Bisphenols

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Outline

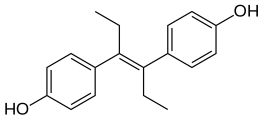
- The Basics
- Must Now Consider **All** Bisphenols, Not Just BPA
- Sources of Bisphenols
- Detoxification of Bisphenols
- Impact of Bisphenols on Health
- Assessment
- Intervention

The Basics

BPA — Troubled History

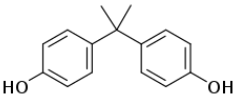
- BPA and DES are synthetic estrogens developed during the 1930s:
  - DES 'won' and was prescribed for pregnant women.
  - Discontinued due to urogenital cancers in children and many other clinical problems.
  - Very similar chemical structures.

DES

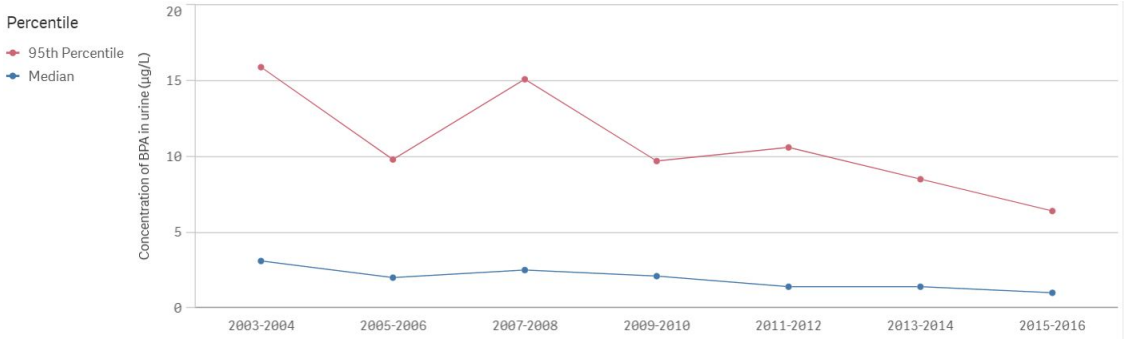


- BPA 'put on the shelf' until 1950s when its ability to harden plastics was discovered.
- So widely used very difficult to avoid exposure:
  - Technically non-persistent, but practically semi-persistent.
- Largest use is in the production of polycarbonate plastics

BPA



There is Good News



Biomonitoring - Bisphenol A (BPA) | US EPA (Accessed 2024-05-17)

However, BPA Being Replaced w Other Bisphenols

Urinary Bisphenol A (creatinine corrected) (2003 – 2010)

CAS Number 80-05-7

Geometric mean and selected percentiles of urine concentrations (in µg/g of creatinine) for the U.S. population from the National Health and Nutrition Examination Survey.

Categories (Survey Years)	Geometric Mean (95% conf. interval)	50th Percentile (95% conf. interval)	75th Percentile (95% conf. interval)	90th Percentile (95% conf. interval)	95th Percentile (95% conf. interval)	Sample Size
Total population (2003 - 2004)	2.58 (2.36-2.82)	2.50 (2.31-2.80)	4.29 (3.88-4.75)	7.67 (6.62-8.66)	11.2 (9.78-12.4)	2514
Total population (2005 - 2006)	[illegible]	[illegible] (1.64-1.79)	3.01 (2.86-3.20)	5.73 (5.29-6.36)	9.70 (8.31-10.9)	2548
Total population (2011 - 2012)	[illegible]	[illegible] (1.30-1.60)	3.00 (2.70-3.30)	5.60 (4.90-6.50)	9.40 (7.70-11.2)	2489
Total population (2013 - 2014)	1.28 (1.20-1.36)	1.30 (1.20-1.40)	2.50 (2.40-2.70)	4.90 (4.10-5.60)	7.70 (6.80-8.30)	2686

2003/4 = 2.58

2013/4 = 1.28

Urinary Bisphenol F (creatinine corrected) (2013 – 2014)

CAS Number 80-05-7

Geometric mean and selected percentiles of urine concentrations (in µg/g of creatinine) for the U.S. population from the National Health and Nutrition Examination Survey.

