Preliminary Screen for Possible Future Consideration as Potential Designated Chemicals for Biomonitoring California[1]

Some Bisphenol A Substitutes and Structurally Related Compounds

Materials for March 16, 2012 Meeting Scientific Guidance Panel (SGP)

Agenda Item: Chemical Selection Planning

The purpose of this document is to provide background information for the Scientific Guidance Panel's (SGP's) discussion of candidate chemicals for possible future consideration as potential designated chemicals under Biomonitoring California. At the March 16, 2012 meeting, the SGP will discuss some bisphenol A (BPA) substitutes and structurally related compounds that might be considered in the future as potential designated chemicals.

This document summarizes a preliminary screen of 23 substances. The focus of the preliminary screen was to identify publicly available information related to potential for exposure and known or suspected health effects. A comprehensive literature search was not conducted. Secondary sources and predictive tools were used for some of the information.

Most of these chemicals are structurally related to bisphenol A (BPA), a priority chemical for biomonitoring. Some are known substitutes for BPA, which is used to make protective linings inside food and drink containers and to make polycarbonate plastic. BPA is also used as a developer in thermal paper for cash register receipts. Many manufacturers are beginning to use alternatives to BPA. The US Environmental Protection Agency's Design for the Environment is conducting an assessment of some of the chemicals in this document as possible substitutes for BPA in the manufacture of thermal paper.[2]

The preliminary screen includes a brief summary of information located so far on:

- Chemical identity and structure;
- Use and production;
- Physical chemical properties;
- Predicted bioaccumulation and persistence;

[1] California Environmental Contaminant Biomonitoring Program, codified at Health and Safety Code section 105440 et seq.

[2] See http://www.epa.gov/dfe/pubs/projects/bpa/about.htm for more information. Draft report expected out in late March or early April, 2012.

- Approximate extent of toxicity data and types of toxicity endpoints; and
- Detection in biological or environmental samples or in products.

At the March 16 meeting, the Panel will recommend what next steps, if any, should occur. One option would be for the SGP to recommend further screening of BPA substitutes and structurally related compounds. The SGP could also recommend that the Program develop a potential designated document on a particular subset of these chemicals or on specific chemicals.

CASRN	Chemical name Synonym	Type of use Example products	Production volume (lbs)[5] or Other indication of use
1675-54-3	**Bisphenol A diglycidyl ether (BADGE)** 2,2'-[(1-methylethylidene)bis(4,1-phenyleneoxymethylene)]bis-oxirane	**Epoxy and other resins[83]** Food and beverage cans[18,19] restorative dental materials[56]	1986: 1 - < 10M 1990: 1 - < 10M 1994: 1 - < 10M 1998: 1 - < 10M 2002: 1 - < 10M 2006: 1 - < 10M
1478-61-1	**Bisphenol AF** 4,4'-(hexafluoroisopropylidene)diphenol	**Epoxy resins and base-resistant primers[9,10.12]** Fluoroelastomers; O-rings/gaskets for food and pharmaceutical processing; electronic materials; restorative dental materials[9]	1986: 10-500K 1990: 10-500K 1994: 10-500K 1998: 10-500K 2002: 10-500K 2006: < 500K
1571-75-1	**Bisphenol AP** 4,4'-(α-Methylbenzylidene)diphenol	**Developer for thermal paper**[91] Cash register receipts	
77-40-7	**Bisphenol B** 2,2-Bis(4-hydroxyphenyl)butane	**Resins and plastics** Food and beverage cans[14]	
79-97-0	**Bisphenol C** 4,4'-(1-methylethylidene)bis(2-methylphenol)	**Developer for thermal paper[91]** Cash register receipts	
620-92-8	**Bisphenol F** 4,4'-di(hydroxydiphenyl)methane	**Epoxy resins and polycarbonates[14]** Food and beverage cans[14]	
2095-03-6	**Bisphenol F diglycidyl ether (BFDGE)** 2,2'-(Methylenebis(p-phenyleneoxymethylene))bisoxirane	**Epoxy and other resins[83]** Food and beverage cans[18,19]	
94-18-8	**PHBB** Benzyl 4-hydroxybenzoate; Benzylparaben (BzP)	**Developer for thermal paper[91]** Cash register receipts	
5129-00-0	**MBHA** Methyl bis(4-hydroxyphenyl)acetate	**Developer for thermal paper[91]** Cash register receipts	
24038-68-4	**BisOPP-A** 2,2-bis(2-hydroxy-5-biphenylyl)propane	**Developer for thermal paper[91]** Cash register receipts	

