

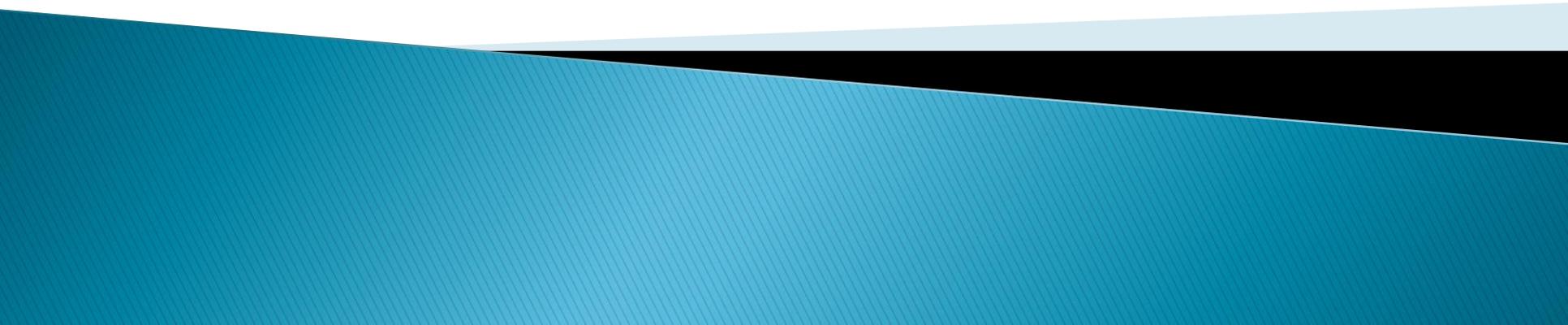
Chemical Selection Update

Sara Hoover and Laurel Plummer

Safer Alternatives Assessment and Biomonitoring Section
Office of Environmental Health Hazard Assessment

*Presentation to Scientific Guidance Panel
Oakland, CA*

July 26, 2012



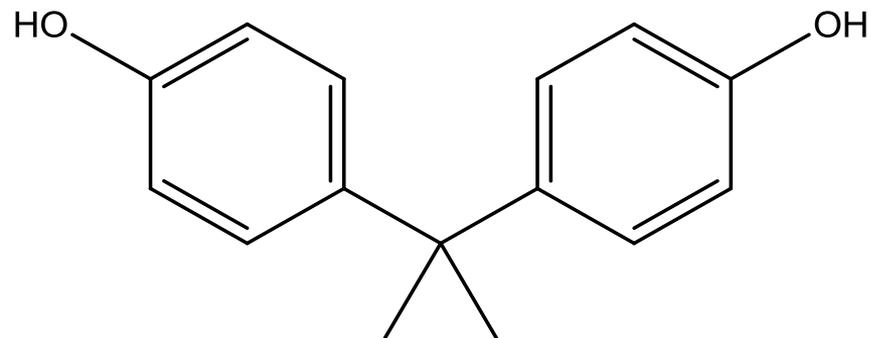
Purpose of agenda item

- ▶ Provide an interim update on additional screening of BPA substitutes and structurally-related compounds
- ▶ Provide a brief update on other chemical selection activities

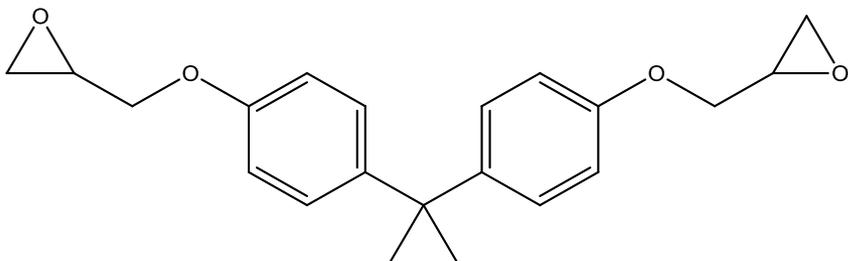
Main suggestions from SGP on screening BPA-related compounds

- ▶ Prioritize the chemicals for further consideration using various approaches
 - Further analyze information in March screening document
 - Evaluate the feasibility of a pilot laboratory screening
 - Conduct additional review of structure-activity information
- ▶ Contact the FDA regarding potential substitutes for food contact applications

