Chemical Information Profile

for

Bisphenol AF
[CAS No. 1478-61-1]

Supporting Nomination for Toxicological Evaluation by the National Toxicology Program

September 2008

National Toxicology Program
National Institute of Environmental Health Sciences
National Institutes of Health
U.S. Department of Health and Human Services
Research Triangle Park, NC
http://ntp.niehs.nih.gov/

Data Availability Checklist for Bisphenol AF [1478-61-1]

Abbreviations: H = human; L = *Lepus* (rabbit); M = mouse; R = rat
Note: No judgement of whether the available data are adequate for evaluation of these endpoints in the context of human health hazard or risk assessment has been made.

ENDPOINT	H	M	R	L	ENDPOINT	H	M	R	L
ADME					**Developmental Toxicity**				
Absorption					Developmental abnormalities				
Distribution					Embryonic/fetal effects				
Metabolism					Newborn effects				
Excretion					**Carcinogenicity**				
Acute Toxicity (up to 1 week)					Dermal				
Dermal					Inhalation				
Inhalation					Oral				
Injection			**X**		**Anticarcinogenicity**				
Ocular					Anticarcinogenic effects		**X**		
Oral			**X**		**Genotoxicity**				
Subchronic Toxicity (1 to <26 weeks)					Cytogenetic effects		**X**		
Dermal					Microbial gene mutation				
Inhalation					Gene mutation *in vitro*				
Injection					Gene mutation *in vivo*				
Oral			**X**		Germ cell effects				
Chronic Toxicity (≥26 weeks)					**Neurotoxicity**				
Dermal					Behavioral activity				
Inhalation					Motor activity			**X**	
Injection					**Immunotoxicity**				
Oral					Immunotoxic effects				
Synergism/Antagonism					**Cardiovascular Toxicity**				
Synergistic effects					Cardiovascular effects				
Antagonistic effects					**Mechanistic Data**				
Cytotoxicity					Target Organs/Tissues				
Cytotoxic effects					Endocrine modulation	**X**	**X**	**X**	
Reproductive Toxicity					Effect on enzymes	**X**			
Fertility effects					Modes of action				
Maternal effects			**X**		Effect on metabolic pathways				
Paternal effects					**Structure-Activity Relationships**	**X**	**X**	**X**	**X**

*data for Syrian hamster embryo and Chinese hamster V79 cells available

The above table shows the endpoints (listed in columns 1 and 6) that are represented in this profile according to species (human, rat, mouse, and rabbit; columns 2-5 and 7-10). An "**X**" entered in a given row and column indicates that data for the corresponding endpoint and species are discussed in the profile. Blank cells indicate that data for the corresponding endpoint and species were not found in the literature.

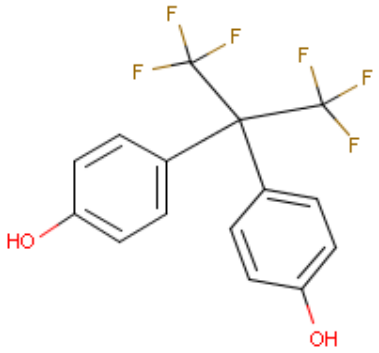
Bisphenol AF Nomination Summary

Chemical Name: Bisphenol AF

CAS RN: 1478-61-1

Formula: $C_{15}H_{10}F_6O_2$

Molecular Wt.: 336.23



Basis for Nomination: Bisphenol AF was nominated by the National Institute of Environmental Health Sciences for comprehensive toxicological characterization based on its moderate production and use as a crosslinking agent for certain fluoroelastomers and as a monomer for polyimides, polyamides, polyesters, polycarbonate copolymers and other specialty polymers, as well as the lack of adequate toxicity data and structural similarity to the synthetic estrogen bisphenol A. The NIOSH National Occupational Exposure Survey (1981-1983) estimated that 4388 employees (1460 females) were potentially exposed to bisphenol AF; this number represented eight occupations in two industries. There also is concern of potential exposure of the general population to bisphenol AF from its use as a monomer of polycarbonate and other polymers and resins, and the use of fluoroelastomer gaskets and hoses in food processing equipment; however, information on specific use and potential exposure were not available. The rat oral LD_{50} was 3400 mg/kg; unspecified changes in the gastrointestinal tract, liver, kidney, ureter, and bladder were observed. In subacute studies in rats, no clinical abnormalities were observed; however, uterine blotted weights were significantly increased. In the Hershberger assay, bisphenol AF significantly increased relative glans penis weight and decreased body weight gain, bulbocavernosus/levator ani muscle weight, and spontaneous locomotion. It was cytotoxic to Syrian hamster embryo (SHE) cells and Chinese hamster V79 cells. In SHE cells, it did not induce gene mutation or chromosomal aberration but did induce aneuploidy in the near-diploid range. Bisphenol AF also induced metaphase arrest and micronuclei in V79 cells. Its estrogenic and anti-androgenic activity *in vitro* has been demonstrated in several reporter gene assays.

A. Chemical Information

Molecular Identification

Chemical Name: Bisphenol AF
CAS RN: 1478-61-1
Synonyms: 1,1,1,3,3,3-Hexafluoro-2,2-bis(4-hydroxyphenyl)propane; 2,2-Bis(4′-hydroxyphenyl)hexafluoropropane; 2,2-Bis(4-hydroxyphenyl)-1,1,1,3,3,3-hexafluoropropane; 2,2-Bis(4-hydroxyphenyl)hexafluoropropane; 2,2-Bis(4-hydroxyphenyl)perfluoropropane; 2,2-Bis(*p*-hydroxyphenyl)hexafluoropropane; 4,4′-[2,2,2-Trifluoro-1-(trifluoromethyl)ethylidene]bisphenol; 4,4′-(Hexafluoroisopropylidene)diphenol; 4,4′-[Trifluoro-1-(trifluoromethyl)ethylidene]diphenol; Biphenol AF; BIS-AF; EINECS 216-036-7; Hexafluoroacetone bisphenol A; Hexafluorobisphenol A; Hexafluorodiphenylolpropane; Hexafluoroisopropylidenebis(4-hydroxybenzene); NSC 152522; Phenol, 4,4′-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]bis- (9CI); Phenol, 4,4′-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]di- (6CI, 7CI); Phenol, 4,4′-[trifluoro-1-(trifluoromethyl)ethylidene]di- (8CI)
Trade Names: Bisphenol AF; Curative 30
Hill Formula: C15H10F6O2
Line Formula: HOC_6H_5-$C(CF_3)_2$-C_6H_5OH
Smiles Notation: C1=CC(=CC=C1C(C2=CC=C(C=C2)O)(C(F)(F)F)C(F)(F)F)O
PubChem CID: 73864 (PubChem, undated-a)
InChI: 1/C15H10F6O2/c16-14(17,18)13(15(19,20)21,9-1-5-11(22)6-2-9)10-3-7-12(23)8-4-10/h1-8,22-23H
Molecular Weight: 336.23
Purity of Commercial Products: up to >99% (ChemExper, 2006; DuPont, 2006; Halocarbon, 2008)
Impurities in Commercial Products: *o,p*-monoadducts, *o,p*-bisphenol AF, bis-hexafluoroacetone, trimer, phenol, hydrofluoric acid, and water [technical grade] (DuPont, 2006); fluoride, color (APHA), methanol insolubles (at 105 ºC), phenol, and water (Halocarbon, 2008)
Mammalian Metabolites: Not available
Biodegradation Products: Not available
Environmental Transformation: Not available

Physical-Chemical Properties

Physical State: white, light gray, or tan coarse powder (DuPont, 2006; Halocarbon, 2007, 2008)
Specific Gravity or Density Value: 1.447±0.06 g/cm^3 @ 760 Torr [calculated] (Registry, 2006)
Boiling Point: 400 ºC (Halocarbon, 2007)
Vapor Pressure: <0.1 mm Hg (Halocarbon, 2007)
Solubility: <2 wt. % at 100 ºC (DuPont, 2006)
Log P = Log K_{ow}: 2.818±0.771 @ 25 ºC [calculated] (Registry, 2006); 5.5 [calculated] (Pubchem, undated-a)
Bioconcentration Factor(s) (species): 81.57@ pH 1-4 and 25 ºC, 81.54 @ pH 5 and 25 ºC, 81.26 @ pH 6 and 25 ºC, 78.46 @ pH 7 and 25 ºC, 54.66 @ pH 8 and 25 ºC, 5.29 @ pH 9 and 25 ºC, 1.0 @ pH 10 and 25 ºC [calculated] (Registry, 2006); 560 [estimated using the PBT Profiler] (U.S. EPA, 2006)

B. Exposure Potential

U.S. Annual Production

1986: 10,000 – 500,000 pounds
1990: 10,000 – 500,000 pounds
1994: 10,000 – 500,000 pounds
1998: 10,000 – 500,000 pounds
2002: 10,000 – 500,000 pounds

(U.S. EPA, 2008 [U.S. EPA IUR database; search by CAS RN = 1478-61-1])

Worldwide Annual Production

Not available

Production Processes

Produced from hexafluoropropanone-2 and phenol as the starting materials (Touzuka and Ohsaka, 1977 pat.). In general, fluorinated bisphenols can be made from the reaction of a phenol and a fluorinated precursor consisting of a fluorinated aldehyde or a fluorinated ketone in the presence of an organic sulfonic acid catalyst (Mark and Hedges, 1982 pat.).