CASRN	Chemical name Synonym	Type of use Example products	Production volume (lbs)[5] or Other indication of use
93589-69-6	**1,7-Bis(4-hydroxyphenylthio)-3,5-dioxaheptane**	**Developer for thermal paper**[91] Cash register receipts	
80-09-1	**4,4'-Bisphenol S** Bis(4-hydroxyphenyl)sulfone	**Epoxy resins**[93] **and glues**[7]**, developer for thermal paper** Cash register receipts[6]	1986: 1 - < 10 M 1990: 1 - < 10 M 1994: 1 - < 10 M 1998: 1 - < 10 M 2002: 1 - < 10 M 2006: 1 - < 10 M
5397-34-2	**2,4'-Bisphenol S** 2,4'-Dihydroxydiphenyl sulfone	**Developer for thermal paper**[91] Cash register receipts	1986: No Reports 1990: No Reports 1994: No Reports 1998: >1M - 10M 2002: 10K - 500K 2006: < 500K
41481-66-7	**TGSA** Bis-(3-allyl-4- hydroxyphenyl) sulfone	**Developer for thermal paper**[91] Cash register receipts	1986: No Reports 1990: No Reports 1994: No Reports 1998: 10K - 500K 2002: 10K - 500K 2006: 1 to < 10 M
95235-30-6	**D-8** 4-[[4-(1-methylethoxy)phenyl]sulfonyl]phenol	**Developer for thermal paper**[91] Cash register receipts	1986: No Match 1990: No Match 1994: No Match 1998: No Match 2002: No Match 2006: 1 to < 10 M
97042-18-7	**BPS-MAE** 4-[[4-(2-propen-1-yloxy)phenyl]sulfonyl]phenol	**Developer for thermal paper**[91] Cash register receipts	

CASRN	Chemical name Synonym		Type of use Example products	Production volume (lbs)[5] or Other indication of use	
63134-33-8	**BPS-MPE** 4-[(4-Benzyloxyphenyl)sulfonyl]phenol		**Developer for thermal paper**[91] Cash register receipts	1986: >500K - 1M 1990: 10K - 500K 1994: 10K - 500K 1998: 10K - 500K 2002: No Reports 2006: No Records	
191680-83-8	**D-90** Phenol, 4,4'-sulfonylbis-, polymer with 1,1'-oxybis[2-chloroethane]		**Developer for thermal paper**[91] Cash register receipts		
232938-43-1	**Pergafast 201** Benzenesulfonamide, 4-methyl-N-[[[3-[[(4-		**Developer for thermal paper**[91] Cash register receipts		
321860-75-7	**Urea urethane compound** Phenol, reaction products with 4,4'-sulfonylbis[benzenamine] and 2,4-TDI		**Developer for thermal paper**[91] Cash register receipts		
151882-81-4	**BTUM** Benzenesulfonamide, N,N'-[methylenebis(4,1-phenyleneiminocarbonyl)]bis[4-methyl-		**Developer for thermal paper**[91] Cash register receipts		
120-61-6	**Tritan™ copolyester**	Dimethyl terephthalate (DMTP)	**Resins and plastics** Plastic water bottles (Nalgene™, Camelbak®), food packaging[25]	Sales of Tritan™ have increased dramatically.[101]	1986:>1B 1990:>1B 1994:>1B 1998:>1B 2002:>1B 2006: >1B
105-08-8		1,4-Cyclohexanedimethanol (CHDM)			1986: >10M - 50M 1990: >10M - 50M 1994: >50M - 100M 1998: >100M - 500M 2002: >50M - 100M 2006: 100 - < 500M
3010-96-6		2,2,4,4-Tetramethyl-1,3-cyclobutanediol (CDBO)			1986: No Match 1990: No Match 1994: No Match 1998: No Match 2002: No Match 2006: < 500K

CASRN	Chemical name Synonym		Type of use Example products	Production volume (lbs)[5] or Other indication of use
--	**Eco Care™**	PROPRIETARY - Griltex® polyester, which is baked on, and additives, including mineral fillers, waxy solids from natural fatty acid, and color pigments.	**Polymer powder coating** Aluminum and stainless-steel reusable bottles	