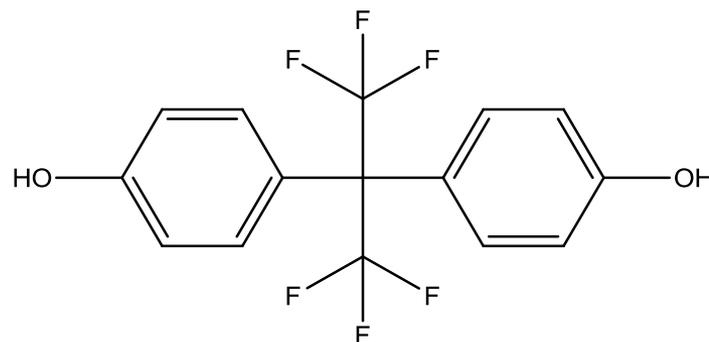
Bisphenol A (BPA)



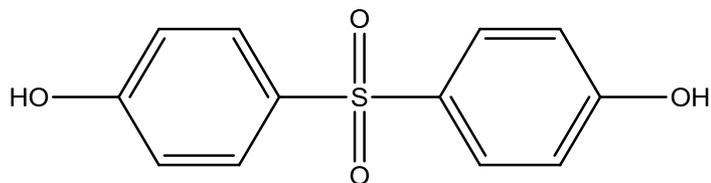
Bisphenol A diglycidyl ether (BADGE)



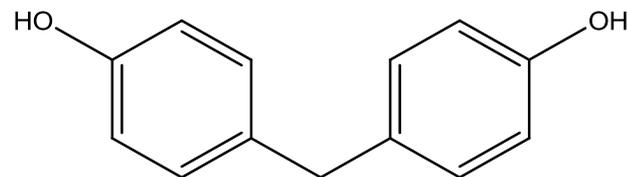
Bisphenol AF



Bisphenol S



Bisphenol F



Excerpt from March Initial Screening Document

Volume (lbs)	Chemicals
> 1 billion	BPA (<i>for comparison</i>)
1 - <10 million	BADGE BPS (4,4'-) TGSA D-8
<500 thousand	BPAF BPS (2,4'-)

Detected in biomonitoring studies

Detected in consumer products

In vivo evidence of estrogenicity

In vitro indications of endocrine activity

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Notes:

- 2006 data on production/import volume
- Absence of *in vivo*, *in vitro* data does not mean absence of effect

Additional chemicals of potential interest from initial screen

BPAP

BPB

BPF

BFDGE

PHBB

BisOPP-A

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Detected in biomonitoring studies

Detected in consumer products

In vivo evidence of estrogenicity

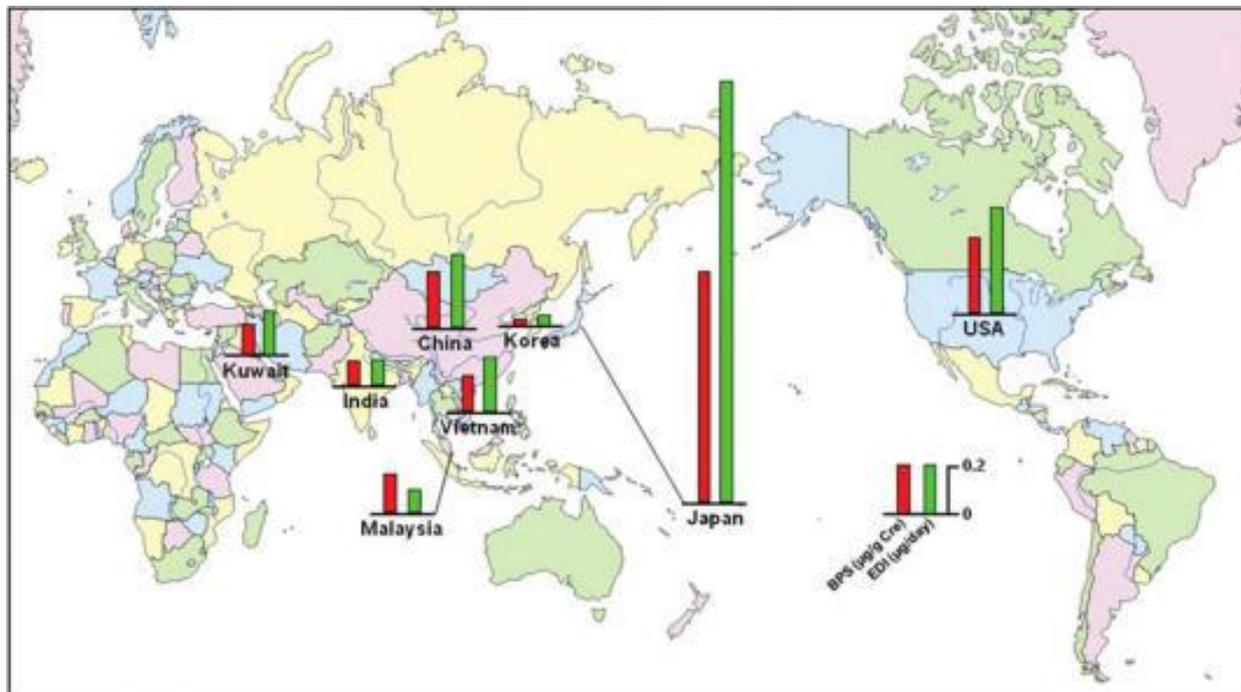
In vitro indications of endocrine activity

