Sensitizer, but the result may be not reliable. A check of the information given in the following section should be done, paying particular attention to the following issues:
- accuracy of prediction for similar molecules found in the training set is not adequate
- similar molecules found in the training set have experimental values that disagree with the predicted value
- a prominent number of atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (1 unknown fragments found)

Compound: Molecule 0
Compound SMILES: Oc1c(cc(cc1C)Cc2cc(c(O)c(c2)C)C)C
Experimental value: -
Predicted skin sensitization activity: Sensitizer
O(Active): 0.59
O(Inactive): 0.41
Reliability: the predicted compound is outside the Applicability Domain of the model
Remarks:
none

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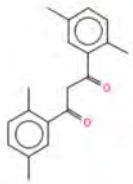
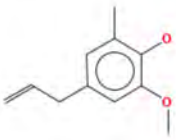
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: N.A.
Dataset id: 21 (Training set)
SMILES: O=C(c1cc(ccc1C)C)CC(=O)c2cc(ccc2C)C
Similarity: 0.832

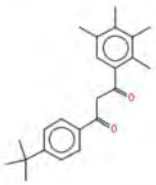
Experimental value: NON-Sensitizer
Predicted value: Sensitizer



Compound #2

CAS: 186743-24-8
Dataset id: 143 (Training set)
SMILES: Oc1c(OC)cc(cc1C)CC=C
Similarity: 0.803

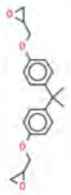
Experimental value: Sensitizer
Predicted value: Sensitizer



Compound #3

CAS: 55846-68-9
Dataset id: 199 (Training set)
SMILES: O=C(c1ccc(cc1)C(C)(C)C)CC(=O)c2cc(c(c(c2C)C)C)C
Similarity: 0.801

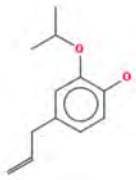
Experimental value: NON-Sensitizer
Predicted value: NON-Sensitizer



Compound #4

CAS: 1675-54-3
Dataset id: 22 (Training set)
SMILES: O(c1ccc(cc1)C(c3ccc(OCC2OC2)cc3)(C)C)CC4OC4
Similarity: 0.797

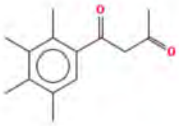
Experimental value: Sensitizer
Predicted value: Sensitizer



Compound #5

CAS: 51474-90-9
Dataset id: 123 (Training set)
SMILES: Oc1ccc(cc1(OC(C)C))CC=C
Similarity: 0.793

Experimental value: NON-Sensitizer
Predicted value: Sensitizer



Compound #6

CAS: 167998-73-4
Dataset id: 200 (Training set)
SMILES: O=C(c1cc(c(c(c1C)C)C)C)CC(=O)C
Similarity: 0.791

Experimental value: Sensitizer
Predicted value: Sensitizer

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3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.379
Explanation: the predicted compound is outside the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.817
Explanation: strongly similar compounds with known experimental value in the training set have been found.

Accuracy of prediction for similar molecules
Accuracy index = 0.489
Explanation: accuracy of prediction for similar molecules found in the training set is not adequate.

Concordance for similar molecules
Concordance index = 0.489
Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value.

Model's descriptors range check
Descriptors range check = True
Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set.

Atom Centered Fragments similarity check
ACF index = 0.6
Explanation: a prominent number of atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (1 unknown fragments found).

Symbols explanation:

The feature has a good assessment, model is reliable regarding this aspect.

The feature has a non optimal assessment, this aspect should be reviewed by an expert.

The feature has a bad assessment, model is not reliable regarding this aspect.

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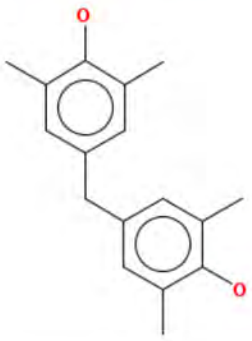
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

(Molecule 0) Reasoning on rare and missing Atom Centered Fragments.
The following Atom Centered Fragments have been found in the molecule, but they are not found or rarely found in the model's training set:

Fragment defined by the SMILES: cCc
The fragment has never been found in the model's training set

1. Prediction Summary

Prediction for compound Molecule 0



Prediction: Reliability:

Prediction is Sensitizer, but the result may be not reliable. A check of the information given in the following section should be done, paying particular attention to the following issues:
- accuracy of prediction for similar molecules found in the training set is not adequate
- similar molecules found in the training set have experimental values that disagree with the predicted value
- a prominent number of atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (1 unknown fragments found)

Compound: Molecule 0
Compound SMILES: Oc1c(cc(cc1C)Cc2cc(c(O)c(c2)C)C)C
Experimental value: -
Predicted skin sensitization activity: Sensitizer
Reliability: the predicted compound is outside the Applicability Domain of the model
Remarks:
none