Chemical name		Molecular weight	Values estimated using PBT Profiler[a], unless otherwise noted								
			Log K_{ow}	BCF	Half-lives (days)				Fish Chronic Value (ChV) (mg/L)	Vapor pressure (mm Hg @ 25°C)	Water solubility (mg/L)
					Water	Soil	Marine sediment	Ambient air			
Bisphenol A diglycidyl ether		340.42	3.84	160	60	120	540	0.2	0.02	1.08E-07	3.69
Bisphenol AF		336.23	4.47	420	180	360	1600	0.2	0.19	1.29E-06	4.3
Bisphenol AP		290.36	4.86	750	38	75	340	0.19	0.076	9.50E-10	3.8
Bisphenol B		242.32	4.13	250	38	75	340	0.2	0.26	2.47E-07	26.9
Bisphenol C		281.13	4.73	620	38	75	340	0.2	0.085	7.50E-08	7.5
Bisphenol F		200.24	2.91 exp	39	15	30	140	0.2	1.2	8.84E-07	54
Bisphenol F diglycidyl ether		312.36	2.97	42	38	75	340	0.8	0.049	2.30E-07	30
PHBB		227.27	3.56 exp	100	15	30	140	0.9	0.007	3.37E-06	108
MBHA		258.27	2.75	31	15	30	140	0.2	0.097	3.30E-08	360
BisOPP-A		380.48	7.17	11,000	38	75	340	0.25	0.001	1.00E-12	0.012
1,7-Bis(4-hydroxyphenylthio)-3,5-dioxaheptane		352.47	3.34	75	38	75	340	0.2	1.3	1.40E-11	31
4,4'-Bisphenol S		250.27	1.65	5.7	15	30	140	1.1	13	4.72E-10	505
2,4'-Bisphenol S		250.27	1.65	5.7	15	30	140	1.1	13	2.71E-09	3520
TGSA		330.4	4.43	390	38	75	340	0.15	0.2	1.30E-11	5.1
D-8		292.35	3.11	53	38	75	340	0.67	0.009	9.60E-09	110
BPS-MAE		290.33	3.05	48	38	75	340	0.26	0.008	5.70E-09	130
BPS-MPE		340.4	3.91	180	38	75	340	0.71	0.01	5.10E-11	12
D-90 (example structure)		570.63	3.8	150	60	120	540	0.31	1.1	<1E-12	0.54
Pergafast 201		460.52	2.6	280	60	120	540	0.079	0.006	1.01E-17	35
Urea urethane compound (example structure)		784.85	6.5	9100	180	360	1600	0.079	0.00016	<1E-12	2.70E-05
BTUM		592.69	4.39	370	60	120	540	0.15	0.006	<1E-12	0.049
Tritan™ copolyester	**DMTP**	194.19	2.25 exp	14	15	30	140	28	4	1.0E-2 exp	19 exp
	CHDM	144.21	1.49	4.4	15	30	140	0.75	32	0.00031 exp	4300
	CDBO	144.22	1.26	3.2	15	30	140	2.4	49	5.80E-03	6700
Eco Care™	**Proprietary**										

a. Predictions generated by PBT Profiler (http://www.pbtprofiler.net/). Orange indicates persistent (P), bioaccumulative (B) or toxic to aquatic organisms (T). Red indicates very persistent (vP), very bioaccumulative (vB) or very toxic to aquatic organisms (vT) according to US EPA criteria.

