

### 1/ BPS et autres Bisphénols :

- 4 études montrent que le BPS a une activité estrogénique plus ou moins comparable à celle du BPA.
- Les bisphénols (BPA, BPB, BF, BPS, BP1, BP2, BP4, BP5, BP6, BP7, BP8, BP9) ont une activité estrogénique inférieure pour certains et supérieure pour d'autres au BPA.
- Une étude mentionne la toxicité (test sur la daphnie) des 7 bisphénols testés (le résumé ne précise pas quels sont tous les bisphénols testés mais le BPS en fait partie)

### 2/ BPF et autres bisphénols

- Le BPAF, BPA (et dérivés), BPF, BPAP, BPB ont un potentiel estrogénique avec des effets combinés entre ces différentes substances. Selon une étude, l'activité estrogénique du BPF serait plus importante que celle du BPA. BPA et BPF montrent également une activité anti-androgénique chez l'humain in vitro.
- Selon une étude, le BPF a une action hépatotoxique.
- Plusieurs études montrent que le BPF a un potentiel génotoxique, tout comme ses dérivés.
- Les résidus de BPF passent la barrière placentaire au cours de la gestation.
- Le BPAF pourrait agir comme un PE (agoniste ou antagoniste des récepteurs des estrogènes).
- L'éther de Bisphénol A diglycidyle (BADGE) et l'éther de Bisphénol F diglycidyle (BFDGE) sont cytotoxiques et génotoxiques.

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- BPS :

1/

Hashimoto Y, Nakamura M. **Estrogenic activity of dental materials and bisphenol-A related chemicals in vitro.** Dent Mater J. 2000 Sep;19(3):245-62. *Department of Biomaterials, Osaka Dental University, 8-1 Kuzuhahanazono-cho, Hirakata, Osaka 573-1121, Japan.*

#### **Abstract**

Twenty-eight chemicals used as dental materials and bisphenol-A related chemicals were diluted with DMSO to concentrations ranging from  $10^{-7}$  to  $10^{-3}$  M and tested for estrogenicity. Bisphenol-A (BPA), bisphenol-F (BPF) and bisphenol-A-bischloroformate (BPACF) showed estrogenic activity using the yeast two-hybrid system, and BPA, BPF, BPACF and bisphenol-S (BPS) showed estrogenic activity using the fluorescence polarization system. However, none of the remaining chemicals and none of the dental materials showed any activity at concentrations between  $10^{-7}$  and  $10^{-3}$  M. Although BPA, BPF, BPACF, bisphenol-A-dimethacrylate and BPS showed estrogenic activity in the E-screen test, the remaining chemicals did not. Thus, most of the chemicals showed consistent results, either positive or negative, by the three testing methods, while two chemicals showed conflicting results. Further studies, together with in vivo and epidemiological examinations, are required. Elucidation of the structure-activity relationships of these chemicals is also needed to estimate the estrogenicity of a chemical from its structure.

➤ BPA, BPF, BPACF et BPS montrent une activité estrogénique avec deux techniques de dosage différentes.

➤ 2/

Hashimoto Y, Moriguchi Y, Oshima H, Kawaguchi M, Miyazaki K, Nakamura M. **Measurement of estrogenic activity of chemicals for the development of new dental polymers.** Toxicol In Vitro. 2001 Aug-Oct;15(4-5):421-5. *Department of Biomaterials, Osaka Dental University, 8-1, Kuzuhahanazonocho, Hirakata, Osaka 573-1121, Japan.* [yoshiya@cc.osaka-dent.ac.jp](mailto:yoshiya@cc.osaka-dent.ac.jp)