Predicted high BCF

- These chemicals had no production/import volume based on 2006 data

Bisphenol S in Urine from the United States and Seven Asian Countries: Occurrence and Human Exposures

Chunyang Liao,^{†,‡} Fang Liu,[†] Husam Alomirah,[§] Vu Duc Loi,^{||} Mustafa Ali Mohd,⁺ Hyo-Bang Moon,[#] Haruhiko Nakata,^{||} and Kurunthachalam Kannan^{*,†,▼}



315 urine samples from U.S. [New York] and Asia

BPS detected in 81% of urine samples

Japan & Vietnam (100%)
New York (97%)

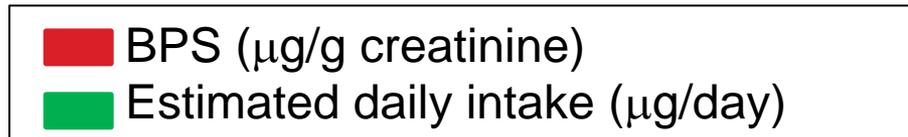
Geometric means:

BPS, this study:

New York: 0.304 µg/g creatinine
Japan: 0.933 µg/g creatinine

BPA, NHANES (03–04):

U.S.: 2.58 µg/g creatinine



Bisphenol S, a New Bisphenol Analogue, in Paper Products and Currency Bills and its Association with Bisphenol A Residues

Chunyang Liao, Fang Liu, and Kurunthachalam Kannan

Environ. Sci. Technol., **Just Accepted Manuscript** • DOI: 10.1021/es300876n • Publication Date (Web): 16 May 2012

Downloaded from <http://pubs.acs.org> on May 24, 2012

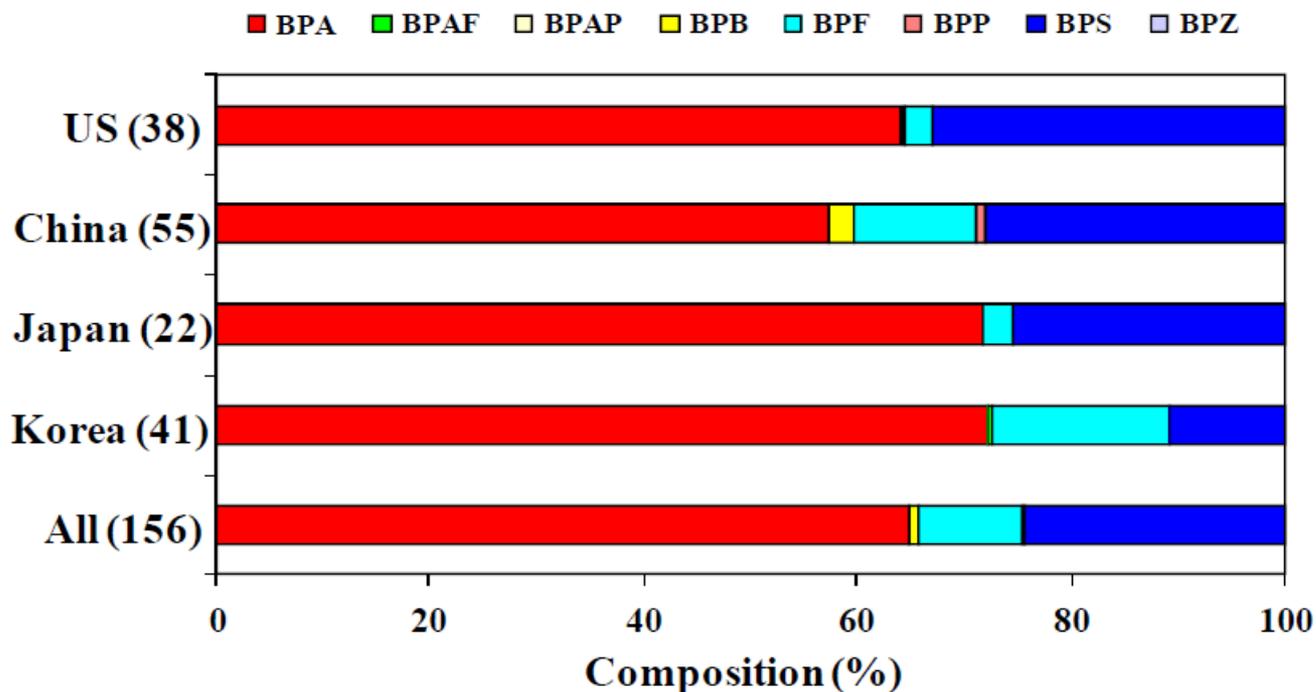
- 16 types of paper and paper products, such as thermal receipts, paper currencies, food cartons, flyers
- From U.S., Japan, Korea and Vietnam
- BPS detected in:
 - 100% of thermal receipt paper samples
 - ~90% of currency samples
 - Other paper: Flyers, 80%; Food cartons, 57%
- A significant negative correlation found between BPS and BPA in same set of thermal receipts