Chemical name		Approximate Extent of Toxicity Data Identified in Preliminary Screen	Types of Toxicity Endpoints from Selected Studies	
			***In vitro* data**	***In vivo* data in mammals**
Bisphenol A diglycidyl ether (BADGE)		Several *in vitro* studies	Evidence of endocrine disrupting activity.[18,29,56] BADGE is an EC category 2 endocrine disruptor (BPA is category 1).[104]	
Bisphenol AF		Multiple *in vitro* and several *in vivo* studies	Evidence of endocrine disrupting activity.[13,27,29,36,38,40,41,94] Evidence of genotoxicity.[9]	Estrogenic based on uterotrophic assay.[36,38,51]
Bisphenol AP		*In vitro* studies	Evidence of endocrine disrupting activity.[41,94,98]	
Bisphenol B		Multiple *in vitro* studies and one *in vivo* study	Evidence of endocrine disrupting activity.[27,34,37,41,43,46,54,94]	Estrogenic based on uterotrophic assay.[46]
Bisphenol C				
Bisphenol F		Multiple *in vitro;* two *in vivo* studies	Evidence of endocrine disrupting activity.[18,27, 29, 34, 36,41,43,45, 46, 49, 94] Evidence of genotoxicity.[44,45]	Estrogenic based uterotrophic assay.[36,46]
Bisphenol F diglycidyl ether (BFDGE)		Multiple *in vitro* studies	Evidence of endocrine distrupting activity.[18] Evidence of genotoxicity.[45, 58]	
PHBB		Two *in vitro* and one *in vivo* study	Evidence of endocrine disrupting activity.[80]	Weak response in mouse uterine weight study.[80]
MBHA				
BisOPP-A				
1,7-Bis(4-hydroxyphenylthio)-3,5-				
4,4' -Bisphenol S		Multiple *in vitro* and two *in vivo* studies	Evidence of endocrine disrupting activity. [27,34,35,36,37]	Estrogenic based on uterotrophic assay.[36]
2,4'-Bisphenol S				
TGSA				
D-8		*In vitro* study	Evidence of endocrine disrupting activity.[35]	
BPS-MAE				
BPS-MPE				
D-90				
Pergafast 201		*In vitro* study	Evidence of genotoxicity.[97]	
Urea urethane compound				
BTUM				
Tritan™ copolyester	**DMTP**	Primarily unpublished *in vitro* and *in vivo* studies to test for endocrine disruption of Tritan™ and Tritan™ monomers; reported negative by Eastman.[103]		DMTP mutagenic in the micronucleus test in mice.[88]
	CHDM			
	CDBO			
Eco Care™	**PROPRIETARY**			

			Selected Sampling Data Identified in Preliminary Screen		
CASRN	**Chemical name**		**Human biomonitoring**	**Detection in products**	**Environmental samples**
1675-54-3	**Bisphenol A diglycidyl ether (BADGE)**		Detected in saliva of recently treated dental patients.[56]	Detected in dental composites and sealants,[56] canned food [19, 21,22,78,79] and beverages.[21]	Detected in wastewater.[71]
1478-61-1	**Bisphenol AF**		Detected in human female mammary or abdominal adipose tissue extracts.[9]		
1571-75-1	**Bisphenol AP**				
77-40-7	**Bisphenol B**		Detected in urine;[76] blood from endometriotic women.[61]	Detected in canned tomatoes [66] and beverages.[77]	
79-97-0	**Bisphenol C**				
620-92-8	**Bisphenol F**			Detected in some canned beverages.[63]	Detected in municipal landfill leachates[99], surface water[74,75] and sewage water,[74] wastewater[71] and river sediment.[4,74,75]
2095-03-6	**Bisphenol F diglycidyl ether (BFDGE)**			Detected in canned food [21,24,64,78,79,83] and beverages.[21]	Detected in wastewater.[71]
94-18-8	**PHBB**		Detected in urine.[95,96]		
5129-00-0	**MBHA**				
24038-68-4	**BisOPP-A**				
93589-69-6	**1,7-Bis(4-hydroxyphenylthio)-3,5-dioxaheptane**				
80-09-1	**4,4'-Bisphenol S**			Detected in some canned foods.[7]	
5397-34-2	**2,4'-Bisphenol S**				
41481-66-7	**TGSA**				
95235-30-6	**D-8**				Detected in surface water and sediment near paper recycling facility.[6]
97042-18-7	**BPS-MAE**				
63134-33-8	**BPS-MPE**				
191680-83-8	**D-90**				
232938-43-1	**Pergafast 201**				
321860-75-7	**Urea Urethane Compound**				
151882-81-4	**BTUM**				
120-61-6	**Eastman Tritan™**	**DMTP**		Detected in water stored in polyethylene terephthalate (PET) plastic bottles.[85]	
105-08-8		**CHDM**			
3010-96-6		**CDBO**			
--	**Eco Care™**	**PROPRIETARY**			