#### **Abstract**

The estrogenic activities of 13 Bisphenol-A (BPA)-related chemicals for development of new polymers by three in vitro bioassay have been examined in the presence and absence of a post-mitochondrial metabolizing system (S9 mix). BPA, Bisphenol-B (BPB), Bisphenol-F (BPF), **Bisphenol-S** (BPS), 4,4-ethylidenebisphenol (BP1), 4,4-dihydroxybenzophenone (BP2), 2,2-bis (4-hydroxyphenyl)-hexafluoropropane (BP3), 4,4-(1,4-phenylenediisopropylidene) bisphenol (BP4), 4,4-cyclohexylidenebisphenol (BP5), 4,4-dihydroxydiphenyl ether (BP6), 4-hydroxydiphenylmethane (BP7), 4-cumylphenol (BP8) and 4,4-dihydroxydiphenyl sulfide (BP9) were each diluted with dimethyl sulfoxide to final concentrations ranging from  $10^{-7}$  to  $10^{-3}$  M in both the yeast two-hybrid system and in a fluorescence polarization system. Dilutions of  $10^{-9}$  to  $10^{-4}$  M were assayed in the E-screen, respectively. Except for BPS and BP4, the chemicals tested showed estrogenic activity in the absence of cut S9 mix preparation and the activity was enhanced with S9 mix. BPS, which was initially negative, was active with S9 mix in the yeast two-hybrid system. BP2 was weakly estrogenic with or without S9 mix. Chemicals other than BP2 were positive in the competition binding assay. All chemicals tested showed estrogenic activity in the E-screen, the concentration level of which was  $10^4$  times lower than those of the other two assays.

- **Activité estrogénique pour le BPA, BPB, BF, BPS, BP1, BP2, BP4, BP5, BP6, BP7, BP8, BP9 en fonction de la technique d'évaluation retenue.**

3/

Chen MY, Ike M, Fujita M. **Acute toxicity, mutagenicity, and estrogenicity of bisphenol-A and other bisphenols.** Environ Toxicol. 2002 Feb;17(1):80-6. *Department of Environmental Engineering, Graduate School of Engineering, Osaka University, 2-1, Yamada-Oka, Suita, Osaka 565-0871, Japan.*

#### **Abstract**

Although abundant data are available on the toxicity of bisphenol-A (2,2-bis (4-hydroxydiphenyl)propane; BPA), little is known about the toxicities of the structurally similar compounds, namely bisphenols (BPs). A variety of BPs were examined for their acute toxicity against *Daphnia magna*, mutagenicity, and estrogenic activity using the Daphtokit (Creasel Ltd.), the umu test system, and the yeast two-hybrid system, respectively, in comparison with BPA. BPA was moderately toxic to *D. magna* (48-h EC<sub>50</sub> was 10 mg/l) according to the current U.S. EPA acute toxicity evaluation standard, and it was weakly estrogenic with 5 orders of magnitude lower activity than that of the natural estrogen 17 beta-estradiol in the yeast screen, while no mutagenicity was observed. All seven BPs tested here showed moderate to slight acute toxicity, no mutagenicity, and weak estrogenic activity as well as BPA. Some of the BPs showed considerably higher estrogenic activity than BPA, and others exhibited much lower activity. Among the tested BPs, two compounds, i.e., **bisphenol-S** (bis(4-hydroxydiphenyl)sulfone) and bis(4-hydroxyphenyl)sulfide, have never been reported for their estrogenic activity previously.

- **Cette étude portant sur 7 bisphénols (dont le BPS) structurellement similaires au BPA montre qu'ils sont tous plus ou moins toxiques et qu'ils ont une activité estrogénique, pour certains d'entre eux bien plus élevée que celle du BPA et plus faible que le BPA pour d'autres.**

4/

Kuruto-Niwa R, Nozawa R, Miyakoshi T, Shiozawa T, Terao Y. **Estrogenic activity of alkylphenols, bisphenol S, and their chlorinated derivatives using a GFP expression system.** Environ Toxicol Pharmacol. 2005 Jan;19(1):121-30. *Laboratory of Microbiology and Host Defenses, School of Food and Nutritional Sciences, University of Shizuoka, 52-1 Yada, Shizuoka 422-8526, Japan.*

#### **Abstract**

Alkylphenol ethoxylates, widely used non-ionic surfactants, are biodegraded into alkylphenols such as nonylphenol (NP) and t-octylphenol (OP), short-chain ethoxylates such as NP-monoethoxylate (NP1EO) and NP-diethoxylate (NP2EO), and alkylphenoxy carboxylic acids such as 4-t-octylphenoxyacetic acid (OP1EC). **Bisphenol S** (BPS) is more heat-stable and photo-resistant than bisphenol A (BPA), and therefore replaces BPA. These chemicals could be chlorinated during wastewater treatment. We synthesized these compounds and their chlorinated derivatives to estimate their estrogenic activities using a GFP expression system. The EC<sub>50</sub> ranking of NP-related compounds was NP > ClNP > diClNP > NP1EO > ClNP1EO > NP2EO. The estrogenic activity of OP1EC was 10 times less potent than parent OP. Furthermore, BPS showed comparable estrogenic

activity with BPA. The EC(50) ranking of BPS-related compounds was  $BPA \geq BPS > \text{triClBPS} > \text{diClBPS} > \text{ClBPS}$ . Other tested BPS derivatives had no estrogenic activity. Chlorination of the tested chemicals did not enhance their estrogenic activity, in contrast to certain chlorinated BPAs. Thus, our results demonstrated that chlorinated derivatives of NP, OP, and BPS, even if artificially produced during wastewater processing, were less estrogenic than their parent chemicals, known as endocrine disruptors.