Uses

Curing agent or crosslinker (vulcanizing agent) for fluoroelastomers and heat-resistant adhesives; precipitation agent for polymer-preparation emulsions; monomer for polyimides, polyamides, polyesters, polycarbonates, and other specialty polymers (e.g., epoxy resins and base-resistant primers) (DuPont, 2006; Halocarbon, 2008).

Occupational Exposure

For eight occupations in two industries (manufacture of rubber and plastics products [3599 employees] and production of electrical/electronic equipment [789 employees]), the NIOSH National Occupational Exposure Survey (1981 to 1983) estimated 4388 employees (1460 females) were potentially exposed to bisphenol AF. Molding and casting machine operators in the plastic products industry (2861, almost half of whom were women) were estimated to have the greatest potential exposure (NIOSH, undated). Bisphenol AF is the preferred crosslinking agent for fluoroelastomers. Precured fluoroelastomer compositions containing 0.5-4% by weight bisphenol AF undergo final curing during molding at elevated temperatures (DuPont, 2006).

General Population Exposure

Exposure may occur from use of bisphenol AF as a monomer of polycarbonate, which is used in various plastic products and other resins including epoxy resins. No detailed information was identified regarding the use of bisphenol AF in the manufacture of specific consumer products. Bisphenol AF-produced polycarbonate copolymers with improved hydrolytic stability and caustic resistance can be used to coat dishwasher interiors (DuPont, 2006). Other polycarbonate monomers such as bisphenol A, a structural analog of bisphenol AF [see Structure-Activity Relationships in Section D], leached from epoxy resins lining food cans and from some dental materials (CERHR, 2008). Specified crosslinking agents are approved in 21 CFR 177.2600 (indirect food additives: polymers, rubber articles intended for repeated use) for production of fluoroelastomers. Bisphenol AF-containing fluoroelastomers (crosslinked with bisphenol AF or its benzyltriphenylphosphonium salt) were approved after petition under 21 CFR 170.39 (U.S. FDA, 2008a, b; U.S. FDA, 2007). These fluoroelastomers can contain up to 2% by weight bisphenol AF or 1.9% of its benzyltriphenylphosphonium salt (U.S. FDA, 2007).

Foods and Beverages, Cosmetics, etc.: Bisphenol AF-crosslinked FDA-compliant fluoroelastomers find use in seals (such as O-rings and gaskets) for equipment used in the food and pharmaceutical processing industries (DuPont, 2007 press release). These fluoroelastomers likely have limited use in food-transfer tubing (Cole-Parmer Instrument Co., 2002) and possible use as processing aids for polyolefins used for food and drug packaging (film wraps and containers) or as a fluoroelastomer component of such products (e.g., Duff et al., 1994 pat.; Miharu et al., 1999 pat.; Masuda et al., 2008 patent [CAPLUS abstract 2008:468403]). Very limited evidence was found for bisphenol AF use in dental materials. One patent was found on a bisphenol AF ether di(meth)acrylate monomer for use as a UV-light-curable dental material suitable for fillings (Moszner et al., 2007 pat.).

Ambient Environment

Air Limit: Not available

Water Limit(s): Not available

Soil Limit: Not available

Environmental Exposure in the United States: Not available

Levels in Tissues, Body Fluids, and Excreta: Bisphenol AF (elution time: 16.41 min; quantity not given) was found in the β fraction (chemicals with elution times >13 min) of human female mammary or abdominal adipose tissue extracts (Fernández et al., 2004 [PMID:15024544]).

Environmental Occurrence

Natural Occurrence: Not naturally occurring

U.S. Environmental Releases: Not available

Concentrations in Environmental Media: Not available

C. Regulatory Information

U.S. Regulations

Exposure Limits (Standards and Criteria)

ACGIH TLV: Not available

NIOSH REL: Not available

OSHA PEL: Not available

U.S. EPA

The Interagency Testing Committee in its 51st report rescinded its request to the U.S. EPA to add bisphenol AF to the TSCA Section 8(a) PAIR rule (68 FR 8975, February 26, 2003 [U.S. EPA, 2003]).

U.S. FDA

Certain fluoroelastomers crosslinked with bisphenol AF (2%) or its benzyltriphenylphosphonium salt (1.9%) were approved for use as vulcanization agents in the manufacture of vinyl fluoride-hexafluoropropylene and vinyl fluoride-hexafluoropropylenetetrafluoroethylene copolymers after petition under 21 CFR 170.39 (U.S. FDA, 2007).

European Union Scientific Committee Regulations

Listed as a Low Production Volume Chemical (European Commission, undated)

Canadian Domestic Substances List (DSL) and Non Domestic Substances List (NDSL)

Included on the Canadian Domestic Substances List (Environment Canada, 2008)

D. Toxicological Information

General Toxicity

Human Studies: Bisphenol AF is a skin and eye irritant (DuPont, 2006).

Animal Studies: Not available

Chemical Disposition, Metabolism, and Toxicokinetics

Not available

Acute Exposures

LC_{50}/LD_{50} Values: oral LD_{50} = 3400 mg/kg [rat] (ChemIDplus, undated-a; Halocarbon, 2007)

Route:	oral
Species:	rat; strain and sex not provided
Dose/Duration:	up to 3400 mg/kg (LD_{50})
Observation Time:	not provided
Effects:	unspecified changes in the gastrointestinal tract, liver, kidney, ureter, and bladder
Source(s):	ChemIDplus (undated-a); Halocarbon (2007)

Route:	s.c. injection (*uterotrophic assay*)
Species:	rat, Crj:CD (SD), males and females
Dose/Duration:	8, 40, or 100 mg/kg/day for 3 consecutive days
Observation Time:	not provided

Effects:	no clinical abnormalities; normally increased body weights; water uterine content grossly detected at 100 mg/kg; significantly increased uterine blotted weight at all doses; significantly decreased uterine weight at 40 mg/kg + ethynyl estradiol
Source(s):	Yamasaki et al. (2003a [PMID:12504345], 2003b [PMID:12765246])

Subchronic Exposures

Route:	oral via stomach tube (*Hershberger assay*)
Species:	rat, Brl Han:WIST Jcl (GALAS), males
Dose/Duration:	50, 200, or 600 (reduced to 400 due to toxicity) mg/kg/day for 10 consecutive days beginning on postnatal day 56
Observation Time:	not provided
Effects:	decreased body weight gain and decreased spontaneous locomotion at 200 and 600 mg/kg; decreased bulbocavernosus/levator ani muscle weights at 200 mg/kg; increased relative glans penis weight at 600 mg/kg and at 50 mg/kg and 600 mg/kg in the presence of testosterone propionate (TP); significantly increased relative seminal vesicle weight at 50 mg/kg and 600 mg/kg + TP; significantly increased relative Cowper's gland at 600 mg/kg + TP
Source(s):	Yamasaki et al. (2003a [PMID:12504345])

Chronic Exposures

Not available

Synergistic/Antagonistic Effects

Not available

Cytotoxicity

Syrian hamster embryo (SHE) cells:

- Dose-dependent decrease in colony-forming efficiencies (Kanai et al., 2001 [PMID:11391616])
- Inhibition of cellular growth (Tsutsui et al., 2000 [PMID:10738239])

Chinese hamster V79 cells:

- Reduction of cell growth to 22.5% (Pfeiffer et al., 1997 [PMID:9150749])
- Inhibition of microtubule assembly (EC_{50} = ~30 µM) (Pfeiffer et al., 1997 [PMID:9150749])
- Significant reduction in cytoplasmic microtubule complex and disruption of mitotic spindle; both effects were reversible (Pfeiffer et al., 1997 [PMID:9150749])

Reproductive and Developmental Toxicity

Not available

Carcinogenicity

Not available

Anticarcinogenicity

Human Studies: Not available

Animal Studies: Inactive in the NCI *in vivo* anticancer drug screen for tumor model L1210 leukemia in BDF1 mice (PubChem, undated-b)

Genetic Toxicity

Microbial Gene Mutation: Not available

Human Studies (*in vitro* and *in vivo*): Not available

Animal Studies (*in vitro* and *in vivo*)

Gene Mutation: Did not induce gene mutations at the Na^+/K^+ ATPase or *hprt* locus in SHE cells (Tsutsui et al., 2000 [PMID:10738239])

Cell Transformation: Dose-dependent induction of morphological transformation in SHE cells (Kanai et al., 2001 [PMID:11391616]; Tsutsui et al., 2000 [PMID:10738239])

Cytogenetic Effects: Did not induce chromosomal aberrations in SHE cells but induced aneuploidy in the near-diploid range (Tsutsui et al., 2000 [PMID:10738239]); induced metaphase arrest, which

was reversible, and micronuclei (aneugenic effect) in V79 cells (Pfeiffer et al., 1997 [PMID:9150749])

