United States Environmental Protection Agency

Design for the Environment

Partnership to Evaluate Alternatives to Bisphenol A in Thermal Paper: Results

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The views are those of the authors and do not represent Agency policy or endorsement.

DfE Voluntary Partnership Programs

- **Safer Choice Labeling Program:**

  Label innovative formulations made with lower hazard ingredients with the Safer Choice logo as incentive.

- **Chemical Alternatives Assessment:**

  Characterize environmental and human health impacts of chemicals & alternatives; promote informed substitution.

Alternatives Assessment Program

- Chemical alternatives assessments:
  - Identify and evaluate alternatives.
  - DfE focus is on comparative hazard assessment, taking into consideration exposure and life cycle issues.
  - Involve stakeholders from across the spectrum of interested parties.
- The outcome of an alternatives assessment:
  - Provides the best information on hazard from existing data (e.g., toxicity testing, analogs, and models).
    - Based on EPA New Chemicals Program approaches.
    - Does not rank (benchmark) chemicals.
  - Helps minimize the potential for unintended consequences by reducing the likelihood of moving to alternatives that could pose a concern.
  - Can be integrated into a company's performance and cost analysis.

DfE Criteria for Safer Chemicals

- Human Health Traits:
  - Carcinogenicity
  - Mutagenicity/Genotoxicity
  - Acute mammalian toxicity
  - Respiratory & Skin Sensitization
  - Eye & Skin Irritation/Corrosivity
  - Reproductive and Developmental Toxicity
  - Repeated Dose Toxicity
  - Neurotoxicity
  - Immunotoxicity
  - Endocrine activity
- Environmental Traits
  - Acute aquatic toxicity
  - Chronic aquatic toxicity
  - Persistence
  - Bioaccumulation
  - Framework allows for additional criteria, when relevant and available:
    - Physical hazards
    - Ecosystem impacts

Why did DfE conduct an alternatives assessment?

- EPA action plan (March 2010) for bisphenol A (BPA) under Existing Chemical Management Program identified potential concerns.
- DfE assessed and compared potential hazards associated with BPA and functional alternatives.
- Report will help product manufacturers reduce the likelihood of unintended consequences of using substitutes for BPA.

http://www2.epa.gov/saferchoice/partnership-evaluate-alternatives-bisphenol-thermal-paper

DfE's BPA alternatives assessment partnership

- Partnership stakeholders helped identify alternatives to BPA in thermal paper and associated information.
- DfE evaluated the hazards associated with BPA and the functional alternatives.
  - Prepared human health and environmental profiles for each chemical based on:
    - Review of literature in the public domain,
    - Structure-activity relationship modeling, and
    - Proprietary information shared by stakeholders.

http://www2.epa.gov/saferchoice/partnership-evaluate-alternatives-bisphenol-thermal-paper

Background on BPA

- Thermal printing: BPA functions as a developer, reacts with white/colorless dyes in presence of heat, converting to a dark color.
- Unreacted BPA has been reported in thermal paper.
- Workers in certain occupations (e.g., cashiers and restaurant servers) may be at greater risk of exposure.
- Children may experience greater exposures due to hand-to-mouth behavior and mouthing of inappropriate object.
- Recycling of thermal paper may contribute residual BPA to the supply of recycled paper and may be an additional source of release to the environment.

http://www2.epa.gov/saferchoice/partnership-evaluate-alternatives-bisphenol-thermal-paper

Hazard Criteria

Helps organize toxicological information to compare chemicals based on hazard profile.

Needed for Comparison:

- Data or models to evaluate endpoints.
- Transparent framework for comparison.
- Method to communicate results.

See:
http://www2.epa.gov/saferchoice/alternatives-assessment-criteria-hazard-evaluation