- Le Bisphénol S est plus stable à la chaleur et photo-résistant que le bisphénol A et remplace donc le BPA. Le BPS montre une activité estrogénique comparable à celle du BPA. Les dérivés du BPS et BPA lorsque chlorés (eaux usées) ont une activité estrogénique moindre que leur parent chimiques.

- BPF :

1/ [Zhang HC](#), [Chen LY](#), [Liu SS](#), [Yin DQ](#). [Jointed estrogenic activities of bisphenol A and three of its analogs]. *Huan Jing Ke Xue*. 2009 Jan;30(1):260-5. [Article in Chinese]  
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#### Abstract

The combined effect of environmental endocrine disruptors (EEDs) is one of the hottest topics. The estrogenic activities of BPA, BPAF, BPAP, BPF were tested based on recombinant gene yeast assay. Six mixtures were designed based on the result of the test, each of which had an equitoxic ratio (EC10 or EC50). The EC50 values are  $6.81 \times 10^{-6} \text{ mol} \times \text{L}^{-1}$ ,  $7.44 \times 10^{-7} \text{ mol} \times \text{L}^{-1}$ ,  $1.43 \times 10^{-5} \text{ mol} \times \text{L}^{-1}$ ,  $7.52 \times 10^{-6} \text{ mol} \times \text{L}^{-1}$  for BPA, BPAF, BPAP and BPF respectively, which reveals that the estrogenic activities order among the four bisphenols was BPAF > BPA > BPF > BPAP. The experiment shows that when BPA mixes with BPAF, BPAP and BPF in different ratios individually, different combination effects are produced. It reveals that the combined ratios of the components may affect the combined effect. The dose addition model and the independent action model are used to identify the combined effect. They are testified to be more intuitionistic and more comprehensive than other joint effect indices.

- Le potentiel estrogénique : BPAF > BPA > BPF > BPAP. Ces substances ont des effets combinés entre elles.

2/ Cabaton N, Dumont C, Severin I, Perdu E, Zalko D, Cherkaoui-Malki M, Chagnon MC. **Genotoxic and endocrine activities of bis(hydroxyphenyl)methane (bisphenol F) and its derivatives in the HepG2 cell line.** *Toxicology*. 2009 Jan 8;255(1-2):15-24. Epub 2008 Oct 7. *ENSBANA, UMR FLAVIC 1129, 1 Esplanade Erasme, 21000 Dijon, France.*

#### Abstract

Human can be exposed to bis(hydroxyphenyl)methane (**bisphenol F** or BPF) and its derivatives as environment and food's contaminants. This study was investigated to identify and to compare toxic potency of BPF, BFDGE, and two of BPF metabolites using in vitro methods. BPF did not induce any genic mutation in bacteria when the Ames test was performed according to the OECD guideline. In contrast, using Human cell lines and Comet assay, we demonstrated that BPF and **Bisphenol F** Diglycidyl Ether (BFDGE) were effective on HepG2 cell DNA fragmentation at non-cytotoxic concentrations. DHB was also positive but at higher concentrations, near its limit of solubility. Neither BPF, nor DHB induced a positive response in the micronucleus assay. The increase of micronuclei observed when cells were exposed to BFDGE was mostly due to a cytotoxic effect. Concerning endocrine activities, BPF increased the luciferase activity in HepG2 cells transiently transfected with a concentration dependant pattern, DHB also induced a positive response but at highest concentrations. Estrogenic responses in the HepG2 cells differed with the estrogen receptor (ER) involved. Using MDA-kb2 cell line stably transfected with pMMTV-neo-Luc, only BPF was anti-androgenic at the highest concentration ( $10^{-5} \text{ M}$ ). Then, we demonstrated using human cell lines, especially HepG2, BPF was the most toxic compound in term of genotoxicity and endocrine activities compared to DHB and BPF-OH, the free metabolites identified in rat urine when BPF was administrated to rats.