Germ Cell Effects: Not available

Neurotoxicity

Not available

Immunotoxicity

Not available

E. Mechanistic Data

Target Organs/Tissues

Not available

Endocrine Modulation

Human

estrogenic activity

- MCF-7 breast cancer cells:
  - induced cell proliferation; EC_{50} was 0.05 µM (compared to $8.6x10^{-6}$ M for 17β-estradiol) (Hashimoto et al., 2001 [PMID:11566573]; Kitamura et al., 2005 [PMID:15635150]; Rivas et al., 2002 [PMID:12429138]); co-treatment with ICI 182,780 (ICI) blocked cell proliferation (Kanai et al., 2001 [PMID:11391616])
  - significantly increased progesterone receptor (PgR) levels and secretion into culture medium (similar to that for natural estrogen) and PgR mRNA; blocked by co-treatment with ICI (Kanai et al., 2001 [PMID:11391616]; Rivas et al., 2002 [PMID:12429138])
  - induced higher luciferase activity than 17β-estradiol (E2) (Rivas et al., 2002 [PMID:12429138]) but did not inhibit the estrogenic activity of E2 (Kitamura et al., 2005 [PMID:15635150])
  - showed full agonist response in all above assays (Rivas et al., 2002 [PMID:12429138])
- E-Screen assay (MCF-7 cells), 82% of the β fraction (which contained bisphenol AF) of adipose tissue extracts was positive for estrogenicity (mean = 696.6 pM Eeq/g lipid); total xenobiotic estrogenic burden was 13.9, 103.6, and 549.4 pM Eeq/g lipid for the 25, 50, the 75th percentiles, respectively (Fernández et al., 2004 [PMID:15024544]).
- Reporter gene assay (transfected hERα/HeLa cells), bisphenol AF was estrogen receptor (ER)-α agonist positive and ER-α antagonist negative (Yamasaki et al., 2003b [PMID:12765246]).
- Fluorescence polarization system, bisphenol AF increased displacement of the fluorescent ligand from purified recombinant human ER (Hashimoto et al., 2001 [PMID:11566573]).
- Recombinant human ER-α competitive binding assay, relative binding affinity of bisphenol AF was -0.11 (Akahori et al., 2008 [PMID:17904329]).
- Human estrogen-related receptor (ERR)-γ competitive binding affinity, binding affinity of bisphenol AF was 358 ± 30.5 nM. Additionally, inhibited the inverse agonist activity of 4-hydroxytamoxifen (4-OHT) in a luciferase reporter gene assay (Okada et al., 2008).

Animal

estrogenic activity

- Rat uterine cytosolic ER-competitive binding assay, relative binding affinity of bisphenol AF to ER was 1 (Perez et al., 1998 [PMID:9449681]).
- Male carp hepatocytes, vitellogenin production was induced (at 100 µM induction was 8% of maximum induction by E2). Induction of vitellogenin production by E2 was inhibited by bisphenol AF; IC_{50} = 68.4 µM (Letcher et al., 2005 [PMID:15907334]).
- Uterotrophic assay and Hershberger assay, bisphenol AF was ER-α agonist positive and ER-α antagonist negative [see Acute Exposure in Section C] (Yamasaki et al., 2003a [PMID:12504345], 2003b [PMID:12765246]). The lowest effective dose to induce estrogenic

and anti-estrogenic effects in the immature rat Uterotrophic assay were 1.08 ad 1.08 µmole/kg/day, respectively (Akahori et al., 2008 [PMID:17904329]).

- Rat uterine cytosolic ER-competitive binding assay, bisphenol AF produced nearly complete competitive binding curve (IC_{50} = 1.2 µM), displacing >75% of radiolabel E2 (Laws et al., 2006 [PMID:16940337]).

androgenic activity: In mouse NIH3T3 fibroblasts transfected with an androgen receptor responsive luciferase reporter gene, bisphenol AF was not androgenic but did inhibit the androgenic activity of dihydrotestosterone (DHT) in non-transfected cells; IC_{50} = 1.3 µM (EC_{50} for DHT = $1.1x10^{-5}$ M) (Kitamura et al., 2005 [PMID:15635150]).

thyroid hormonal activity: In the rat pituitary cell line GH3, bisphenol AF did not increase the release of growth hormone (Kitamura et al., 2005 [PMID:15635150]).

Microbes

- Yeast two-hybrid system using strain Y190, β-galactosidase activity increased without S9; estrogenicity was enhanced with S9 (Hashimoto et al., 2001 [PMID:11566573]).
- Receptor binding assay (recombinant human ER ligand binding domain fused with glutathione S-transferase expressed in *Escherichia coli*), bisphenol AF was positive (Yamasaki et al., 2003b [PMID:12765246]).

Effect on Enzymes

Human: Did not inhibit aromatase (CYP19) activity in human H295R adrenocortical carcinoma cells [up to 100 µM] (Letcher et al., 2005 [PMID:15907334])

Animal: Did not induce ethoxyresorufin-*O*-deethylase activity (CYP1A enzyme induction) in carp hepatocytes [up to 100 µM] (Letcher et al., 2005 [PMID:15907334])

Modes of Action

Aneugenic potential via interaction with tubulin (Pfeiffer et al., 1997 [PMID:9150749])

Human: Not available

Animal: Not available

Effect on Metabolic Pathways: Not available

Structure-Activity Relationships (SAR)

Results from studies of SAR among bisphenol compounds have been reported by several investigators (Chen et al., 2002 [PMID:11847978]; Kitamura et al., 2005 [PMID:15635150]; Kuruto-Niwa et al. 2002; Perez et al., 1998 [PMID:9449681]). The results of the functional estrogen studies suggest the following:

- Hydrophobic substitution on the bridging carbon (between the phenols) increases estrogenic activity.
- Decreased polarity of the compound potentially enhances estrogenic activity.
- Modified linkages between the phenol groups (e.g., substitution of the methylene with a ketone) have positive and negative impacts on activity.
- At least one hydroxyl group is needed for moderate activity.
- While chlorination on the phenol rings is associated with increased estrogenic activity, increased bromination is associated with decreased estrogenic activity.

SAR analyses in a single functional androgen study (Kitamura et al., 2005 [PMID:15635150]) suggest the following:

- At least one para hydroxyl group is needed for antagonistic activity.
- 3,5-Substituents influence anti-androgenic activity.

The data reported for bisphenol A and bisphenol F (two bisphenol AF analogs) are outlined below followed by a table that summarizes the endocrine activity for 39 Bisphenol A analogs and derivatives, including bisphenol AF. The table shows whether a chemical was an antagonist, agonist, or showed no effect for estrogen, androgen, thyroid, and vitellogenin activity. Receptor binding capacity is also shown when reported.

Isomers: Not available

Congeners

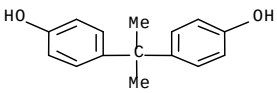
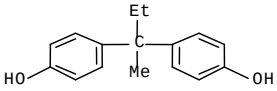
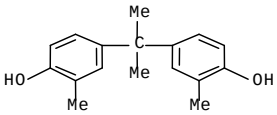
Bisphenol A (BPA) [CAS No. 80-05-7] (PubChem CID:6623 [PubChem, undated-a]):

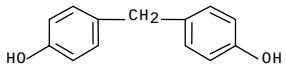
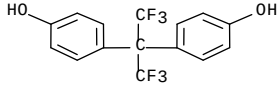
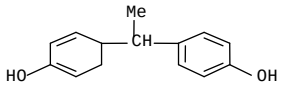
- Potential exposure occurs from inhalation and dermal contact during manufacture, use, transport, or packaging or use of epoxy powder paint; one clinical case reported photoallergic contact dermatitis in eight workers (HSDB, 2008).
- LD_{50} values: mouse - 150 mg/kg i.p., 2400-5280 mg/kg oral; rat - 3250-4100 mg/kg oral; rabbit - 2230 mg/kg oral, 3000 mL/kg skin; and guinea pig - 4000 mg/kg oral (ChemIDplus, undated-b; HSDB, 2008).
- Maternally toxic concentrations given via gavage caused fetal toxicity in mice but not rats; changes in fetal morphologic development were not seen in either species. In a multi-generation study with mice, first and second generations exhibited reductions in the number of litters per pair, live pups per litter, and live pup weights (HSDB, 2008).
- Subchronic inhalation and oral studies with rats generally produced decreases in body weight; appearance, general behavior, survival, male and female fertility, female estrous cycle, hematology, etc. were not consistently affected (HSDB, 2008).
- Not carcinogenic in female and male $B6C3F_1$ mice and F344 rats (HSDB, 2008).
- Not mutagenic in *Salmonella typhimurium* strains TA97A, TA98, TA100, TA102, TA1535, TA1537 and *Escherichia coli* strain WP2UVRA with and without S9, *Saccharomyces cerevisiae*, Chinese hamster V79 cells, and epithelial cells (CCRIS, 2006; HSDB, 2008).
- Can bind DNA after metabolic activation (Kitamura et al., 2005 [PMID:15635150]).
- In SHE cells, inhibited cellular growth and induced morphological transformation. It did not induce gene mutations in the Na^+/K^+ ATPase or *hprt* locus or chromosomal aberrations but did induce aneuoploidy in the near-diploid range (Tsutsui et al., 2000 [PMID:10738239]).
- In V79 cells, inhibited microtubule assembly, disrupted the cytoplasmic microtubule complex and mitotic spindle, caused cell death, produced metaphase arrest, and induced micronuclei (Pfeiffer et al., 1997 [PMID:9150749]).
- Estrogenic in several assays (e.g., MCF-7 cells, yeast two-hybrid system, and fluorescence polarization system) and an endocrine disruptor *in vivo* (e.g., Hashimoto et al., 2001 [PMID:11566573] and Kitamura et al., 2005 [PMID:15635150]). Additionally, has high affinity for the ERRγ receptor and blocks inverse agonist effects of 4-OHT (Okada et al., 2008).
- Not androgenic in NIH3T3 cells transfected with AR responsive luciferase receptor but anti-androgenic (inhibited the activity of DHT [IC_{50}=4.3 μM; EC_{50} for DHT=$1.1x10^{-5}$ M]) (Kitamura et al., 2005 [PMID:15635150]).
- No thyroid hormonal activity in GH3 cells (Kitamura et al., 2005 [PMID:15635150]).