Human Health Effects

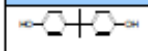
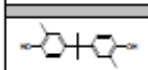
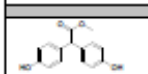
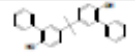
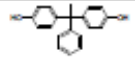
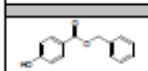
Acute Mammalian Toxicity	**Very High**	**High**	**Moderate**	**Low**	
Oral LD50 (mg/kg)	≤ 50	> 50 - 300	> 300 - 2000	> 2000	
Dermal LD50 (mg/kg)	≤ 200	> 200 - 1000	> 1000 - 2000	> 2000	
Inhalation LC50 (vapor/gas) (mg/L)	≤ 2	> 2 -10	> 10 - 20	> 20	
Inhalation LC50 (dust/mist/fume) (mg/L)	≤ 0.5	> 0.5 - 1.0	> 1.0 - 5	> 5	
Carcinogenicity	**Very High**	**High**	**Moderate**	**Low**	
	Known or presumed human carcinogen (GHS Category 1A and 1B)	Suspected human carcinogen (GHS Category 2)	Limited or marginal evidence of carcinogenicity in animals (and inadequate evidence in humans)	Negative studies or robust mechanism-based SAR	
Mutagenicity/Genotoxicity	**Very High**	**High**	**Moderate**	**Low**	
Germ cell mutagenicity	GHS Category 1A or 1B: Substances known to induce heritable mutations or to be regarded as if they induce heritable mutations in the germ cells of humans	GHS Category 2: Substances which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans	Evidence of mutagenicity supported by positive results in *in vitro* OR *in vivo* somatic cells of humans or animals	Negative for chromosomal aberrations and gene mutations or no structural alerts	
Mutagenicity and Genotoxicity in Somatic Cells		OR Evidence of mutagenicity supported by positive results in *in vitro* AND *in vivo* somatic cells and/or germ cells of humans or animals			
Reproductive Toxicity		**High**	**Moderate**	**Low**	**Very Low**
Oral (mg/kg/day)		< 50	50 - 250	> 250 - 1000	> 1000
Dermal (mg/kg/day)		< 100	100 - 500	> 500 - 2000	> 2000
Inhalation (vapor, gas, mg/L/day)		< 1	1 - 2.5	> 2.5 - 20	> 20
Inhalation (dust/mist/fume, mg/L/day)		< 0.1	0.1 - 0.5	> 0.5 - 5	> 5
Developmental Toxicity		**High**	**Moderate**	**Low**	**Very Low**
Oral (mg/kg/day)		< 50	50 - 250	> 250	> 1000
Dermal (mg/kg/day)		< 100	100 - 500	> 500	> 2000
Inhalation (vapor, gas, mg/L/day)		< 1	1 - 2.5	> 2.5	> 20
Inhalation (dust/mist/fume, mg/L/day)		< 0.1	0.1 - 0.5	> 0.5	> 5
Neurotoxicity (90 day study)		**High**	**Moderate**	**Low**	
Oral (mg/kg-bw/day)		< 10	10 - 100	> 100	
Dermal (mg/kg-bw/day)		< 20	20 - 200	> 200	
Inhalation (vapor/gas) (mg/L/6h/day)		< 0.2	0.2 - 1.0	> 1.0	
Inhalation (dust/mist/fume) (mg/L/6h/day)		< 0.02	0.02 - 0.2	> 0.2	
Repeated Dose Toxicity (90 day study)		**High**	**Moderate**	**Low**	
Oral (mg/kg-bw/day)		< 10	10 - 100	> 100	
Dermal (mg/kg-bw/day)		< 20	20 - 200	> 200	
Inhalation (vapor/gas) (mg/L/6h/day)		< 0.2	0.2 - 1.0	> 1.0	
Inhalation (dust/mist/fume) (mg/L/6h/day)		< 0.02	0.02 - 0.2	> 0.2	

Alternatives Assessment Criteria

Environmental Toxicity and Fate					
Aquatic Toxicity	**Very High**	**High**	**Moderate**	**Low**	
Acute Aquatic Toxicity (LC50 or EC50) (mg/L)	< 1.0	1 - 10	> 10 - 100	> 100	
Chronic Aquatic Toxicity (LOEC) (mg/L)	< 0.1	0.1 - 1	> 1 - 10	> 10	
Environmental Persistence	**Very High**	**High**	**Moderate**	**Low**	**Very Low**
Persistence in water, soil or sediment	Half-life > 180 days or recalcitrant	Half life of 60 – 180 days	Half-life < 60 but ≥ 16 days	Half-life < 16 days OR passes Ready Biodegradability test not including the 10-day window.	Passes Ready Biodegradability test with 10-day window.
Persistence in air (half-life days)	For this endpoint, High/Moderate/Low etc. characterizations will not apply. A qualitative assessment of available data will be prepared.				
Bioaccumulation (BAF / BCF)	**Very High**	**High**	**Moderate**	**Low**	
BCF/BAF	> 5,000	5,000 – 1,000	<1,000 – 100	< 100	
Log BCF/BAF	>3.7	3.7-3	<3-2	<2	