Occurrence of Eight Bisphenol Analogues in Indoor Dust from the United States and Several Asian Countries: Implications for Human Exposure

Chunyang Liao, Fang Liu, Ying Guo, Hyo-Bang Moon,
Haruhiko Nakata, Qian Wu, and Kurunthachalam Kannan

Environ. Sci. Technol., Just Accepted Manuscript • DOI: 10.1021/es302004w • Publication Date (Web): 11 Jul 2012

Downloaded from <http://pubs.acs.org> on July 20, 2012



- **BPA**: 99% detection
- **BPS**: 100% detection
- **BPF**: 74% detection
- Highest concentrations of **BPS** in Japan and U.S.
- **BPAF**: Korea
- **BPB**, **BPP**: China

Status update on pilot laboratory screening

- ▶ Pilot would focus on a subset of compounds structurally related to BPA
 - Choose most relevant in terms of potential health concern and exposure
- ▶ EHL is exploring predictive multiple reaction monitoring as a possible analytical approach
- ▶ Pilot laboratory screening could be conducted under the “ECL Pilot Study”

EHL - Environmental Health Lab (CDPH)

ECL - Environmental Chemistry Lab (DTSC)

Example structure–activity studies

Comparative Study of the Endocrine-Disrupting Activity of Bisphenol A and 19 Related Compounds

Shigeyuki Kitamura,*¹ Tomoharu Suzuki,* Seigo Sanoh,* Ryuki Kohta,* Norimasa Jinno,* Kazumi Sugihara,* Shin'ichi Yoshihara,* Nariaki Fujimoto,† Hiromitsu Watanabe,† and Shigeru Ohta*

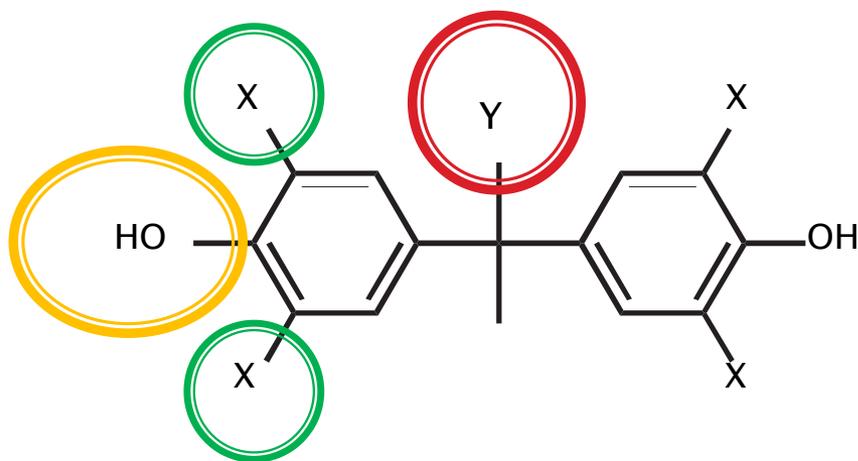
- ▶ *In vitro* hormone-responsive reporter assays:
 - Human breast cancer cell-line MCF-7 for estrogenic activity
 - Mouse fibroblast cell line NIH3T3 for androgenic activity
 - Pituitary cell line GH3 for thyroid hormonal activity

- ▶ *In vivo* uterotrophic assay in mice

- ▶ Compounds tested in one or more assays:
 - BPA, BPB, BPF, BPS, BPAF and others