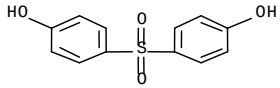
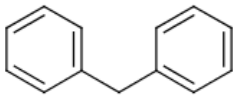
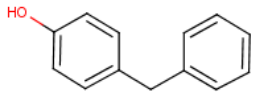
Bisphenol F (BPF) [CAS No. 2467-02-9] (PubChem CID:75575 [PubChem, undated-a]): BPF showed estrogenic activity in MCF-7 cells, the yeast two-hybrid system, and the fluorescence polarization system (Hashimoto et al., 2001 [PMID:11566573]). Shown to have affinity for the ERRγ receptor (Okada et al., 2008). In SHE cells, it inhibited cellular growth but did not induce morphological transformation, gene mutations, or chromosomal aberrations (Tsutsui et al., 2000 [PMID:10738239]). In V79 cells, BPF had no effect on cell-free microtubule assembly, cytoplasmic microtubule complex or mitotic spindle, nor on cell growth, mitotic arrest, or the induction of micronuclei (Pfeiffer et al., 1997 [PMID:9150749]).

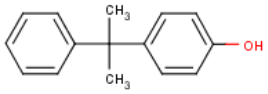
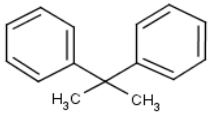
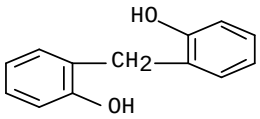
Reactive Moieties: Not available

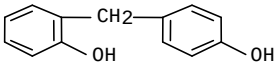
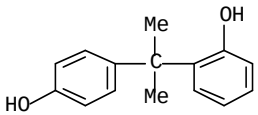
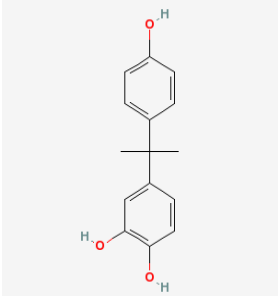
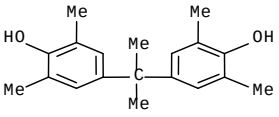
OVERVIEW OF ENDOCRINE ACTIVITY OF THE 39 BISPHENOL A ANALOGS AND DERIVATIVES

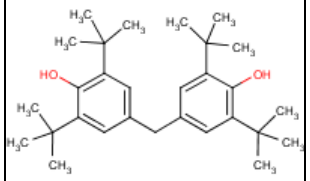
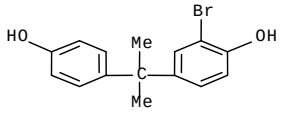
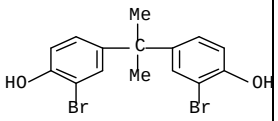
Chemical (CA Index) Name and Synonyms	CASRN	Molecular Formula	PubChem CID	Structure	TSCA	IUR Production Volume	PBT Profiler Values: Half-lives (days)	PBT Profiler Values: BFC	Estrogen	Androgen	Thyroid	Vitellogenin
Bisphenol A, B, C, F, AF, E, and S												
Phenol, 4,4'-(1-methylethylidene)bis- (CA INDEX NAME) OTHER CA INDEX NAMES: Phenol, 4,4'-isopropylidenedi- (8CI) OTHER NAMES: **Bisphenol A** ABBREVIATION USED IN DATA TABLES: BPA	80-05-7	$C_{15}H_{16}O_2$	6623		X	1986: >500M-1B 1990: >1B 1994: >1B 1998: >1B 2002: >1B	Water: 38 Soil: 75 Sed*: 340 Air: 0.2	72	Agonist in all studies evaluated (36/36) Bound to estrogen receptors[a]	Antagonist or no activity in studies evaluated (3/3)	Antagonist or no activity in studies evaluated (7/7) Did not bind	Agonist (1/1)
Phenol, 4,4'-(1-methylpropylidene)bis- (CA INDEX NAME) OTHER CA INDEX NAMES: Phenol, 4,4'-sec-butylidenedi- (6CI, 7CI, 8CI) OTHER NAMES: **Bisphenol B** ABBREVIATION USED IN DATA TABLES: BPB	77-40-7	$C_{16}H_{18}O_2$	66166			NO REPORTS	Water: 38 Soil: 75 Sed: 340 Air: 0.2	300	Agonist in all studies evaluated (13/13) Bound to estrogen receptors[a]	Antagonist or no activity in studies evaluated (2/2)	Antagonist or no effect in studies evaluated (1/1) No binding data	No data
Phenol, 4,4'-(1-methylethylidene)bis[2-methyl- (CA INDEX NAME) OTHER CA INDEX NAMES: o-Cresol, 4,4'-isopropylidenedi- (7CI, 8CI) OTHER NAMES: **Bisphenol C** ABBREVIATION USED IN DATA TABLES: BPC	79-97-0	$C_{17}H_{20}O_2$	6620			NO REPORTS	Water: 38 Soil: 75 Sed: 340 Air: 0.16	890	Agonist in all studies evaluated (6/6) Bound to estrogen receptors	Antagonist or no activity in studies evaluated (1/1)	Antagonist or no effect in studies evaluated (1/1) Bound to TTR	No data

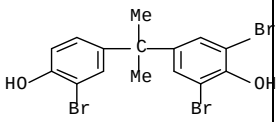
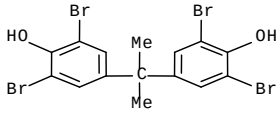
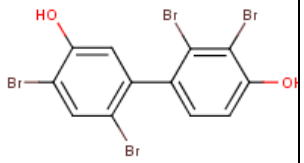
Chemical (CA Index) Name and Synonyms	CASRN	Molecular Formula	PubChem CID	Structure	TSCA	IUR Production Volume	PBT Profiler Values: Half-lives (days)	PBT Profiler Values: BFC	Estrogen	Androgen	Thyroid	Vitellogenin
Phenol, 4,4'-methylenebis- (CA INDEX NAME) OTHER CA INDEX NAMES: Phenol, 4,4'-methylenedi- (8CI) Phenol, p,p'-methylenedi- (4CI) OTHER NAMES: **Bisphenol F** HDM NSC 401136 p,p'-BPF p-(p-Hydroxybenzyl)phenol PP-BIP-F ABBREVIATION USED IN DATA TABLES: BPF	620-92-8 1333-16-0 (mixture/ unspecified; replaced 87139-40-0)	$C_{13}H_{12}O_2$	12111		X	NO REPORTS	Water: 15 Soil: 30 Sed: 140 Air: 0.2	35	Agonist in all studies evaluated (14/14) Bound to estrogen receptors[a]	Antagonist or no activity in studies evaluated (3/3)	Antagonist or no effect in studies evaluated (1/1) No binding data	No data
Phenol, 4,4'-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]bis- (CA INDEX NAME) OTHER CA INDEX NAMES: Phenol, 4,4'-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]di- (6CI, 7CI) Phenol, 4,4'-[trifluoro-1-(trifluoromethyl)ethylidene]di- (8CI) OTHER NAMES: **Bisphenol AE** **Bisphenol AF** ABBREVIATION USED IN DATA TABLES: BPAF	1478-61-1	$C_{15}H_{10}F_6O_2$	73864		X	1986: 10-500K 1990: 10-500K 1994: 10-500K 1998: 10-500K 2002: 10-500K	Water: 180 Soil: 360 Sed: 1600 Air: 0.2	560	Agonist in all studies evaluated (10/10) Bound to estrogen receptors[a]	Antagonist or no activity in studies evaluated (1/1)	Antagonist or no effect in studies evaluated (1/1) No binding data	No data
Phenol, 4,4'-ethylidenebis- (CA INDEX NAME) OTHER CA INDEX NAMES: Phenol, 4,4'-ethylidenedi- (6CI, 7CI, 8CI) OTHER NAMES: **Bisphenol AD** **Bisphenol E** ABBREVIATION USED IN DATA TABLES: BPE	2081-08-5	$C_{14}H_{14}O_2$	N/A			NO REPORTS	Water: 15 Soil: 30 Sed: 140 Air: 0.2	57	Agonist in all studies evaluated (11/11) Bound to estrogen receptors[a]	Antagonist or no activity in studies evaluated (2/2)	Antagonist or no effect in studies evaluated (1/1) No binding data	No data