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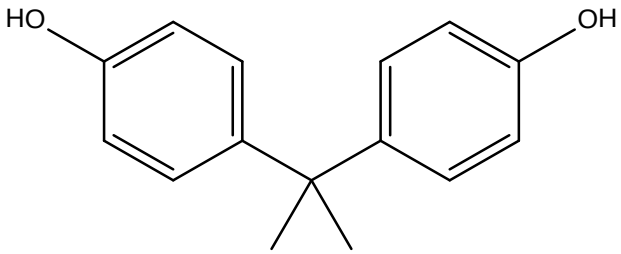
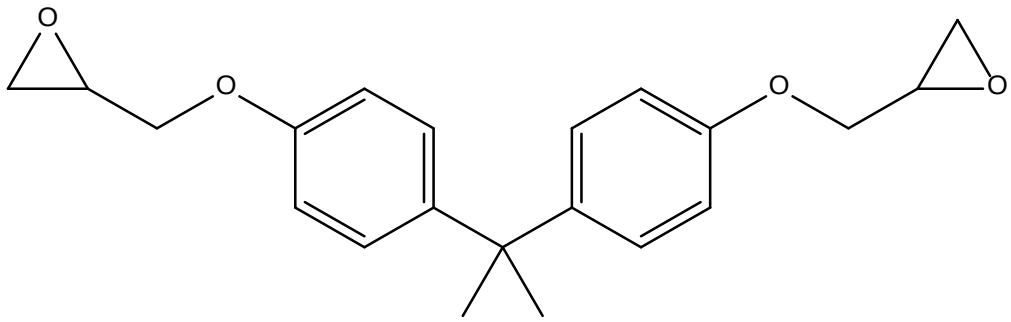
CHEMICAL STRUCTURES

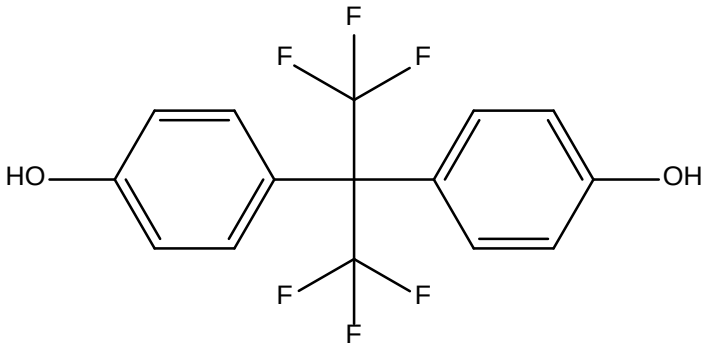
Bisphenol A (*for comparison purposes*)



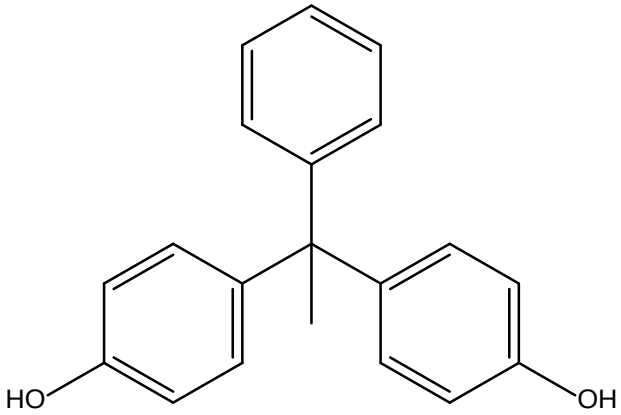
Bisphenol A diglycidyl ether (BADGE):
2,2'-[(1-methylethylidene)bis(4,1-phenyleneoxymethylene)]bis-oxirane



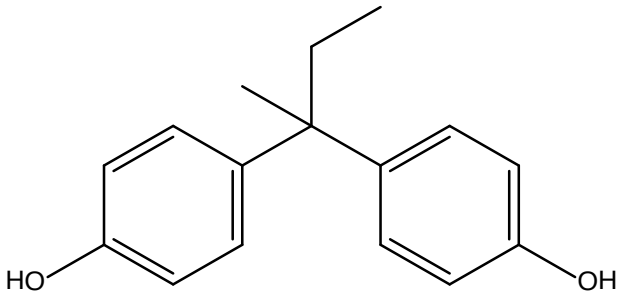
Bisphenol AF: 4,4-hexafluoroisopropylidene)diphenol



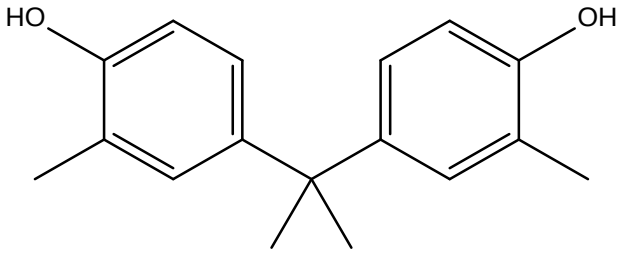
Bisphenol AP: 4,4'-(α-Methylbenzylidene)diphenol