- Le BPF et ses dérivés contaminent l'environnement et l'alimentation. Les auteurs ont démontré en utilisant des lignées cellulaires humaines que le BPF est le composé ayant le potentiel génotoxique le plus important comparé à ses dérivés.

3/ Higashihara N, Shiraiishi K, Miyata K, Oshima Y, Minobe Y, Yamasaki K. **Subacute oral toxicity study of bisphenol F based on the draft protocol for the "Enhanced OECD Test Guideline no. 407"**. Arch Toxicol. 2007 Dec;81(12):825-32. Epub 2007 Jul 13. *Chemicals Evaluation and Research Institute, 3-822, Ishii, Hita, Oita, 877-0061, Japan.*

#### Abstract

Since **bisphenol F** (4,4'-dihydroxydiphenylmethane) has been reported to exhibit estrogen agonistic properties in the uterotrophic assay, we performed a 28-day repeated-dose toxicity study (enhanced OECD test guideline No. 407) on **bisphenol F** based on the OECD draft protocols to determine whether it has endocrine-mediated properties. **Bisphenol F** was orally administered at doses 0, 20, 100 and 500 mg/kg per day for at least 28 days, but no clear endocrine-mediated changes were detected, and it was concluded to have no endocrine-mediated effects in young adult rats. On the other hand, the main effect of **bisphenol F** was concluded to be liver toxicity based on clinical biochemical parameters and liver weight, but without histopathological changes. The no-observed-effect level for **bisphenol F** is concluded to be under 20 mg/kg per day since decreased body weight accompanied by decreased serum total cholesterol, glucose, and albumin values were observed in the female rats given 20 mg/kg per day or higher doses of **bisphenol F**.

- Les auteurs de cette étude clinique concluent que le BPF a une action hépatotoxique, sans modifications histopathologiques. La dose sans effets observés pour le BPF se situe en dessous de 20mg/kg/j.

4/ Cabaton N, Chagnon MC, Lhuguenot JC, Cravedi JP, Zalko D. **Disposition and metabolic profiling of bisphenol F in pregnant and nonpregnant rats**. J Agric Food Chem. 2006 Dec 27;54(26):10307-14. *ENSBANA, UMR 1234 Toxicologie Alimentaire, 1 esplanade Erasme, 21000 Dijon, France.*

#### Abstract

The distribution of **bisphenol F** (4,4'-dihydroxydiphenyl-methane, BPF) was studied in female Sprague-Dawley rats. Pregnant and nonpregnant animals were gavaged with a single dose of 7 or 100 mg/kg [3H]BPF and were kept for 96 h in metabolic cages. The excretion of BPF residues occurred mainly in urine (43-54% of the administered dose), which was found to contain at least six different metabolites, and to a lesser extent in feces (15-20% of the administered dose). Sulfatase treatment and subsequent high-performance liquid chromatography analyses suggest that the major urinary metabolite (more than 50% of the radioactivity present in urine) is a sulfate conjugate of BPF. At 96 h, BPF residues were detectable in all tissues examined with the largest amounts in the liver (0.5% of the dose). In pregnant rats dosed at day 17 of gestation, BPF residues were detected in the uterus, placenta, amniotic fluid, and fetuses (0.9-1.3% of the administered dose). Large amounts of radioactivity (8-10% of the dose) were still located in the digestive tract lumen at the end of the study. After administration of a single oral dose of [3H]BPF, 46% of the distributed radioactivity was excreted in bile over a 6 h period. In rats, BPF and/or its metabolites very likely undergo enterohepatic cycling, which could be responsible for the relatively high amounts of residues still excreted 4 days after BPF administration. This bisphenol is efficiently absorbed and distributed to the reproductive tract in female rats, and its residues pass the placental barrier at a late stage of gestation in rats.

- Le BPF est efficacement absorbé et distribué dans l'appareil reproducteur des rates gavées avec une dose unique du bisphénol. Ses résidus passent la barrière placentaire à un stade tardif de la gestation chez le rat.