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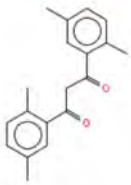
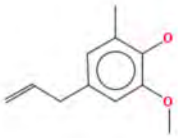
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: N.A.
Dataset id: 208 (Training set)
SMILES: O=C(c1cc(ccc1C)C)CC(=O)c2cc(ccc2C)C
Similarity: 0.832

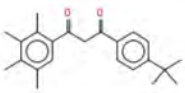
Experimental value: NON-Sensitizer
Predicted value: Sensitizer



Compound #2

CAS: 186743-24-8
Dataset id: 118 (Training set)
SMILES: Oc1c(OC)cc(cc1C)CC=C
Similarity: 0.803

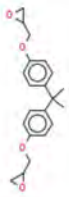
Experimental value: Sensitizer
Predicted value: Sensitizer



Compound #3

CAS: 55846-68-9
Dataset id: 215 (Training set)
SMILES: O=C(c1ccc(cc1)C(C)(C)C)CC(=O)c2cc(c(c(c2C)C)C)C
Similarity: 0.801

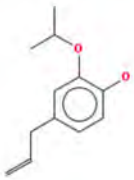
Experimental value: NON-Sensitizer
Predicted value: NON-Sensitizer



Compound #4

CAS: 1675-54-3
Dataset id: 10 (Training set)
SMILES: O(c1ccc(cc1)C(c3ccc(OCC2OC2)cc3)(C)C)CC4OC4
Similarity: 0.797

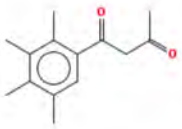
Experimental value: Sensitizer
Predicted value: Sensitizer



Compound #5

CAS: 51474-90-9
Dataset id: 212 (Training set)
SMILES: Oc1ccc(cc1(OC(C)C))CC=C
Similarity: 0.793

Experimental value: NON-Sensitizer
Predicted value: NON-Sensitizer



Compound #6

CAS: 167998-73-4
Dataset id: 298 (Test set)
SMILES: O=C(c1cc(c(c(c1C)C)C)C)CC(=O)C
Similarity: 0.791

Experimental value: Sensitizer
Predicted value: NON-Sensitizer

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3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.379
Explanation: the predicted compound is outside the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.817
Explanation: strongly similar compounds with known experimental value in the training set have been found.

Accuracy of prediction for similar molecules
Accuracy index = 0.489
Explanation: accuracy of prediction for similar molecules found in the training set is not adequate.

Concordance for similar molecules
Concordance index = 0.489
Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value.

Model's descriptors range check
Descriptors range check = True
Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set.

Atom Centered Fragments similarity check
ACF index = 0.6
Explanation: a prominent number of atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (1 unknown fragments found).

Symbols explanation:

The feature has a good assessment, model is reliable regarding this aspect.
The feature has a non optimal assessment, this aspect should be reviewed by an expert.
The feature has a bad assessment, model is not reliable regarding this aspect.

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4.1 Reasoning:
Relevant Chemical Fragments and Moieties

(Molecule 0) Reasoning on rare and missing Atom Centered Fragments.
The following Atom Centered Fragments have been found in the molecule, but they are not found or rarely found in the model's training set:

Fragment defined by the SMILES: cCc
The fragment has never been found in the model's training set