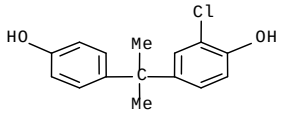
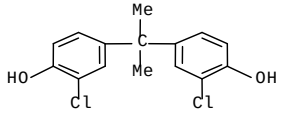
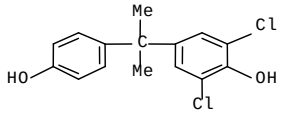
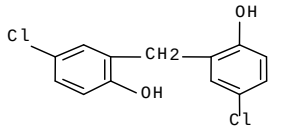
Chemical (CA Index) Name and Synonyms	CASRN	Molecular Formula	PubChem CID	Structure	TSCA	IUR Production Volume	PBT Profiler Values: Half-lives (days)	PBT Profiler Values: BFC	Estrogen	Androgen	Thyroid	Vitellogenin
Phenol, 4,4'-sulfonylbis- (CA INDEX NAME) OTHER CA INDEX NAMES: Phenol, 4,4'-sulfonyldi- (6CI, 8CI) OTHER NAMES: **Bisphenol S** ABBREVIATION USED IN DATA TABLES: BPS	80-09-1	$C_{12}H_{10}O_4S$	6626		X	1986: >1-10M 1990: >1-10M 1994: >1-10M 1998: >1-10M 2002: >1-10M	Water: 15 Soil: 30 Sed: 140 Air: 1.1	3.7	Agonist in all studies evaluated (6/6); single study notes agonist activity after activation with S9 Bound to estrogen receptors	Antagonist or no activity in studies evaluated (1/1)	Antagonist or no effect in studies evaluated (1/1) No binding data	No data
0 or 1-OH Group on the Diphenyl Moiety												
Benzene, 1,1'-methylenebis- (CA INDEX NAME) OTHER CA INDEX NAMES: Methane, diphenyl- (8CI) OTHER NAMES: Diphenylmethane ABBREVIATION USED IN DATA TABLES: DPM	101-81-5	$C_{13}H_{12}$	7580		X	1986: no reports 1990: no reports 1994: 10-500K 1998: >1-10M 2002: 10-500K	Water: 15 Soil: 30 Sed: 140 Air: 1.5	310	Antagonist or produced no effect in studies evaluated (2/2) Did not bind to ER (1 study)	Antagonist or no activity in studies evaluated (1/1)	No data	No data
Phenol, 4-(phenylmethyl)- (CA INDEX NAME) OTHER CA INDEX NAMES: p-Cresol, α-phenyl- (6CI, 8CI) OTHER NAMES: 4-Hydroxydiphenylmethane ABBREVIATION USED IN DATA TABLES: HDM	101-53-1	$C_{13}H_{12}O$	7563		X	NO REPORTS	Water: 15 Soil: 30 Sed: 140 Air: 0.35	94	Agonist in all studies evaluated (5/5) Bound to estrogen receptors[a]	Antagonist or no activity in studies evaluated (1/1)	No data	No data

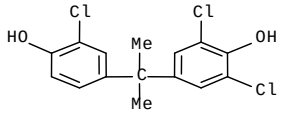
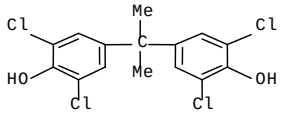
Chemical (CA Index) Name and Synonyms	CASRN	Molecular Formula	PubChem CID	Structure	TSCA	IUR Production Volume	PBT Profiler Values: Half-lives (days)	PBT Profiler Values: BFC	Estrogen	Androgen	Thyroid	Vitellogenin
Phenol, 4-(1-methyl-1-phenylethyl)- (CA INDEX NAME) OTHER CA INDEX NAMES: Phenol, p-(α,α-dimethylbenzyl)- (6CI, 7CI, 8CI) OTHER NAMES: 2-(4-Hydroxyphenyl)-2-phenylpropane ABBREVIATION USED IN DATA TABLES: HPP	599-64-4	$C_{15}H_{16}O$	11742		X	1986: >1-10M 1990: >10-50M 1994: >10-50M 1998: >10-50M 2002: >10-50M	Water: 38 Soil: 75 Sed: 340 Air: 0.36	300	Agonist in all studies evaluated (5/5) Bound to estrogen receptors[a]	Antagonist or no activity in studies evaluated (2/2)	No data	No data
Benzene, 1,1'-(1-methylethylidene)bis- (CA INDEX NAME) OTHER CA INDEX NAMES: Propane, 2,2-diphenyl- (6CI, 7CI, 8CI) OTHER NAMES: 2,2-Diphenylpropane Dimethyldiphenylmethane ABBREVIATION USED IN DATA TABLES: DPP	778-22-3	$C_{15}H_{16}$	13065			NO REPORTS	Water: 38 Soil: 75 Sed: 340 Air: 1.8	700	Antagonist or produced no effect in studies evaluated (1/1) No binding data	Antagonist or no activity in studies evaluated (1/1)	No functional data No binding to TTR	No data
Modified Phenol Substitution Patterns Compared to Bisphenol A and F												
Phenol, 2,2'-methylenebis- (CA INDEX NAME) OTHER CA INDEX NAMES: Phenol, 2,2'-methylenedi- (7CI, 8CI) OTHER NAMES: 2,2'-Bis(hydroxyphenyl)methane Bisphenol F ABBREVIATION USED IN DATA TABLES: 2,2'-BPF	2467-02-9	$C_{13}H_{12}O_2$	75575		X	NO REPORTS	Water: 15 Soil: 30 Sed: 140 Air: 0.2	45	Agonist in studies evaluated (1/1) No binding data	No data	No data	No data

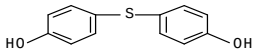
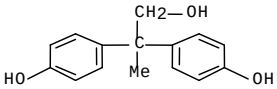
Chemical (CA Index) Name and Synonyms	CASRN	Molecular Formula	PubChem CID	Structure	TSCA	IUR Production Volume	PBT Profiler Values: Half-lives (days)	PBT Profiler Values: BFC	Estrogen	Androgen	Thyroid	Vitellogenin
Phenol, 2-[(4-hydroxyphenyl)methyl]- (CA INDEX NAME) OTHER CA INDEX NAMES: Phenol, 2,4'-methylenedi- (7CI, 8CI) OTHER NAMES: 2,4'-Bis(hydroxyphenyl)methane ABBREVIATION USED IN DATA TABLES: 2,4'-BPF	2467-03-0	$C_{13}H_{12}O_2$	75576		X	NO REPORTS	Water: 15 Soil: 30 Sed: 140 Air: 0.2	45	No data	No data	No data	No data
Phenol, 2-[1-(4-hydroxyphenyl)-1-methylethyl]- (CA INDEX NAME) OTHER CA INDEX NAMES: Phenol, 2,4'-isopropylidenedi- (8CI) OTHER NAMES: 2,4'-Bisphenol A ABBREVIATION USED IN DATA TABLES: 2,4'-BPA	837-08-1	$C_{15}H_{16}O_2$	70044		X	1986: no reports 1990: no reports 1994: no reports 1998: >1-10M 2002: >1-10M	Water: 38 Soil: 75 Sed: 340 Air: 0.2	45	Agonist in studies evaluated (1/1) No binding data	No data	No data	No data
1,2-Benzenediol, 4-[1-(4-hydroxyphenyl)-1-methylethyl]- (CA INDEX NAME) OTHER NAMES: BPA catechol ABBREVIATION USED IN DATA TABLES: BPA Catechol	79371-66-7	$C_{15}H_{16}O_3$	656689			NO REPORTS	Water: 38 Soil: 75 Sed: 340 Air: 0.18	54	Agonist in studies evaluated (2/2) Bound to estrogen receptors	Antagonist or no activity in studies evaluated (1/1)	No data	No data
Alkyl Substitution on Phenol Moieties												
Phenol, 4,4'-(1-methylethylidene)bis[2,6-dimethyl- (CA INDEX NAME) OTHER CA INDEX NAMES: 2,6-Xylenol, 4,4'-isopropylidenedi- (7CI, 8CI) OTHER NAMES: Tetramethylbisphenol A ABBREVIATION USED IN DATA TABLES: TMBPA	5613-46-7	$C_{19}H_{24}O_2$	79717		X	NO REPORTS	Water: 60 Soil: 120 Sed: 540 Air: 0.39	6200	Agonist in studies evaluated (2/2) No binding data	Antagonist or no activity in studies evaluated (1/1)	Discordant results in antagonist studies (1/2) Bound to TTR	No data

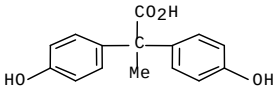
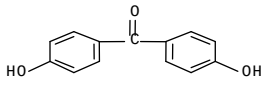
Chemical (CA Index) Name and Synonyms	CASRN	Molecular Formula	PubChem CID	Structure	TSCA	IUR roduction Volume	PBT Profiler Values: Half-lives (days)	PBT Profiler Values: BFC	Estrogen	Androgen	Thyroid	Vitellogenin
Phenol, 4,4'-methylenebis[2,6-bis(1,1-dimethylethyl)- (CA INDEX NAME) OTHER CA INDEX NAMES: Phenol, 4,4'-methylenebis[2,6-di-tert-butyl- (6CI, 8CI) OTHER NAMES: 4,4'-Methylenebis[2,6-di-tert-butylphenol] ABBREVIATION USED IN DATA TABLES: 4,4'-MBTBP	118-82-1	$C_{29}H_{44}O_2$	8372		X	1986: >1-10M 1990: >1-10M 1994: >1-10M 1998: >1-10M 2002: >1-10M	Water: 180 Soil: 360 Sed: 1600 Air: 0.46	43	Agonist in studies evaluated (1/2) Bound to ER	No data	No data	No data
Halogenation on Phenol Moieties												
Phenol, 2-bromo-4-[1-(4-hydroxyphenyl)-1-methylethyl]- (CA INDEX NAME) OTHER CA INDEX NAMES: Phenol, 2-bromo-4,4'-isopropylidenedi- (7CI, 8CI) OTHER NAMES: Bromobisphenol A ABBREVIATION USED IN DATA TABLES: BrBPA	6073-11-6	$C_{15}H_{15}BrO_2$	656688			NO REPORTS	Water: 38 Soil: 75 Sed: 340 Air: 0.31	620	Agonist in studies evaluated (3/3) Bound to ER	No data	Antagonist or no effect in studies evaluated (1/1) No binding data	No data
Phenol, 4,4'-(1-methylethylidene)bis[2-bromo- (CA INDEX NAME) OTHER CA INDEX NAMES: Phenol, 4,4'-isopropylidenebis[2-bromo- (8CI) OTHER NAMES: Dibromobisphenol A ABBREVIATION USED IN DATA TABLES: di-BrBPA	29426-78-6	$C_{15}H_{14}Br_2O_2$	656687			NO REPORTS	Water: 60 Soil: 120 Sed: 540 Air: 0.67	1200	Agonist in studies evaluated (1/1) No binding data	No data	Antagonist or no effect in studies evaluated (1/1) No binding data	No data