5/ Ramilo G, Valverde I, Lago J, Vieites JM, Cabado AG. **Cytotoxic effects of BADGE (bisphenol A diglycidyl ether) and BFDGE (bisphenol F diglycidyl ether) on Caco-2 cells in vitro**. Arch Toxicol. 2006

### Abstract

Bisphenol A diglycidyl ether (BADGE) and **bisphenol F** diglycidyl ether (BFDGE) are used as starting substances for the manufacturing of epoxy resins used in internal can coatings. They are obtained by a condensation reaction between epichlorohydrin with bisphenol A and **bisphenol F**, respectively. These potential endocrine disrupting chemicals are able to enter the food chain and to reach the intestinal epithelium, causing structural and functional damages. The human colorectal adenocarcinoma cell line Caco-2 is a widely used in vitro model of the intestinal cells. The aim of this study was to characterize BADGE and BFDGE toxicity in Caco-2 cells, in particular, at the cellular and molecular level. Using several approaches, we characterized BADGE- and BFDGE-induced cell toxicity in Caco-2 cells. The treatment was done using different concentrations up to cytotoxic doses and different times of exposure to the agents. We evaluated the effect of these compounds on cell morphology, cell detachment, cell proliferation, F-actin disruption and plasma membrane integrity. Both compounds are able to induce morphological changes, cell detachment from the substratum and to inhibit cell proliferation, being these effects time and dose-dependent. Moreover, BADGE and BFDGE induce F-actin depolymerization, this effect is very potent at 24 h of incubation with the agents and a complete F-actin disruption can be observed at 200 microM BADGE or BFDGE. In addition, cell integrity is not damaged, since neither propidium iodide uptake nor LDH release takes place in Caco-2 cells exposed to high doses of these agents for 24 h.

- L'éther de Bisphénol A diglycidyle (BADGE) et l'éther de Bisphénol F diglycidyle (BFDGE) induisent des modifications morphologiques cellulaires (lignée cellulaire colorectale d'adénocarcinome humain), un détachement cellulaire du substrat et une inhibition de prolifération cellulaire, dépendants du temps et de la dose. BADGE et BFDGE induisent également une dépolymérisation de la F-actine.

*Note : L'actine est une protéine bi-globulaire de 5,46nm de diamètre importante pour l'architecture et les mouvements cellulaires*

6/ Satoh K, Ohyama K, Aoki N, Iida M, Nagai F. **Study on anti-androgenic effects of bisphenol a diglycidyl ether (BADGE), bisphenol F diglycidyl ether (BFDGE) and their derivatives using cells stably transfected with human androgen receptor, AR-EcoScreen.** Food Chem Toxicol. 2004 Jun;42(6):983-93. *Department of Environmental Health and Toxicology, Tokyo Metropolitan Institute of Public Health, 24-1 Hyakunincho 3-chome, Shinjuku-ku, Tokyo 169-0073, Japan.*

### Abstract

We studied in vitro hormonal activity of bisphenol A diglycidyl ether (BADGE) and **bisphenol F** diglycidyl ether (BFDGE), which are used as a material of interior coating for food cans. We also examined related compounds such as 2,2-bis[4-(3-chloro-2-hydroxypropoxy)phenyl]propane (BADGE.2HCl), and bis[4-(3-chloro-2-hydroxypropoxy)phenyl]methane (BFDGE.2HCl) etc. For this purpose, we constructed two stably transfected CHO-K1 cell lines (AR-EcoScreen for androgenic activity and c-luc for cell toxicity evaluation). One stably expresses luciferase with induction of androgen. The other stably expresses luciferase without androgen induction. Also, we have determined the androgenic and anti-androgenic effects of the test chemicals by reporter gene assay with these cell lines. None of the chemicals tested by this assay exhibited androgen agonistic activity. However, BADGE.2HCl and BFDGE.2HCl had the conspicuous antagonistic activity for androgen. These compounds had a high binding affinity for androgen receptor. Furthermore, these two compounds did not show the estrogenic activity in vitro assays. On the contrary, bisphenol A and **bisphenol F** exhibited anti-androgenic activity in vitro in addition to the estrogenic activity. These results suggest that these chlorohydroxy compounds of BADGE and BFDGE act as androgen antagonist through the process of binding to androgen receptor.

- Le BPA et le BPF montrent une activité estrogénique et anti-androgénique chez l'humain in vitro.

7/ Stroheker T, Picard K, Lhuguenot JC, Canivenc-Lavier MC, Chagnon MC. **Steroid activities comparison of natural and food wrap compounds in human breast cancer cell lines.** Food Chem Toxicol. 2004 Jun;42(6):887-97. UMR 1234 Toxicologie Alimentaire, University of Burgundy/INRA, 1 Esplanade Erasme, 21000 Dijon, France.