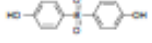
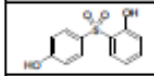
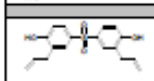
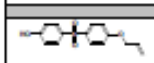
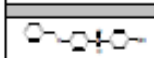
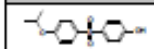
Results: BPA Alternatives, BPA-like

VL = Very Low hazard L = Low hazard M = Moderate hazard H = High hazard VH = Very High hazard — Endpoints in colored text (VL, L, M, H, and VH) were assigned based on empirical data. Endpoints in black italics (*VL, L, M, H,* and *VH*) were assigned using values from estimation software and professional judgment.
§ Based on analogy to experimental data for a structurally similar compound.

Structure	Chemical (for TSCA inventory name and relevant trade names see the individual profiles in Section 4.8)	CASRN	Human Health Effects											Aquatic Toxicity		Environmental Fate	
			Acute Toxicity	Carcinogenicity	Genotoxicity	Reproductive	Developmental	Neurological	Repeated Dose	Skin Sensitization	Respiratory Sensitization	Eye Irritation	Dermal Irritation	Acute	Chronic	Persistence	Bioaccumulation
Bisphenol A and Phenolic Alternatives																	
	Bisphenol A 2,2-bis(p-hydroxyphenyl)propane	80-05-7	L	M	L	M	H	*M*	M	M		M	M	H	H	VL	L
	Bisphenol F Bis(4-hydroxyphenyl)methane	620-92-8	L	*M*	L	*M*§	*H*§	*M*	H	L		VH	*M*§	M	*H*	L	L
	Bisphenol C 2,2'-Bis(4-hydroxy-3-methylphenyl)propane	79-97-0	*L*§	*M*	M	*M*§	*H*§	*M*	*M*§	*M*§		*H*§	*M*§	H	*H*	M	*M*
	MBHA Methyl bis(4-hydroxyphenyl)acetate	5129-00-0	*L*§	*M*	*L*§	*M*§	*H*§	*M*	*M*§	L		*M*§	*M*§	*H*	*H*	*M*	*L*
	BisOPP-A 4,4'-Isopropyllidenebis(2-phenylphenol)	24038-68-4	*L*§	*M*	*L*§	*M*§	*H*§	*M*	*M*§	*M*§		*M*§	*M*§	*L*	*H*	*H*	*M*
	Bisphenol AP 4,4'-(1-Phenylethylidene)bisphenol	1571-75-1	*L*§	*M*	*L*§	*M*§	*H*§	*M*	*M*§	*M*§		*M*§	*M*§	*H*	*H*	*H*	*M*
	Substituted phenolic compound, PROPRIETARY #1		*L*§	*M*	L	*M*§	*H*§	*M*	*M*§	*M*§		*M*§	*M*§	*H*	*M*	*M*	*L*
	Substituted phenolic compound, PROPRIETARY #2		*L*§	*M*	*L*§	*M*§	*H*§	*M*	*M*§	*M*§		*M*§	*M*§	*H*	*H*	*H*	*H*
	PHBB Benzyl 4-hydroxybenzoate	94-18-8	L	*M*	*M*	*L*	*M*	*M*	*L*	*M*§		VL	VL	H	*H*	*L*§	*L*

Results: BPA Alternatives, BPS-like

VL = Very Low hazard L = Low hazard M = Moderate hazard H = High hazard VH = Very High hazard — Endpoints in colored text (VL, L, M, H, and VH) were assigned based on empirical data. Endpoints in black italics (*VL, L, M, H,* and *VH*) were assigned using values from estimation software and professional judgment.
§ Based on analogy to experimental data for a structurally similar compound.