Categories (Survey Years)	Geometric Mean (95% conf. interval)	50th Percentile (95% conf. interval)	75th Percentile (95% conf. interval)	90th Percentile (95% conf. interval)	95th Percentile (95% conf. interval)	Sample Size
Total population (2013 - 2014)	[illegible]	.444 (.385-.515)	1.07 (.899-1.21)	3.33 (2.39-4.76)	8.39 (5.90-12.0)	2680

2013/4 = 0.53

Urinary Bisphenol S (creatinine corrected) (2013 – 2014)

CAS Number 80-05-7

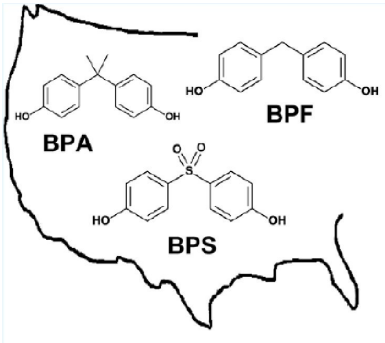
Geometric mean and selected percentiles of urine concentrations (in µg/g of creatinine) for the U.S. population from the National Health and Nutrition Examination Survey.

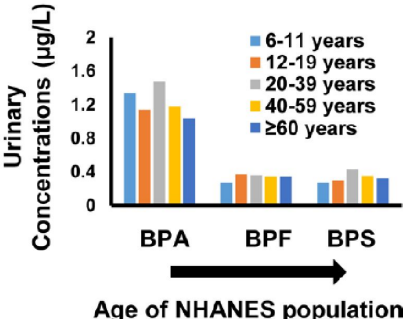
Categories (Survey Years)	Geometric Mean (95% conf. interval)	50th Percentile (95% conf. interval)	75th Percentile (95% conf. interval)	90th Percentile (95% conf. interval)	95th Percentile (95% conf. interval)	Sample Size
Total population (2013 - 2014)	.428 (.387-.474)	.380 (.352-.411)	.797 (.690-.903)	1.80 (1.49-2.10)	3.33 (2.60-4.68)	2680

2013/4 = 0.43

Bisphenols: Ubiquitous Exposure

- Nutrition Examination Survey (NHANES) 2013–2014
  - BPA, BPS, and BPF were detected in 95.7, 89.4, and 66.5% of randomly selected urine samples





Lehmler HJ, Liu B, Gadogbe M, et al. Exposure to Bisphenol A, Bisphenol F, and Bisphenol S in U.S. Adults and Children: The National Health and Nutrition Examination Survey 2013-2014. ACS Omega. 2018 Jun 30;3(6):6523-6532.

Alternatives Are NOT Safer!

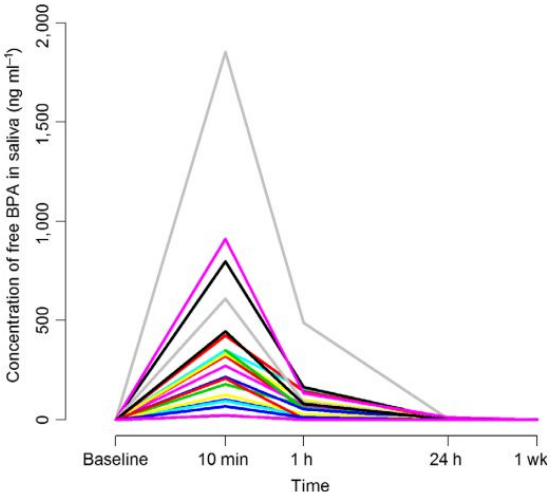
- Typical substitutes are BPF, BPS, BPZ
- Very similar endocrine disruption
- Considered semi-persistent because so prevalent in society
- As BPA levels have gone down, other bisphenols have gone up in proportion

Bisphenol - Wikipedia

Structural formula	Name
	Bisphenol A
	Bisphenol AP
	Bisphenol AF
	Bisphenol B
	Bisphenol BP
	Bisphenol C
	Bisphenol C 2
	Bisphenol E
	Bisphenol F
	Bisphenol G
	Bisphenol M
	Bisphenol S
	Bisphenol P
	Bisphenol PH
	Bisphenol TMC
	Bisphenol Z

Sources of Bisphenols

Plastic Tooth Fillings



Berge, T. L. L., Lygre, G. B., Lie, S. A., Lindh, C. H., & Björkman, L. (2019). Bisphenol A in human saliva and urine before and after treatment with dental polymer-based restorative materials. European journal of oral sciences, 127(5), 435–444. https://doi.org/10.1111/eos.12647