#### Abstract

In this study, we tested and compared the endocrine disruption activities of compounds in materials used to package foods (bisphenol A, **bisphenol F**, and bisphenol A diglycidylether BADGE) with natural molecules (genistein, apigenin, kaempferol, and tangeretin) in the human breast cancer cell lines MCF-7 (ER(+)) and MDA-MB453 (AR(+); GR(+)). Octylphenol was also chosen as a xenoestrogen reference. Two compounds had no estrogenic activity: BADGE and tangeretin. Genistein was the most active compound in the E-Screen assay with MCF-7, followed by octylphenol, **bisphenol F**, bisphenol A and apigenin, with kaempferol the least potent. All estrogenic compounds competed with 17beta-estradiol for binding to the MCF-7 ER and their estrogenic effects were abolished in the presence of tamoxifen, an ER antagonist. In MDA-MB453 cells transfected with pMMTVneo-Luc, all compounds had anti-androgenic activities, with octylphenol the most potent. Kaempferol, genistein, and apigenin were more potent anti-androgens than bisphenols A or F. The natural compounds had a biphasic effect on luciferase activity. At high concentrations, genistein (10(-5)M) and apigenin (10(-6)M) acted as GR agonists in transfected MDA-MB453 cells. Furthermore, apigenin, at a concentration of 10(-5)M, may act as a partial androgen receptor (AR) agonist, as nilutamide, an AR antagonist, inhibited its activity by 26%.

- **Activité estrogénique du BPF plus importante que celle du BPA. Dans une lignée cellulaire de cancer du sein humaine, BPA et BPF avaient une activité anti-androgénique.**

8/ Perez P, Pulgar R, Olea-Serrano F, Villalobos M, Rivas A, Metzler M, Pedraza V, Olea N. **The estrogenicity of bisphenol A-related diphenylalkanes with various substituents at the central carbon and the hydroxy groups.** Environ Health Perspect. 1998 Mar;106(3):167-74.

Laboratory of Medical Investigation, Department of Radiology, School of Medicine, HUSC-University of Granada, Granada, Spain.

#### Abstract

The chemical structure of hydroxylated diphenylalkanes or bisphenols consists of two phenolic rings joined together through a bridging carbon. This class of endocrine disruptors that mimic estrogens is widely used in industry, particularly in plastics. **Bisphenol F**, bisphenol A, fluorine-containing bisphenol A (bisphenol AF), and other diphenylalkanes were found to be estrogenic in a bioassay with MCF7 human breast cancer cells in culture (E-SCREEN assay). Bisphenols promoted cell proliferation and increased the synthesis and secretion of cell type-specific proteins. When ranked by proliferative potency, the longer the alkyl substituent at the bridging carbon, the lower the concentration needed for maximal cell yield; the most active compound contained two propyl chains at the bridging carbon. Bisphenols with two hydroxyl groups in the para position and an angular configuration are suitable for appropriate hydrogen bonding to the acceptor site of the estrogen receptor. Our data suggest that estrogenicity is influenced not only by the length of the substituents at the bridging carbon but also by their nature. Because diphenylalkane derivatives are widespread and their production and use are increasing, potential exposure of humans to estrogenic bisphenols is becoming a significant issue. The hazardous effects of inadvertent exposure to bisphenol-releasing chemicals in professional workers and the general populations therefore deserve investigation.

- **BPA, BPF et BPAF ont une activité estrogénique.**

9/ Matsushima A, Liu X, Okada H, Shimohigashi M, Shimohigashi Y. **Bisphenol AF is a full agonist for the estrogen receptor ERalpha but a highly specific antagonist for ERbeta.** Environ Health Perspect. 2010 Sep;118(9):1267-72. Epub 2010 Apr 28. Laboratory of Structure-Function Biochemistry, Department of Chemistry, Research-Education Centre of Risk Science, Faculty and Graduate School of Sciences, Kyushu University, Fukuoka, Japan.

## Abstract

### BACKGROUND:

**Bisphenol AF** has been acknowledged to be useful for the production of CF3-containing polymers with improved chemical, thermal, and mechanical properties. Because of the lack of adequate toxicity data, **bisphenol AF** has been nominated for comprehensive toxicological characterization.