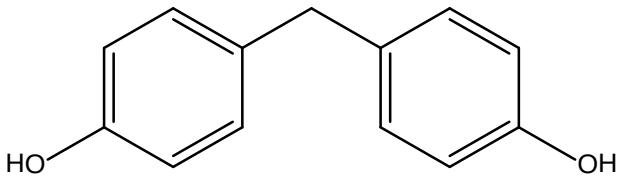
Bisphenol B: 2,2-Bis(4-hydroxyphenyl)butane



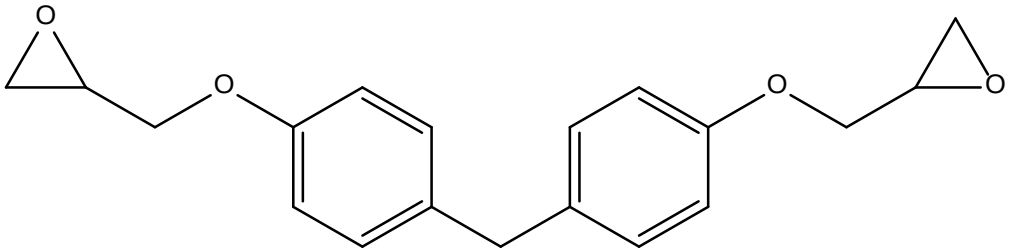
Bisphenol C: 4,4'-(1-methylethylidene)bis(2-methylphenol)



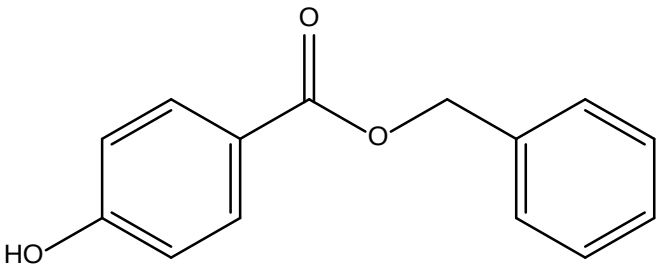
Bisphenol F: 4,4'-di(hydroxydiphenyl)methane)



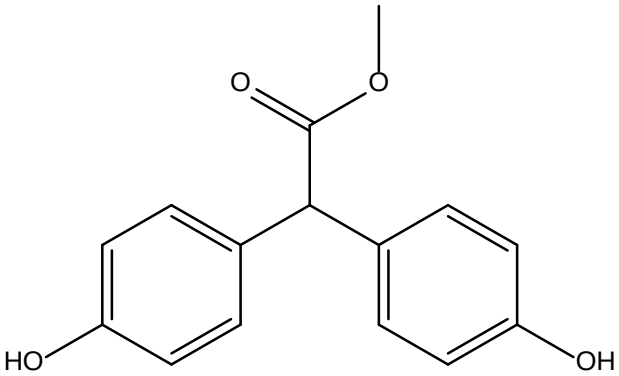
Bisphenol F diglycidyl ether (BFDGE):
2,2'-(Methylenebis(p-phenyleneoxymethylene))bisoxirane



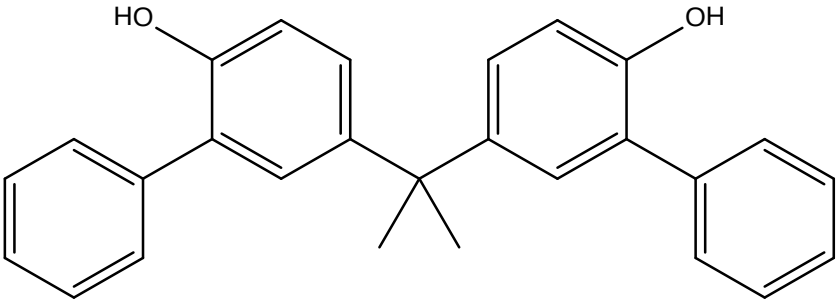
PHBB: Benzyl 4-hydroxybenzoate, benzyl paraben



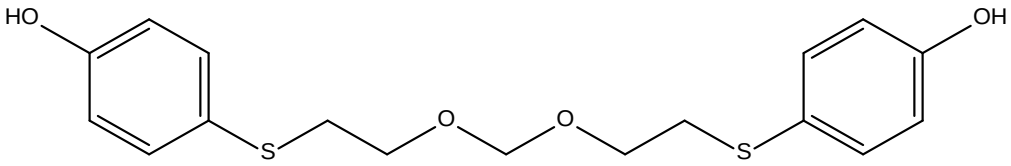
MBHA: Methyl bis(4-hydroxyphenyl)acetate