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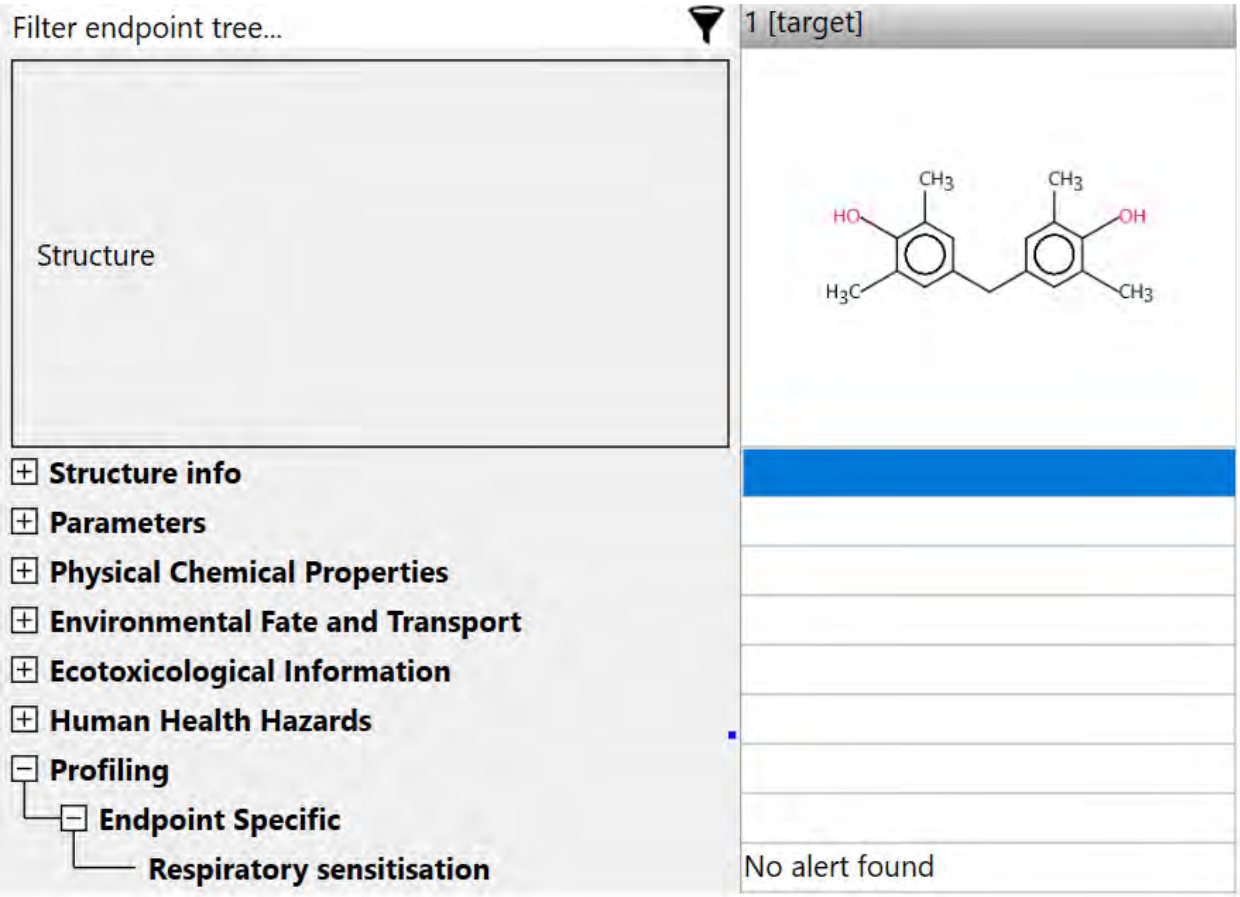
APPENDIX L: OECD Toolbox Respiratory Sensitization Results for Tetramethyl Bisphenol F (CAS #5384-21-4)



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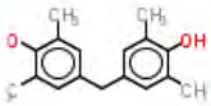
APPENDIX M: ECOSAR Modeling Results for Tetramethyl Bisphenol F (CAS #5384-21-4)

Organic Module Report

Results of Organic Module Evaluation

CAS	Name	SMILES
5384214	PHENOL, 4,4'-METHYLENEBIS[2,6-DIMETHYL-	Oc(c(cc1Cc(cc(c2O)C)cc2C)C)c(c1)C

Structure



Details	
Mol Wt	256.35
Selected LogKow	5.24
Selected Water Solubility (mg/L)	100
Selected Melting Point (°C)	170
Estimated LogKow	5.24
Estimated Water Solubility (mg/L)	0.78
Measured LogKow	
Measured Water Solubility (mg/L)	
Measured Melting Point (°C)	

Class Results:	

Phenols, Poly

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Fish	96h	LC50	0.16	7	

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Class Results:	

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Daphnid	48h	LC50	0.35	5	• If the Log Kow of the chemical is greater than the endpoint specific cut-offs presented, then no effects at saturation are expected for those endpoints
Green Algae	96h	EC50	0.43	6.4	
Fish		ChV	0.05	8	
Daphnid		ChV	0.11	8	
Green Algae		ChV	0.09	8	

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APPENDIX N: EPI Suite™ Modeling Results for Tetramethyl Bisphenol F (CAS #5384-21-4)

(Estimated values included in the GreenScreen® are highlighted and bolded)

CAS Number: 5384-21-4
SMILES : Oc(c(cc1Cc(cc(c2O)C)cc2C)C)c(c1)C
CHEM : PHENOL, 4,4'-METHYLENEBIS[2,6-DIMETHYL-
MOL FOR: C17 H20 O2
MOL WT : 256.35
---------- EPI SUMMARY (v4.11) ----------
Physical Property Inputs:
Log Kow (octanol-water): ------
Boiling Point (deg C) : ------
Melting Point (deg C) : 170.00
Vapor Pressure (mm Hg) : 1.92E-008
Water Solubility (mg/L): 100
Henry LC (atm-m3/mole) : ------

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.69 estimate) = 5.24

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 398.32 (Adapted Stein & Brown method)
Melting Pt (deg C): 162.04 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 1.56E-008 (Modified Grain method)
VP (Pa, 25 deg C) : 2.08E-006 (Modified Grain method)
Subcooled liquid VP: 5.22E-007 mm Hg (-999 deg C, user-entered VP)
: 6.95E-005 Pa (-999 deg C, user-entered VP)