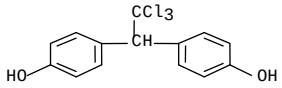
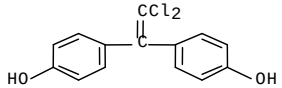
Chemical (CA Index) Name and Synonyms	CASRN	Molecular Formula	PubChem CID	Structure	TSCA	IUR Production Volume	PBT Profiler Values: Half-lives (days)	PBT Profiler Values: BFC	Estrogen	Androgen	Thyroid	Vitellogenin
Phenol, 2,6-dibromo-4-[1-(3-bromo-4-hydroxyphenyl)-1-methylethyl]- (CA INDEX NAME) OTHER CA INDEX NAMES: Phenol, 2,2',6-tribromo-4,4'-isopropylidenedi- (7CI, 8CI) OTHER NAMES: Tribromobisphenol A ABBREVIATION USED IN DATA TABLES: tri-BrBPA	6386-73-8	$C_{15}H_{13}Br_3O_2$	80801		X	NO REPORTS	Water: 180 Soil: 360 Sed: 1600 Air: 1.2	5800	Agonist in studies evaluated (3/3) Bound to ER	No data	Discordant functional data (1 study) No binding data	No data
Phenol, 4,4'-(1-methylethylidene)bis[2,6-dibromo- (CA INDEX NAME) OTHER CA INDEX NAMES: Phenol, 4,4'-isopropylidenebis[2,6-dibromo- (6CI, 7CI, 8CI) OTHER NAMES: Tetrabromobisphenol A ABBREVIATION USED IN DATA TABLES: tetra-BrBPA	79-94-7	$C_{15}H_{12}Br_4O_2$	6618		X	1986: >10-50M 1990: >50-100M 1994: >100-500M 1998: >100-500M 2002: >100-500M	Water: 180 Soil: 360 Sed: 1600 Air: 5.4	14000	Agonist in majority of studies evaluated (10/13) Bound to ER in majority of studies evaluated (2/3)	Antagonist or no activity in studies evaluated (1/1)	Discordant results in antagonist studies (4/8) Bound to TTR	No data
[1,1'-Biphenyl]-ar,ar'-diol, tetrabromo- (9CI) (CA INDEX NAME) OTHER NAMES: Tetrabromobisphenol ABBREVIATION USED IN DATA TABLES: tri-BrBP	36511-35-0	$C_{12}H_6Br_4O_2$	37467			NO REPORTS	Water: 180 Soil: 360 Sed: 1600 Air: 3	6200	No data	No data	No data	No data

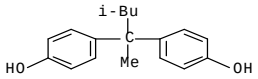
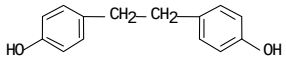
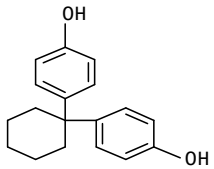
Chemical (CA Index) Name and Synonyms	CASRN	Molecular Formula	PubChem CID	Structure	TSCA	IUR Production Volume	PBT Profiler Values: Half-lives (days)	PBT Profiler Values: BFC	Estrogen	Androgen	Thyroid	Vitellogenin
Phenol, 2-chloro-4-[1-(4-hydroxyphenyl)-1-methylethyl]- (CA INDEX NAME) OTHER CA INDEX NAMES: Phenol, 2-chloro-4,4'-isopropylidenedi- (7CI) OTHER NAMES: 3-Chlorobisphenol A Chlorobisphenol A ABBREVIATION USED IN DATA TABLES: ClBPA	74192-35-1	$C_{15}H_{15}ClO_2$	N/A			NO REPORTS	Water: 38 Soil: 75 Sed: 340 Air 0.31	400	Agonist in studies evaluated (7/7); addition of S9 inactivated chemical (2/2) Bound to ER	No data	Antagonist or no effect in studies evaluated (1/1) Bound to TTR	Agonist (1/1)
Phenol, 4,4'-(1-methylethylidene)bis[2-chloro- (CA INDEX NAME) OTHER CA INDEX NAMES: Phenol, 4,4'-isopropylidenebis[2-chloro- (6CI, 7CI, 8CI) OTHER NAMES: 3,3'-Dichlorobisphenol A ABBREVIATION USED IN DATA TABLES: 3,3'-di-ClBPA	79-98-1	$C_{15}H_{14}Cl_2O_2$	66238		X	NO REPORTS	Water: 60 Soil: 120 Sed: 540 Air: 0.67	500	Agonist in studies evaluated (6/6); addition of S9 inactivated chemical (2/2) Bound to ER	No data	Antagonist or no effect in studies evaluated (1/1) Bound to TTR	Agonist (1/1)
Phenol, 2,6-dichloro-4-[1-(4-hydroxyphenyl)-1-methylethyl]- (CA INDEX NAME) OTHER CA INDEX NAMES: Phenol, 2,6-dichloro-4,4'-isopropylidenedi- (7CI, 8CI) OTHER NAMES: 3,5-Dichlorobisphenol A ABBREVIATION USED IN DATA TABLES: 3,5-di-ClBPA	14151-65-6	$C_{15}H_{14}Cl_2O_2$	N/A			NO REPORTS	Water: 60 Soil: 120 Sed: 540 Air: 0.38	500	Agonist in studies evaluated (4/4); addition of S9 inactivated chemical (1/1) No binding data	No data	No functional data Bound to TTR	No data
Phenol, 2,2'-methylenebis[4-chloro- (CA INDEX NAME) OTHER NAMES: 5,5'-Dichloro-2,2'-dihydroxydiphenylmethane DDM; Dichlorophen; ABBREVIATION USED IN DATA TABLES: DDM	97-23-4	$C_{13}H_{10}Cl_2O_2$	3037		X	1986: 10-500K 1990: no reports 1994: 10-500K 1998: 10-500K 2002: 10-500K	Water: 60 Soil: 120 Sed: 540 Air: 0.62	150	Agonist in studies evaluated (1/1) Bound to ER	No data	No data	No data

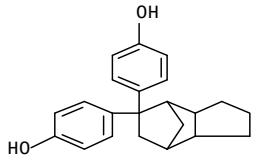
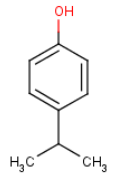
Chemical (CA Index) Name and Synonyms	CASRN	Molecular Formula	PubChem CID	Structure	TSCA	IUR Production Volume	PBT Profiler Values: Half-lives (days)	PBT Profiler Values: BFC	Estrogen	Androgen	Thyroid	Vitellogenin
Phenol, 2,6-dichloro-4-[1-(3-chloro-4-hydroxyphenyl)-1-methylethyl]- (CA INDEX NAME) OTHER NAMES: 3,3',5-Trichlorobisphenol A Trichlorobisphenol A ABBREVIATION USED IN DATA TABLES: tri-ClBPA	40346-55-2	$C_{15}H_{13}Cl_3O_2$	N/A			NO REPORTS	Water: 180 Soil: 360 Sed: 1600 Air: 1.2	1600	Agonist in studies evaluated (6/6); addition of S9 inactivated chemical (2/2) No binding data	No data	Antagonist or no effect in all studies (1/1) Bound to TTR	Agonist (1/1)
Phenol, 4,4'-(1-methylethylidene)bis[2,6-dichloro- (CA INDEX NAME) OTHER CA INDEX NAMES: Phenol, 4,4'-isopropylidenebis[2,6-dichloro- (6CI, 8CI) OTHER NAMES: 2,2',6,6'-Tetrachlorobisphenol A 3,3',5,5'-Tetrachlorobisphenol A 3,5,3',5'-Tetrachlorobisphenol A Tetrachlorobisphenol A ABBREVIATION USED IN DATA TABLES: tetra-ClBPA	79-95-8	$C_{15}H_{12}Cl_4O_2$	6619		X	NO REPORTS	Water: 180 Soil: 360 Sed: 1600 Air: 4.6	4900	Agonist in studies evaluated (11/11); addition of S9 inactivated chemical (1/1) Bound to ER	Antagonist or no activity in studies evaluated (1/1)	Discordant results in antagonist studies (4/8) Bound to TTR	Antagonist or no effect (1/1)