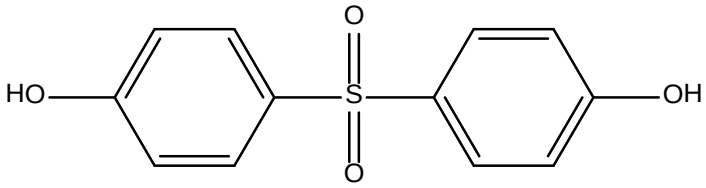
BisOPP-A: 2,2-bis(2-hydroxy-5-biphenylyl)propane



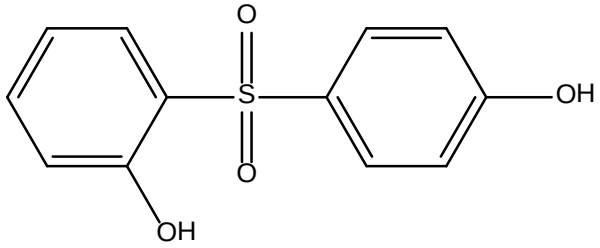
1,7-bis(4-Hydroxyphenylthio)-3,5-dioxaheptane



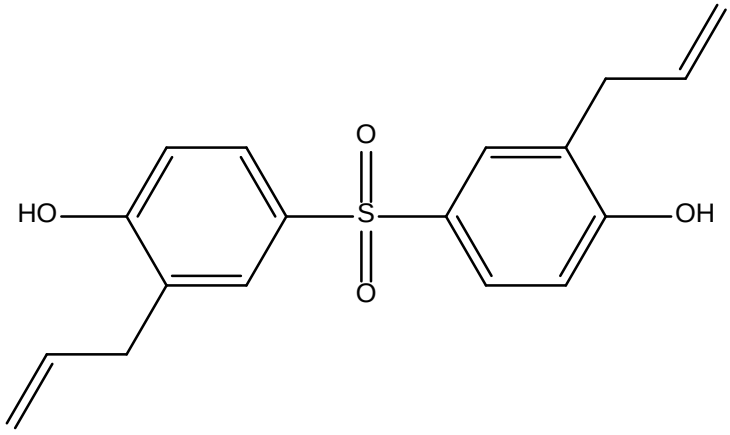
4,4' Bisphenol S: Bis(4-hydroxyphenyl)sulfone



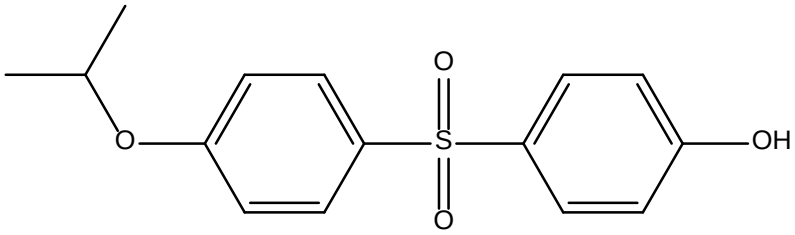
2,4'-Bisphenol S: 2,4-Dihydroxydiphenyl sulfone



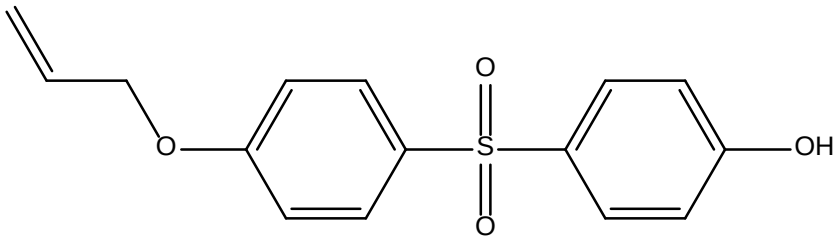
TGSA: Bis-(3-allyl-4- hydroxyphenyl) sulfone