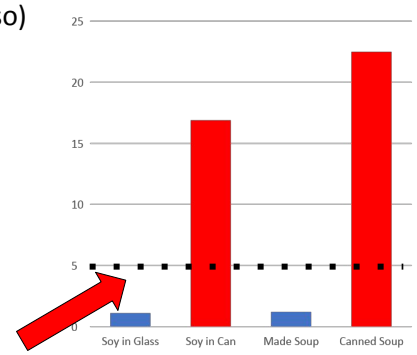
Sources of Bisphenols

- ID 7 polycarbonate food containers
- Food stored in cans
- Receipts
- Some clothing
- Old children's bottles (banned now)

Packaging Puts BPA Into Food

- One 12oz serving daily for 1 week of either fresh soup or canned lentil soup (Progresso)
  - 12-fold increase in BPA
- 2 servings of 6 ounces Soy milk in can compared to glass
  - 16-fold increase in BPA
  - Systolic BP elevated 4.5 mm Hg

- **Diabetes 2x risk threshold?**



Carwile JL, Ye X, Zhou X, et al. Canned soup consumption and urinary bisphenol A: a randomized crossover trial. JAMA. 2011 Nov 23;306(20):2218-20.
Bae S, Hong YC. Exposure to bisphenol A from drinking canned beverages increases blood pressure: randomized crossover trial. Hypertension. 2015 Feb;65(2):313-9.

Health Effects of Bisphenols

Bisphenols Increase Diabetes Risk

- 242 PubMed hits:
  - Bisphenols / diabetes / human

Odd ratios (ORs) [95% confidence interval (CI)] for T2DM by log-transformed urinary concentrations of bisphenols in logistic regression analyses.

	Unadjusted		Multiple adjusted [a]	
	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
BPAF [b]	4.70 (3.29, 6.71)	<0.001	4.95 (3.15, 7.79)	<0.001
BPS [b]	1.46 (1.22, 1.74)	<0.001	1.73 (1.37, 2.18)	<0.001
BPA [b]	0.85 (0.69, 1.05)	0.138	1.02 (0.78, 1.32)	0.897
∑BPs [b]	1.01 (0.75, 1.37)	0.936	1.28 (0.89, 1.85)	0.189

Note: BPAF, bisphenol AF; BPS, bisphenol S; BPA, bisphenol A; ∑BPs, the mass sum of eight bisphenol concentrations.

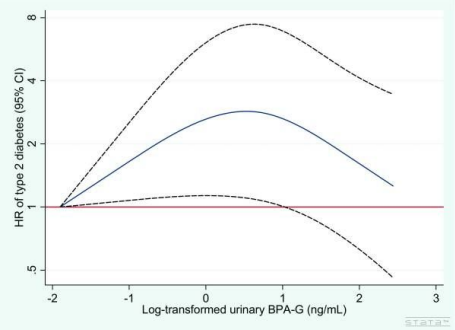
[a] Adjusted for sex, age, body mass index, urinary creatinine, smoking and alcohol-drinking status, exercising status, education level, family history of diabetes, and blood pressure.

[b] Variable was log-transformed.

Duan Y, Yao Y, Wang B, *et al.* Association of urinary concentrations of bisphenols with type 2 diabetes mellitus: A case-control study. Environ Pollut. 2018 Dec;243(Pt B):1719-1726. PMID: 30408859.

Bisphenols & Diabetes

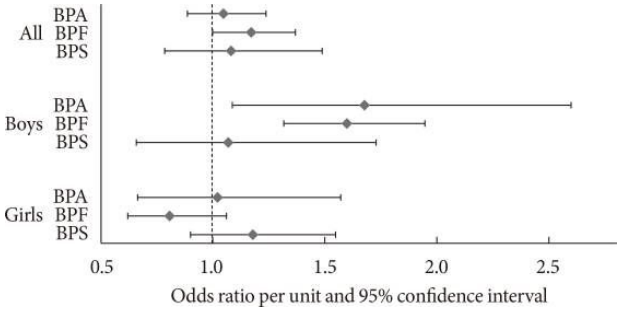
- French Cohort Study, 755 participants without diabetes at baseline
- Compared with participants with the lowest average BPA exposure (below the first quartile), participants in the second, third, and fourth quartile groups of exposure had a near doubling of the risk of type 2 diabetes, with a hazard ratio of 2.56, 2.35, and 1.56 respectively.
- The **detection** of BPS-G at one or both time points in the study was associated with a *HR 2.81* for incident diabetes.



Rancière F, Botton J, Slama R, et al; D.E.S.I.R. Study Group. Exposure to Bisphenol A and Bisphenol S and Incident Type 2 Diabetes: A Case-Cohort Study in the French Cohort D.E.S.I.R. Environ Health Perspect. 2019 Oct;127(10):107013.