Comparative Study of the Endocrine-Disrupting Activity of Bisphenol A and 19 Related Compounds

Shigeyuki Kitamura,^{*,1} Tomoharu Suzuki,^{*} Seigo Sanoh,^{*} Ryuki Kohta,^{*} Norimasa Jinno,^{*} Kazumi Sugihara,^{*} Shin'ichi Yoshihara,^{*} Nariaki Fujimoto,[†] Hiromitsu Watanabe,[†] and Shigeru Ohta^{*}



Essential for **estrogenic** and **anti-androgenic** activities

Regulating for **estrogenic** and **anti-androgenic** activities

Regulating for **estrogenic** and **anti-androgenic** activities

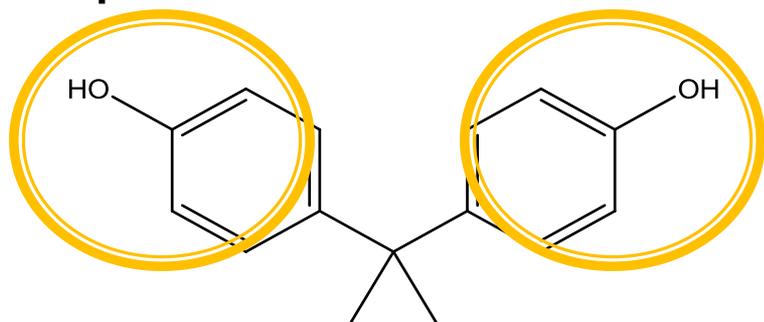
Excerpt from Figure 7 in Kitamura et al. 2005

QSAR Models of the *in vitro* Estrogen Activity of Bisphenol A Analogs

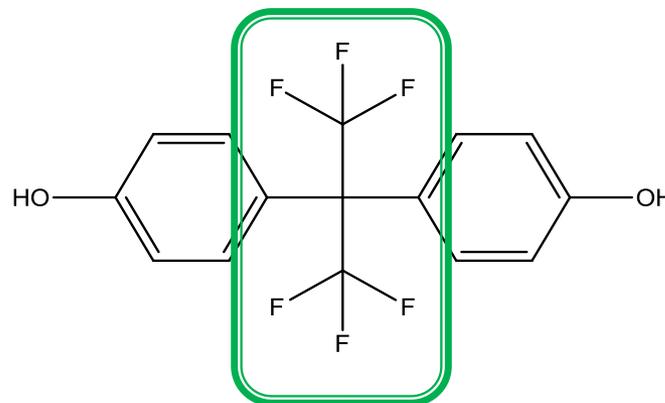
Kelly P. Coleman^a, William A. Toscano, Jr.^a, Thomas E. Wiese^{b*}

- ▶ Developed models for the interaction of BPA analogs with the estrogen receptor, based on data from *in vitro* assays:
 - Relative binding affinity for estrogen receptor (ER)
 - MVLN reporter gene induction assay
 - MCF-7 cell proliferation assay
- ▶ Based on their analysis, Coleman et al. suggested that the most estrogenic bisphenols have:
 - Two unencumbered *para* phenolic rings with multiple, longer chain alkyl substituents bound to the ring-linking carbon
 - Compounds with halogens attached to carbon bridge

Bisphenol A



Bisphenol AF



Food and Drug Administration: *Food Contact Substance Review Program*

- ▶ FDA authorizes new uses for food contact substances
- ▶ Approved food contact substances are listed in an on-line database
- ▶ Database includes:
 - Identity of food contact substance
 - Manufacturer
 - Intended use
 - Approval date
- ▶ Database available at:
<http://www.fda.gov/Food/FoodIngredientsPackaging/FoodContactSubstancesFCS/ucm116567.htm>

Design for the Environment (DfE) update

- ▶ US EPA's DfE conducting assessment of functional alternatives for BPA in thermal paper
- ▶ Draft report posting delayed
 - Posting date July 2012
- ▶ Dr. Cal Baier-Anderson of US EPA, Project Manager for this effort, has offered to provide ongoing advice on further screening of BPA-related compounds

Next steps for BPA-related chemicals

- ▶ Continue mapping out pilot laboratory screening
- ▶ Continue structure-activity review
 - Review additional literature, contact experts
- ▶ Search FDA food contact database
- ▶ Report findings to SGP



SGP could suggest candidates for future consideration as potential designated chemicals

Upcoming chemical selection activities

- ▶ Screening document on:
 - Selected pesticides from CDPR Top 100 List
 - Synthetic musks
- ▶ Potential designated chemical document on:
 - Selected organotins
 - Selected BPA-related compounds