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L): 0.7751
log Kow used: 5.24 (estimated)
melt pt used: 170.00 deg C

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 6.2599 mg/L

ECOSAR Class Program (ECOSAR v1.11):
Class(es) found:
Phenols, Poly

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method : 7.71E-012 atm-m3/mole (7.81E-007 Pa-m3/mole)
Group Method: 1.90E-012 atm-m3/mole (1.92E-007 Pa-m3/mole)
For Henry LC Comparison Purposes:
User-Entered Henry LC: not entered
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:
HLC: 6.476E-011 atm-m3/mole (6.562E-006 Pa-m3/mole)
VP: 1.92E-008 mm Hg (source: User-Entered)

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WS: 100 mg/L (source: User-Entered)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used: 5.24 (KowWin est)
Log Kaw used: -9.501 (HenryWin est)
Log Koa (KOAWIN v1.10 estimate): 14.741
Log Koa (experimental database): None

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : 1.1305
Biowin2 (Non-Linear Model) : 0.9832
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 2.3712 (weeks-months)
Biowin4 (Primary Survey Model) : 3.2146 (weeks)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : 0.2864
Biowin6 (MITI Non-Linear Model): 0.1326
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): -0.9931
Ready Biodegradability Prediction: NO

Hydrocarbon Biodegradation (BioHCwin v1.01):
Structure incompatible with current estimation method!

Sorption to aerosols (25 Dec C)[AEROWIN v1.00]:
Vapor pressure (liquid/subcooled): 6.96E-005 Pa (5.22E-007 mm Hg)
Log Koa (Koawin est): 14.741
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 0.0431
Octanol/air (Koa) model: 135
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 0.609
Mackay model : 0.775
Octanol/air (Koa) model: 1

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 47.2222 E-12 cm3/molecule-sec
Half-Life = 0.227 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life = 2.718 Hrs
Ozone Reaction:
No Ozone Reaction Estimation
Reaction With Nitrate Radicals May Be Important!
Fraction sorbed to airborne particulates (phi):
0.692 (Junge-Pankow, Mackay avg)
1 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):

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Koc : 1.086E+005 L/kg (MCI method)
Log Koc: 5.036 (MCI method)
Koc : 1.436E+004 L/kg (Kow method)
Log Koc: 4.157 (Kow method)

Aqueous Base/Acid-Catalyzed Hydrolysis (25 deg C) [HYDROWIN v2.00]:
Rate constants can NOT be estimated for this structure!

Bioaccumulation Estimates (BCFBAF v3.01):
Log BCF from regression-based method = 3.127 (BCF = 1340 L/kg wet-wt)
Log Biotransformation Half-life (HL) = -1.1129 days (HL = 0.07711 days)
Log BCF Arnot-Gobas method (upper trophic) = 1.513 (BCF = 32.59)
Log BAF Arnot-Gobas method (upper trophic) = 1.513 (BAF = 32.59)
log Kow used: 5.24 (estimated)

Volatilization from Water:
Henry LC: 6.48E-011 atm-m3/mole (calculated from VP/WS)
Half-Life from Model River: 1.447E+007 hours (6.031E+005 days)
Half-Life from Model Lake : 1.579E+008 hours (6.579E+006 days)

Removal In Wastewater Treatment:
Total removal: 83.98 percent
Total biodegradation: 0.72 percent
Total sludge adsorption: 83.26 percent
Total to Air: 0.00 percent
(using 10000 hr Bio P,A,S)

Level III Fugacity Model: (MCI Method)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	**0.000897**	**5.44**	**1000**
Water	**5.87**	**900**	**1000**
Soil	**61.7**	**1.8e+003**	**1000**
Sediment	**32.5**	**8.1e+003**	**0**

Persistence Time: 2.65e+003 hr

Level III Fugacity Model: (MCI Method with Water percents)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.000897	5.44	1000
Water	5.87	900	1000
water	(5.01)		
biota	(0.0435)		
suspended sediment	(0.816)		
Soil	61.7	1.8e+003	1000
Sediment	32.5	8.1e+003	0

Persistence Time: 2.65e+003 hr

Level III Fugacity Model: (EQC Default)

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	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.000973	5.44	1000
Water	6.9	900	1000
water	(6.18)		
biota	(0.0537)		
suspended sediment	(0.661)		
Soil	66.8	1.8e+003	1000
Sediment	26.3	8.1e+003	0
Persistence Time:	2.45e+003 hr		

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Tetramethyl Bisphenol F GreenScreen® Evaluation Prepared by:

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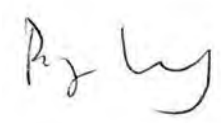

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