Structure	Chemical (for TSCA inventory name and relevant trade names see the individual profiles in Section 4.8)	CASRN	Human Health Effects											Aquatic Toxicity		Environmental Fate	
			Acute Toxicity	Carcinogenicity	Genotoxicity	Reproductive	Developmental	Neurological	Repeated Dose	Skin Sensitization	Respiratory Sensitization	Eye Irritation	Dermal Irritation	Acute	Chronic	Persistence	Bioaccumulation
Hydroxyphenyl Sulfone Alternatives																	
	Bisphenol S 4-Hydroxyphenyl sulfone	80-09-1	L	*M*	M	M	M	*M*	H	L		L	L	M	M	M	L
	2,4-BPS 2,4'-Bis(hydroxyphenyl)sulfone	5397-34-2	*L*§	*M*	M	*M*§	*M*§	*M*	*H*§	*L*§		*L*§	*L*§	*M*	*H*	*M*	*L*
	TGSA Bis-(3-allyl-4-hydroxyphenyl) sulfone	41481-66-7	L	*M*	L	*M*§	*M*§	*M*	H	M	*M*	L	VL	H	M	*H*	*L*
	BPS-MAE Phenol,4-[[4-(2-propen-1-yloxy)phenyl]sulfonyl]-	97042-18-7	L	*M*§	M	*M*§	*M*§	*M*	L	L	*M*	L	VL	H	H	*H*	*L*
	BPS-MPE 4-Hydroxy-4'-benzyloxydiphenylsulfone	63134-33-8	L	*M*	*M*§	*M*§	*M*§	*M*	*H*§	L		L	L	VH	*H*	*H*	*M*
	D-8 4-Hydroxyphenyl 4-isoprooxyphenylsulfone	95235-30-6	L	*M*	L	*M*§	*M*§	*M*	M	*L*§		*L*§	*L*§	H	*H*	M	M

Results: BPA Alternatives, Other

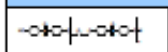
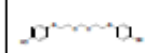
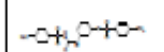
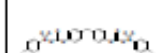
This table only contains information regarding the inherent hazards of the chemicals evaluated. Evaluation of risk considers both the hazard and exposure. The caveats listed in the legend and footnote sections must be taken into account when interpreting the hazard information in the table below.

VL = Very Low hazard L = Low hazard M = Moderate hazard H = High hazard VH = Very High hazard — Endpoints in colored text (VL, L, M, H, and VH) were assigned based on empirical data. Endpoints in black italics (*VL, L, M, H,* and *VH*) were assigned using values from estimation software and professional judgment.

◊ The highest hazard designation of a representative component of the oligomeric mixture with MWs <1,000.

‡ The highest hazard designation of any of the oligomers with MW <1,000

§ Based on analogy to experimental data for a structurally similar compound.

Structure	Chemical (for TSCA inventory name and relevant trade names see the individual profiles in Section 4.8)	CASRN	Human Health Effects											Aquatic Toxicity		Environmental Fate	
			Acute Toxicity	Carcinogenicity	Genotoxicity	Reproductive	Developmental	Neurological	Repeated Dose	Skin Sensitization	Respiratory Sensitization	Eye Irritation	Dermal Irritation	Acute	Chronic	Persistence	Bioaccumulation
Oligomeric and Polymeric Alternatives																	
	D-90 Phenol, 4,4'-sulfonylbis-, polymer with 1,1'-oxybis[2-chloroethane]	191680-83-8	L	*M*	L	*L*	*L*	*M*	L	L		M	VL	*L*‡	*L*‡	*VH*‡	*H*‡
	DD-70 1,7-bis(4-Hydroxyphenylthio)-3,5-dioxaheptane	93589-69-6	*L*	*M*	*L*	*M*	*M*◊	*M*	*M*◊	*M*◊		*H*◊	*M*◊	*H*	*H*	*H*	*L*
	Pergafast 201 N-(p-Toluenesulfonyl)-N'-(3-p-toluenesulfonyloxyphenyl)urea	232938-43-1	L	*M*	L	M	H	*L*	M	L		L	VL	H	H	VH	L
	BTUM 4,4'-bis(*N*-carbamoyl-4-methylbenzenesulfomide)diphenylmethane	151882-81-4	L	*M*	L	*L*	*L*	*L*	M	L		L	L	*H*	*H*	*H*	*L*
	UU Urea Urethane Compound	321860-75-7	L	*M*	L	*L*	*L*	*L*	L	L		L	L	L	*L*◊	VH	L

Example of Hazard Profile

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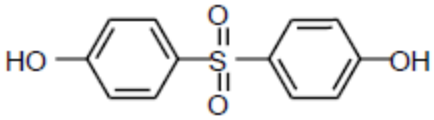
Bisphenol S