### OBJECTIVES:

We aimed to determine the relative preference of **bisphenol AF** for the human nuclear estrogenic receptors ERalpha and ERbeta and the **bisphenol A**-specific estrogen-related receptor ERRgamma, and to clarify structural characteristics of receptors that influence **bisphenol AF** binding.

### METHODS:

We examined receptor-binding activities of **bisphenol AF** relative to [3H]17beta-estradiol (for ERalpha and ERbeta) and [3H]**bisphenol A** (for ERRgamma). Functional luciferase reporter gene assays were performed to assess receptor activation in HeLa cells.

### RESULTS:

We found that **bisphenol AF** strongly and selectively binds to ERs over ERRgamma. Furthermore, **bisphenol AF** receptor-binding activity was three times stronger for ERbeta [IC50 (median inhibitory concentration) = 18.9 nM] than for ERalpha. When examined using a reporter gene assay, **bisphenol AF** was a full agonist for ERalpha. In contrast, it was almost completely inactive in stimulating the basal constitutive activity of ERbeta. Surprisingly, **bisphenol AF** acted as a distinct and strong antagonist against the activity of the endogenous ERbeta agonist 17beta-estradiol.

### CONCLUSION:

Our results suggest that **bisphenol AF** could function as an endocrine-disrupting chemical by acting as an agonist or antagonist to perturb physiological processes mediated through ERalpha and/or ERbeta.

- Le bisphénol AF pourrait fonctionner comme un perturbateur endocrinien en agissant comme un agoniste ou un antagoniste des récepteurs des estrogènes ERalpha et /ou ERbeta.

10/ Kitamura S, Suzuki T, Sanoh S, Kohta R, Jinno N, Sugihara K, Yoshihara S, Fujimoto N, Watanabe H, Ohta S **Comparative study of the endocrine-disrupting activity of bisphenol A and 19 related compounds**. *Toxicol Sci.* 2005 Apr;84(2):249-59. Epub 2005 Jan 5. *Graduate School of Biomedical Sciences, Hiroshima University, Kasumi 1-2-3, Minami-ku, Hiroshima 734-8551, Japan.*

## Abstract

The endocrine-disrupting activities of **bisphenol A** (BPA) and 19 related compounds were comparatively examined by means of different in vitro and in vivo reporter assays. BPA and some related compounds exhibited estrogenic activity in human breast cancer cell line MCF-7, but there were remarkable differences in activity. Tetrachlorobisphenol A (TCBPA) showed the highest activity, followed by **bisphenol B**, BPA, and tetramethylbisphenol A (TMBPA); 2,2-bis(4-hydroxyphenyl)-1-propanol, 1,1-bis(4-hydroxyphenyl)propionic acid and 2,2-diphenylpropane showed little or no activity. Anti-estrogenic activity against 17beta-estradiol was observed with TMBPA and tetrabromobisphenol A (TBBPA). TCBPA, TBBPA, and BPA gave positive responses in the in vivo uterotrophic assay using ovariectomized mice. In contrast, BPA and some related compounds showed significant inhibitory effects on the androgenic activity of 5alpha-dihydrotestosterone in mouse fibroblast cell line NIH3T3. TMBPA showed the highest antagonistic activity, followed by **bisphenol AF**, **bisphenol AD**, **bisphenol B**, and BPA. However, TBBPA, TCBPA, and 2,2-diphenylpropane were inactive. TBBPA, TCBPA, TMBPA, and 3,3'-dimethylbisphenol A exhibited significant thyroid hormonal activity towards rat pituitary cell line GH3, which releases growth hormone in a thyroid hormone-dependent manner. However, BPA and other derivatives did not show such activity. The results suggest that the 4-hydroxyl group of the A-phenyl ring and the B-phenyl ring of BPA derivatives are required for these hormonal activities, and substituents at the 3,5-positions of the phenyl rings and the bridging alkyl moiety markedly influence the activities.

- Dans la lignée cellulaire de cancer du sein MCF-7, le TCBPA (dérivé du BPA) avait l'activité estrogénique la plus élevée, suivi par le bisphénol B, le BPA et le TMBPA. Le TMBPA et le TBBPA montrent une activité

anti-estrogénique contre le 17 bêta-estradiol. TCBPA, TBBPA, et BPA montrent un effet utéro-trophique (prolifération des cellules de l'endomètre) chez la souris.