Chemical (CA Index) Name and Synonyms	CASRN	Molecular Formula	PubChem CID	Structure	TSCA	IUR Production Volume	PBT Profiler Values: Half-lives (days)	PBT Profiler Values: BFC	Estrogen	Androgen	Thyroid	Vitellogenin
Modified Linkages Between Phenol Moieties												
Phenol, 4,4'-thiobis- (CA INDEX NAME) OTHER CA INDEX NAMES: Phenol, 4,4'-thiodi- (6CI, 7CI, 8CI) Phenol, p,p'-thiobis- (3CI) Phenol, p,p'-thiodi- (4CI) OTHER NAMES: 4,4'-Dihydroxydiphenyl sulfide 4,4'-Thiobisphenol 4,4'-Thiodiphenol 4-(4-Hydroxyphenylthio)phenol Bis(4-hydroxyphenyl) sulfide Bis(p-hydroxyphenyl) sulfide Bis(p-hydroxyphenyl)thioether Bisphenol sulfide Bisphenol T NSC 203030 p,p'-Dihydroxydiphenyl sulfide Thiobisphenol ABBRECIATION USED IN DATA TABLES: TBP	2664-63-3	$C_{12}H_{10}O_2S$	17570		X	1986: 10K-500K 1990: 10K-500K 1994: 10K-500K 1998: 10K-500K 2002: no reports	Water: 15 Soil: 30 Sed: 140 Air: 0.39	74	Agonist in studies evaluated (4/4) Bound to ER	No data	No data	No data
Benzeneethanol, 4-hydroxy-β-(4-hydroxyphenyl)-β-methyl- (9CI) (CA INDEX NAME) OTHER NAMES: 2,2-Bis(4-hydroxyphenyl)propanol ABBREVIATION USED IN DATA TABLES: BPA ol	142648-65-5	$C_{15}H_{16}O_3$	656692			NO REPORTS	Water: 38 Soil: 75 Sed: 340 Air: 0.19	2.1	Agonist in studies evaluated (6/7); differential regulation of ER-regulated proteins Bound to ER	Antagonist or no activity in studies evaluated (1/1)	No data	No data

Chemical (CA Index) Name and Synonyms	CASRN	Molecular Formula	PubChem CID	Structure	TSCA	IUR Production Volume	PBT Profiler Values: Half-lives (days)	PBT Profiler Values: BFC	Estrogen	Androgen	Thyroid	Vitellogenin
Benzeneacetic acid, 4-hydroxy-α-(4-hydroxyphenyl)-α-methyl- (9CI) (CA INDEX NAME) OTHER CA INDEX NAMES: Propionic acid, 2,2-bis(p-hydroxyphenyl)- (7CI) OTHER NAMES: 2,2-Bis(4-hydroxyphenyl)propionic acid ABBREVIATION USED IN DATA TABLES: BPAacid	92549-67-2	$C_{15}H_{14}O_4$	656694			NO REPORTS	Water: 15 Soil: 30 Sed: 140 Air: 0.2	3.2	Agonist in studies evaluated (2/2) No binding data	Antagonist or no activity in studies evaluated (1/1)	No data	No data
Methanone, bis(4-hydroxyphenyl)- (CA INDEX NAME) OTHER CA INDEX NAMES: Benzophenone, 4,4'-dihydroxy- (7CI, 8CI) OTHER NAMES: 4,4'-Hydroxybenzophenone Bis(p-hydroxy)benzophenone ABBREVIATION USED IN DATA TABLES: HBP	611-99-4	$C_{13}H_{10}O_3$	3102			NO REPORTS	Water: 15 Soil: 30 Sed: 140 Air: 0.26	1.4	Agonist in studies evaluated (11/12); differential regulation of ER-regulated proteins Discordant results on ER binding (1/2)	Antagonist or no activity in studies evaluated (1/1)	No data	No data

Chemical (CA Index) Name and Synonyms	CASRN	Molecular Formula	PubChem CID	Structure	TSCA	IUR Production Volume	PBT Profiler Values: Half-lives (days)	PBT Profiler Values: BFC	Estrogen	Androgen	Thyroid	Vitellogenin
Phenol, 4,4'-(2,2,2-trichloroethylidene)bis- (CA INDEX NAME) OTHER CA INDEX NAMES: Phenol, 4,4'-(2,2,2-trichloroethylidene)di- (6CI, 7CI, 8CI) OTHER NAMES: α,α-Bis(4-hydroxyphenyl)-β,β,β-trichloroethane 1,1-Bis(4-hydroxyphenyl)-2,2,2-trichloroethane 1,1-Bis(p-hydroxyphenyl)-2,2,2-trichloroethane 2,2-Bis(4-hydroxyphenyl)-1,1,1-trichloroethane 2,2-Bis(p-hydroxyphenyl)-1,1,1-trichloroethane ABBREVIATION USED IN DATA TABLES: HPTE	2971-36-0	$C_{14}H_{11}Cl_3O_2$	76302		X	NO REPORTS	Water: 60 Soil: 120 Sed: 540 Air: 0.2	630	Agonist in studies evaluated (2/3) No binding data	Antagonist or no activity in studies evaluated (2/2)	No data	No data
Phenol, 4,4'-(2,2-dichloroethenylidene)bis- (CA INDEX NAME) OTHER CA INDEX NAMES: Phenol, 4,4'-(dichloroethenylidene)bis- (9CI) Phenol, 4,4'-(dichlorovinylidene)di- (6CI, 8CI) OTHER NAMES: Bisphenol C 2 ABBREVIATION USED IN DATA TABLES: Bisphenol C 2	14868-03-2	$C_{14}H_{10}Cl_2O_2$	84677		X	NO REPORTS	Water: 38 Soil: 75 Sed: 340 Air: 0.21	150	Discordant activity results (1/2) No binding data	Antagonist or no activity in studies evaluated (1/1)	No data	No data

Chemical (CA Index) Name and Synonyms	CASRN	Molecular Formula	PubChem CID	Structure	TSCA	IUR Production Volume	PBT Profiler Values: Half-lives (days)	PBT Profiler Values: BFC	Estrogen	Androgen	Thyroid	Vitellogenin
Phenol, 4,4'-(1,3-dimethylbutylidene)bis- (CA INDEX NAME) OTHER CA INDEX NAMES: Phenol, 4,4'-(1,3-dimethylbutylidene)di- (6CI, 7CI, 8CI) OTHER NAMES: 2,2-(4-Hydroxyphenyl)-4-methylpentane 2,2-Bis(4-hydroxyphenyl)-4-methylpentane NSC 73727 ABBREVIATION USED IN DATA TABLES: Bis-MP	6807-17-6	$C_{18}H_{22}O_2$	81259			NO REPORTS	Water: 38 Soil: 75 Sed: 340 Air: 0.19	1500	Agonist in studies evaluated (2/2) Bound to ER	No data	No data	No data
Phenol, 4,4'-(1,2-ethanediyl)bis- (CA INDEX NAME) OTHER CA INDEX NAMES: Phenol, 4,4'-ethylenedi- (6CI, 7CI, 8CI) OTHER NAMES: α,α'-Bi-p-cresol 1,2-Bis(4-hydroxyphenyl)ethane 1,2-Bis(p-hydroxyphenyl)ethane 1,2-Di(4-hydroxyphenyl)ethane 4,4'-Dihydroxybibenzyl ABBREVIATION USED IN DATA TABLES: Bi-p-cresol	6052-84-2	$C_{14}H_{14}O_2$	80152			NO REPORTS	Water: 38 Soil: 75 Sed: 340 Air: 0.19	160	No data	No data	No data	No data
Phenol, 4,4'-cyclohexylidenebis- (CA INDEX NAME) OTHER CA INDEX NAMES: Phenol, 4,4'-cyclohexylidenedi- (6CI, 8CI) OTHER NAMES: 1,1-Bis(4-hydroxyphenyl)cyclohexane 1,1-Bis(p-hydroxyphenyl)cyclohexane 4,4'-Cyclohexylidenebisphenol 4,4'-Cyclohexylidenediphenol Bisphenol Z ABBREVIATION USED IN DATA TABLES: BPCH	843-55-0	$C_{18}H_{20}O_2$	232446			NO REPORTS	Water: 38 Soil: 75 Sed: 340 Air: 0.18	3300	Agonist in studies evaluated (1/1) No binding data	Antagonist or no activity in studies evaluated (1/1)	No data	No data

Chemical (CA Index) Name and Synonyms	CASRN	Molecular Formula	PubChem CID	Structure	TSCA	IUR Production Volume	PBT Profiler Values: Half-lives (days)	PBT Profiler Values: BFC	Estrogen	Androgen	Thyroid	Vitellogenin
Phenol, 4,4'-(octahydro-4,7-methano-5H-inden-5-ylidene)bis- (CA INDEX NAME) OTHER CA INDEX NAMES: Phenol, 4,4'-(tetrahydro-4,7-methanoindan-5(4H)-ylidene)di- (7CI, 8CI) OTHER NAMES: 4,4'-(Hexahydro-4,7-methanoindan-5-ylidene)diphenol 4,4'-(Hexahydro-4,7-methyleneindan-5-ylidene)diphenol 4,4'-(Hexahydro-4,7-methylidenindane-5-ylidene)bisphenol 4,4'-(Octahydro-4,7-methano-5H-inden-5-ylidene)bisphenol 5,5-Bis(p-hydroxyphenyl)hexahydro-4,7-methanoindan ABBRVIATION USED IN DATA TABLES: Bis-HHM	1943-97-1	$C_{22}H_{24}O_2$	102724		X	1986: no reports 1990: 10K-500K 1994: no reports 1998: no reports 2002 no reports	Water: 38 Soil: 75 Sed: 340 Air: 0.18	3000	Agonist in studies evaluated (2/2) Bound to ER	No data	No data	No data
Phenol, 4-(1-methylethyl)- (CA INDEX NAME) OTHER CA INDEX NAMES: Phenol, p-isopropyl- (8CI) OTHER NAMES: 4-Isopropylphenol p-Isopropylphenol ABBREVIATION USED IN DATA TABLES: IPP	99-89-8	$C_9H_{12}O$	7465		X	1986: 10-500K 1990: >500K-1M 1994: >500K-1M 1998: >500K-1M 2002: 10-500K	Water: 15 Soil: 30 Sed: 140 Air: 0.38	34	Agonist in studies evaluated (1/1) No binding data[a]	Antagonist or no activity in studies evaluated (1/1)	No data	No data

Abbreviations: Antagnst. = Antagonist; Diff. Reg. = Differential Regulation; Discord. = Discordant.; ER = estrogen receptor; Sed = sediment.