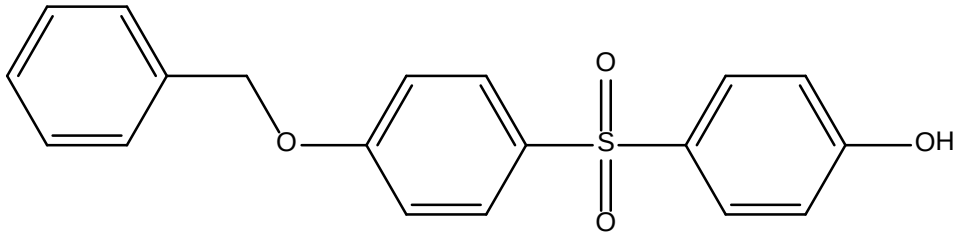
D-8: Phenol, 4-[[4-(1-methylethoxy)phenyl]sulfonyl]-



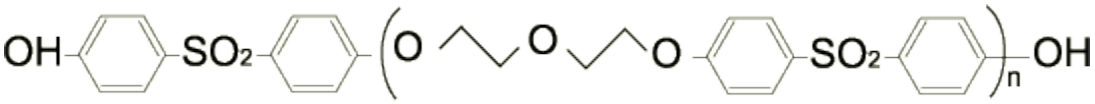
BPS-MAE: Phenol,4-[[4-(2-propen-1-yloxy)phenyl]sulfonyl]-



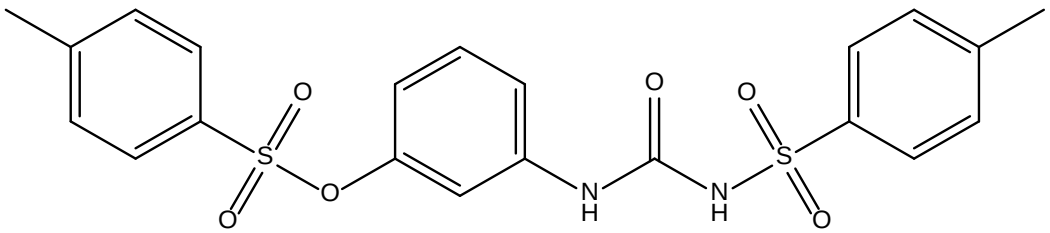
BPS-MPE: 4-[(4-Benzyloxyphenyl)sulfonyl]phenol



D-90: 4-[4'-[(1'-methylethyloxy) phenyl]sulfonyl]phenol

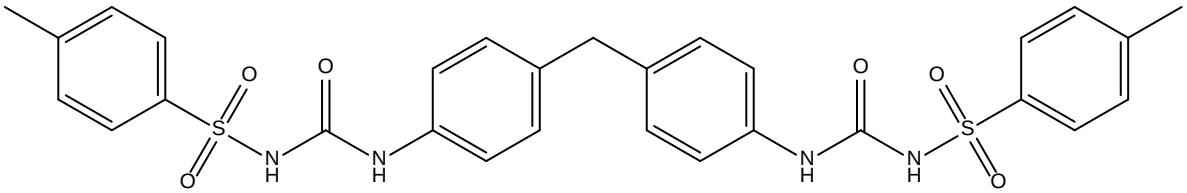


Pergafast 201:
Benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl]amino]carbonyl]-



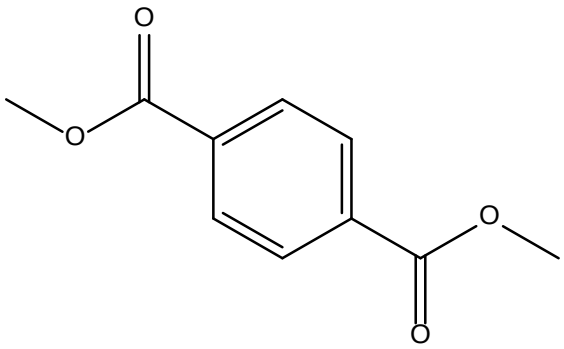
Urea Urethane Compound -- Example structure available here: http://www.epa.gov/dfe/pubs/projects/bpa/functional_bpa_alternatives.pdf

BTUM: Benzenesulfonamide, N,N'-[methylenebis(4,1-phenyleneiminocarbonyl)]bis[4-methyl-

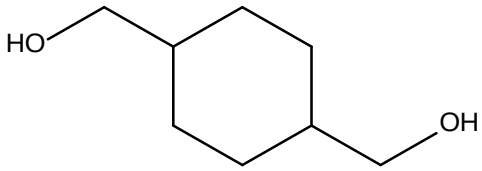


Tritan™ copolyester components

Dimethyl terephthalate (DMTP)



1,4-cyclohexanedimethanol (CHDM)



2,2,4,4-tetramethyl-1,3-cyclobutanediol (CDBO)