	CASRN: 80-09-1
	MW: 250.27
	MF: $C_{12}H_{10}O_4S$
	Physical Forms: Neat: Solid
	Use: Developer for thermal paper
SMILES: O=S(=O)(c1ccc(O)cc1)c2ccc(O)cc2	
Synonyms: Phenol, 4,4'-sulfonylbis-; bis(4-hydroxyphenyl)sulfone; 1,1'-Sulfonylbis(4-hydroxybenzene); 2,4'-Sulfonyldiphenol; 4,4'-Bisphenol S; 4,4'-Dihydroxydiphenyl sulfone; 4,4'-Sulfonylbisphenol; 4,4'-Sulfonyldiphenol; 4-Hydroxyphenyl sulfone; Bis(4-hydroxyphenyl) sulfone; Bis(p-hydroxyphenyl) sulfone; Diphone C; p,p'-Dihydroxydiphenyl sulfone	
Polymeric: No **Oligomers:** Not applicable	
Metabolites, Degradates and Transformation Products: None	
Analog: None **Endpoint(s) using analog values:** Not applicable	**Analog Structure:** Not applicable
Structural Alerts: Phenols, neurotoxicity (U.S. EPA, 2010)	
Risk Phrases: Not classified by Annex VI Regulation (EC) No 1272/2008 (ESIS, 2011).	
Risk Assessments: None identified	

Full report available here:
http://www2.epa.gov/saferchoice/publications-bpa-alternatives-thermal-paper-partnership

Example of Hazard Profile

FINAL REPORT – January 2014

Bisphenol S CASRN 80-09-1				
PROPERTY/ENDPOINT		**DATA**	**REFERENCE**	**DATA QUALITY**
		Not highly flammable EU Method A.10 (Measured)	ECHA, 2011	
Explosivity				No data located.
pH				No data located.
pK_a		8 OECD Method 112 (Measured)	ECHA, 2011	Adequate, guideline study.
HUMAN HEALTH EFFECTS				
Toxicokinetics		**No toxicokinetic data located.**		
Dermal Absorption *in vitro*				No data located.
Absorption, Distribution, Metabolism & Excretion	**Oral, Dermal or Inhaled**			No data located.
Acute Mammalian Toxicity		**LOW: The weight of evidence indicates that the acute oral toxicity of bisphenol S is low. A reported acute oral LD_{50} of 1,600 mg/kg for the mouse could not be verified because no study details were available. Located data suggest a low hazard concern for acute dermal exposure. No data were located regarding the acute inhalation hazard.**		
Acute Lethality	**Oral**	Rat oral LD_{50} >5,000 mg/kg	ECHA, 2011	Adequate guideline study (OECD 401); no deaths at limit dose of 5,000 mg/kg.
		Wistar rat (male) LD_{50} = 2,830 mg/kg	ECHA, 2011	Adequate guideline comparable to OECD guideline 401; the LD_{50} value supports other reported results.
		Rat oral LD_{50} = 4,556 mg/kg	BIOFAX Industrial Bio-Test Laboratories, Inc., 1974, cited in CHEMID	Although no study details were provided in the secondary source, the LD_{50} value supports other reported results.
		Rat (male, female; strain unspecified) LD_{50} = 2,540 mg/kg (females) LD_{50} = >3,200 mg/kg (males)	Eastman Kodak, 1991	Although study details were lacking in the study summary, the LD_{50} value supports other reported results.

Full report available here:
http://www2.epa.gov/saferchoice/publications-bpa-alternatives-thermal-paper-partnership

Trends and Observations

- Most chemicals suggested for inclusion were structurally similar to BPA or BPS.
- Many chemicals had significant data gaps.
- Can be difficult to compare chemicals that exhibit different toxic effects (apples and oranges).
- Hazard trade-offs are common among alternatives.
- Other options to consider include:
  - Redesign of thermal paper,
  - Different type of printer and
  - E-receipts.

Limitations of Existing Hazard Criteria

- Criteria can be used to compare chemical hazards, but
  - Testing is expensive – cost, time, use of animals,
  - Computer models are unavailable for most human health endpoints,
  - Existing test methods are limited aid to chemical design and
  - Data can be difficult to interpret.
- Emerging concerns (e.g., endocrine disruption, wildlife)
  - Most chemicals lack data for these endpoints and
  - Absence of consensus on hazard ranking.
- Strategies to systematically integrate broader range of considerations and trade-offs continue to evolve.

For more information:

DfE and Safer Choice:

http://www2.epa.gov/saferchoicefacebook.com

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