➤ **Cyto- et génotoxicité**

11/ Audebert M, Dolo L, Perdu E, Cravedi JP, Zalko D. **Use of the  $\gamma$ H2AX assay for assessing the genotoxicity of bisphenol A and bisphenol F in human cell lines.** Arch Toxicol. 2011 Jun 9. [Epub ahead of print] INRA, UMR1331, Toxalim, Research Centre in Food Toxicology, 180 chemin de Tournefeuille, BP 93173, 31027, Toulouse Cedex 3, France  
<http://www.ncbi.nlm.nih.gov/pubmed/21656223>

**Abstract**

Bisphenol A (BPA) and bisphenol F (BPF) are widely used to manufacture plastics and epoxy resins. Both compounds have been shown to be present in the environment and are food contaminants, with, as a result, a low but chronic exposure of humans. However, the fate and possible bioactivation of these compounds at the level of human cell lines was not completely elucidated yet. In this study, we investigated the ability of human cells (intestinal cell line: LS174T, hepatoma cell line: HepG2, and renal cell line: ACHN) to biotransform BPA and BPF, and focused on the cytotoxicity and genotoxicity of these two bisphenols, through the use of a novel and efficient genotoxic assay based on the detection of histone H2AX phosphorylation. BPA and BPF were extensively metabolized in HepG2 and LS174T cell lines, with stronger biotransformation capabilities in intestinal cells than observed in liver cells. Both cell lines produced the glucuronide as well as the sulfate conjugates of BPA. Conversely, the ACHN cell line was found to be devoid of any metabolic capabilities for the two examined bisphenols. Cytotoxicity was tested for BPA, BPF, as well as one metabolite of BPF produced in vivo in rat, namely dihydroxybenzophenone (DHB). In the three cell lines used, we observed similar ranges of toxicity, with DHB being weakly cytotoxic, BPF exhibiting an intermediary cytotoxicity, and BPA being the most cytotoxic compound tested. BPA and DHB were not found to be genotoxic, whatever the cell line examined. BPF was clearly genotoxic in HepG2 cells. These results demonstrate that some human cell lines extensively metabolize bisphenols and establish the genotoxic potential of bisphenol F.

- Les auteurs ont étudié la capacité des cellules humaines à biotransformer les bisphénols BPA et BPF et ont examiné les potentiels cytotoxiques et génotoxiques de ces composés. Les résultats montrent que le BPA et le BPF sont largement métabolisés par plusieurs lignées cellulaires, surtout dans les cellules intestinales. Le BPA, présente l'activité cytotoxique la plus importante, sans être cependant génotoxique au contraire du BPF.

12/ Sueiro RA, Suárez S, Araujo M, Garrido MJ. **Mutagenic and genotoxic evaluation of bisphenol F diglycidyl ether (BFDGE) in prokaryotic and eukaryotic systems.** Mutat Res. 2003 Apr 20;536(1-2):39-48. Laboratorio de Microbiología, Instituto de Investigación e Análises Alimentarias, Universidade de Santiago de Compostela, Campus Sur s/n, 15782, Santiago de Compostela, Spain.

**Abstract**

The epoxy resin bisphenol F diglycidyl ether (BFDGE), was examined for its mutagenicity in prokaryotic assays (Salmonella typhimurium His(-) and Escherichia coli Trp(-) tests) and its genotoxicity in eukaryotic systems (sister chromatid exchange (SCE) and micronucleus tests in human lymphocytes), in the presence or absence of an exogenous metabolizing system (S9 from rat liver). In the prokaryotic tests, the concentrations of BFDGE ranged between 100 and 5000 micro g per plate, and in the eukaryotic assays from 12.5 to 62.5 micro g/ml. The compound is able to induce mutagenic effects in bacterial strains TA100, TA1535, WP2uvrA and IC3327, as revealed by the increase observed in the number of induced revertants. With respect to the genotoxicity assays, BFDGE induces an increase in the frequency of sister chromatid exchanges and micronuclei in human peripheral blood lymphocytes.

**Génotoxicité et mutagénicité**

- Le BFDGE est capable d'induire des effets mutagènes chez plusieurs souches de bactéries. Il induit une augmentation de la fréquence d'échanges de chromatides-soeur (SCE) (test de génotoxicité) et des micronoyaux dans les lymphocytes du sang périphérique (dommages cytogénétiques).