[a]Data were compiled from Registry (2006) files; PubChem records (PubChem, undated-a); IUR database (U.S. EPA, 2008); PBT Profiler (U.S. EPA, 2006); and study publications.

[b]One study, Okada et al. (2008), also reported chemical affinity for the estrogen related receptor γ. Additional information on this receptor is available in Giguère (2002 [PMID:12185669]) and Horard and Vanacker (2003).

The above table provides a summary of the endocrine activity of 36 bisphenol A analogs and derivatives including bisphenol AF. The results along with chemical descriptors for each chemical are presented in separate rows which consist of 13 columns. The chemicals are organized into six basic sub-groups starting from the top of the table moving down these are: Bisphenol A, B, C, F, AF, E, and S (7 chemicals); 0 or 1-OH Group on the Diphenyl Moiety (4 chemicals); Modified Phenol Substitution Patterns Compared to Bisphenol A and F (4 chemicals); Alkyl Substitution on Phenol Moieties (2 chemicals); Halogenation on Phenol

Moieties (11 chemicals); and Modified Linkages Between Phenol Moieties (11 chemicals). The chemical descriptors and summary of endocrine activity are shown under the column headings, from left to right: Chemical (CA Index Name and Synonyms); CASRN; Molecular Formula; PubChem CID; Structure (image of chemical structure); TSCA (X indicates that the chemical was included in the TSCA test submissions); IUR Production Volume; PBT Profiler Values for Half-lives (days) and BCF (Bioconcentration Factor); Estrogen (activity); Androgen (activity); Thyroid (activity); and Vitellogenin (activity). Entries for the ED activity indicate whether the chemical was an antagonist, agonist, and/or binding agent.

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Chemical Name	Internet address:
Bisphenol AF	http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=73864
Bisphenol A	http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=6623
Bisphenol B	http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=66166
Bisphenol C	http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=6620
4,4'-Methylenediphenol	http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=12111
Bisphenol S	http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=6626
Diphenylmethane	http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=7580
4-Benzylphenol	http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=7563
p-Cumylphenol	http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=11742
2,2-Diphenyl-propane	http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=13065
Bisphenol F	http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=75575
2,4'-Methylenediphenol	http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=75576
2,4'-Bisphenol A	http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=70044
BPAcatechol	http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=656689
Bisphenol A, tetramethyl	http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=79717
Bimox M	http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=8372
Monobromobisphenol A	http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=656688
Dibromobisphenol A	http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=656687
Tribromobisphenol A	http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=80801
Tetrabromobisphenol A	http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=6618
Tetrabromobisphenol	http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=37467
3,3'-Dichlorodian	http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=66238
Dichlorophen	http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=3037
Tetrachlorodian	http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=6619
4,4'-Dihydroxydiphenyl sulfide	http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=17570
2,2-Bis(4-hydroxy-phenyl)-1-propanol	http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=656692
2,2-Bis(4-hydroxy-phenyl)-propanoic acid	http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=656694
Diphenyl ketone	http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=3102
Hydroxychlor	http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=76302
Dihydroxymethoxychlor olefin	http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=84677
2,2-(4-Hydroxyphenyl)-4-methylpentane	http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=81259
4,4'-Dihydroxybibenzyl	http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=80152
Bisphenol Z	http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=232446
4,4'-(Hexahydro-4,7-methanoindan-5-ylidene)diphenol	http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=102724
p-Cumenol	http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=7465

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Search Strategy (2006, 2007, 2008)

STN International files MEDLINE, NIOSHTIC, EMBASE, ESBIOBASE, BIOTECHNO, IPA, BIOSIS, TOXCENTER, and FSTA searched simultaneously on March 24, 2006, retrieved 69 hits (before duplicate removal). Keywords included the CAS Registry Number and synonyms of bisphenol AF. The search was repeated for an update on December 12, 2007, except that NIOSHTIC was no longer available. The titles of all 77 hits were examined. The search was repeated on September 24, 2008, with addition of the foods database FROSTI to find additional endocrine disruption studies and to try to find out how closely the uses of bisphenol AF paralleled those of bisphenol A. When the 85 hits were limited to 2007-2008 and the duplicates were removed, ten results were retrieved and their titles examined for new endocrine disruption studies. The 85 hits from the STN biomedical and foods databases also were combined with the keywords food? or beverage? or drink? or cans or canned or bottle? to retrieve 12 unique hits and with dental or dentistry or orthodontic? to retrieve two unique hits [the duplicate removal step had been omitted and 6 of the 7 hits in L22 were duplicates]. The studies were all about estrogenic activity of bisphenol A and its analogs. Thus, it was assumed that the remarks regarding the food and dental uses were about bisphenol A except for one study, "Measurement of estrogenic activity of chemicals for the development of new dental polymers" by Hashimoto et al. (2001) (cited in the dossier). The history of the 2008 online session with the biomedical and foods databases is reproduced below.

```
L1          39 S 1478-61-1
L2          16 S BISPHENOL(W)AF
L3           0 S 4(W)4(W)2(W)2(W)2(W)TRIFLUORO(W)1(W)TRIFLUOROMETHYL(W)ETHYLIDENE(W)
                BISPHENOL
L4           1 S HEXAFLUORO(3A)BIS(2A)HYDROXYPHENYL(W)PROPANE
L5          14 S BIS(2A)HYDROXYPHENYL(W)HEXAFLUOROPROPANE
L6          15 S BIS(2A)HYDROXYPHENYL(7A)HEXAFLUOROPROPANE
L7           5 S BIS(2A)HYDROXYPHENYL(W)PERFLUOROPROPANE
L8          28 S HEXAFLUOROISOPROPYLIDENE(W)(BISPHENOL OR DIPHENOL)
L9           0 S BIS(W)AF
L10          8 S HEXAFLUOROBISPHENOL(W)A OR HEXAFLUORO(W)BPA
L11          0 S HEXAFLUORODIPHENYLOLPROPANE
L12          0 S HEXAFLUOROISOPROPYIDENEBIS(W)4(W)(HYDROXYBENZENE OR PHENOL)
L13         85 S L1 OR L2 OR L4-L8 OR L10
                SAVE L13 X0350NAMES/Q
L14         12 S L13 AND (2007-2008)/PY
```

```
                SET DUPORDER FILE
L15          10 DUP REM L14 (2 DUPLICATES REMOVED)
              1 ANSWER '1' FROM FILE AGRICOLA
              2 ANSWERS '2-3' FROM FILE EMBASE
              7 ANSWERS '4-10' FROM FILE TOXCENTER
L16          10 SORT L15 1-10 TI
L17          24 S L13 AND (FOOD? OR BEVERAGE? OR DRINK? OR CANS OR CANNED OR BOTTLE?)
L18          12 DUP REM L17 (12 DUPLICATES REMOVED)
              5  ANSWERS '1-5' FROM FILE MEDLINE
              5  ANSWERS '6-10' FROM FILE EMBASE
              2  ANSWERS '11-12' FROM FILE TOXCENTER
L19          12 SORT L18 1-12 TI
L20           9 S L13 AND (DENTAL OR DENTISTRY OR ORTHODONTIC?)
L21           7 S L20 NOT L19
L22           7 SORT L21 1-7 TI
```

In addition, the STN International file CAPLUS was searched on September 23, 2008, for the roles USES and FFD (food or feed use) in conjunction with the CAS Registry Number. Little potential exposure information was found upon examination of the 329 titles of answer set L6 (see the history of the session reproduced below).

```
L1            0 S 1478-61-1/FFD
L2          401 S 1478-61-1/USES
L3            0 S L2 AND (FOOD? OR BEVERAGE? OR DRINK?)
L4           72 S L2 AND FLUOROELASTOMER? [Uses had already been explored.]
L5            0 S 1478-61-8 AND (FOOD? OR BEVERAGE? OR DRINK?)
L6          329 S L2 NOT L4
                SAVE L6 X350USES/A
```

The Internet addresses were saved for technical and regulatory information in URLs lists during each search period. In September 2008, the Internet search focus was on bisphenol F-containing polymers that might have applications for the food and pharmaceutical industries and for dentistry. Besides general Internet searches with the Google search engine, bisphenol AF was searched in the full-text of U.S. patents (http://www.uspto.gov). Of 35 U.S. patents since 1976 that mentioned both food and bisphenol AF, 11 were not applicable and four were on polymer films that might be used to package food. The remainder were on fluoroelastomers that might be used for seals or hoses in the food processing, chemical, and other industries.