Bisphenols & Obesity

- U.S. National Health and Nutrition Examination Survey 2013 to 2014, 745 participants aged 6 to 17 years old
- Adjusted OR of general obesity comparing the highest with lowest quartile of urinary bisphenol levels was 1.74 for BPA, 1.54 for BPF, and 1.36 for BPS
- Stronger association in boys



Liu B, Lehmler HJ, Sun Y, et al. Association of Bisphenol A and Its Substitutes, Bisphenol F and Bisphenol S, with Obesity in United States Children and Adolescents. Diabetes Metab J. 2019 Feb;43(1):59-75.

BPA Levels Correlate with Obesity

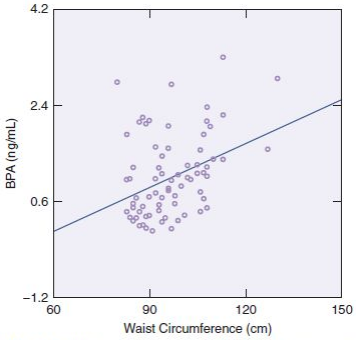
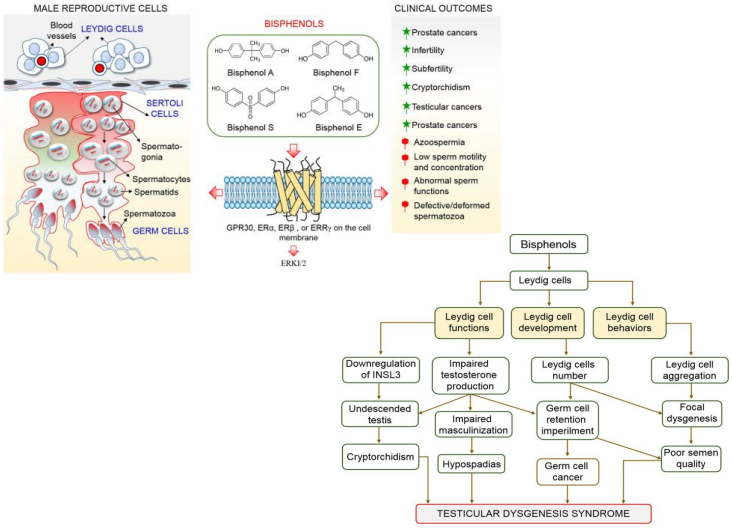


FIG. 25.3 BPA correlates with visceral fat. (From Savastano, S., Tarantino, G., D'Esposito, V., Passaretti, F., Cabaro, S., Liotti, A., Liguoro, D., Perruolo, G., Ariemma, F., Finelli, C., Beguinot, F., Formisano, P., Valentino, R. [2015]. Bisphenol-A plasma levels are related to inflammatory markers, visceral obesity and insulin-resistance: A cross-sectional study on adult male population. *Journal of Translational Medicine, 13*,169.) Licensed under a Creative Commons Attribution-ShareAlike 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

Bisphenols & Reproductive Health

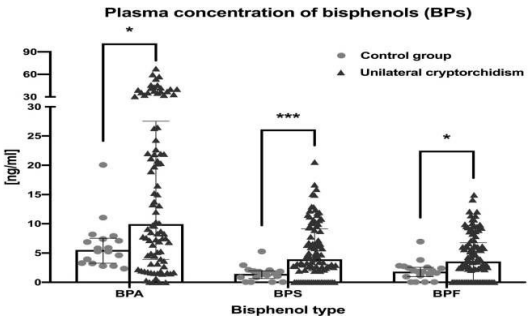
- **Testis a major target of bisphenols**
  - BPA binds with cytoplasm estrogen receptors (cERs) or ERs located in the nucleus (nERs), influencing the transcription/translation of genes and proteins
  - BPA binds to G-protein coupled receptor (GPR30) on the membrane of testicular cells, especially sperm cells
  - BPA causes reactive oxygen species-mediated damage and apoptosis through activation of pro-apoptotic signaling
  - BPA, BPB, BPF, and BPS abated the number of germ cells (spermatocytes and spermatids), reduced sperm motility, and daily sperm production in animal studies



Adegoke EO, Rahman MS, Pang MG. Bisphenols Threaten Male Reproductive Health via Testicular Cells. Front Endocrinol (Lausanne). 2020 Sep 11;11:624.

Bisphenols & Cryptorchidism

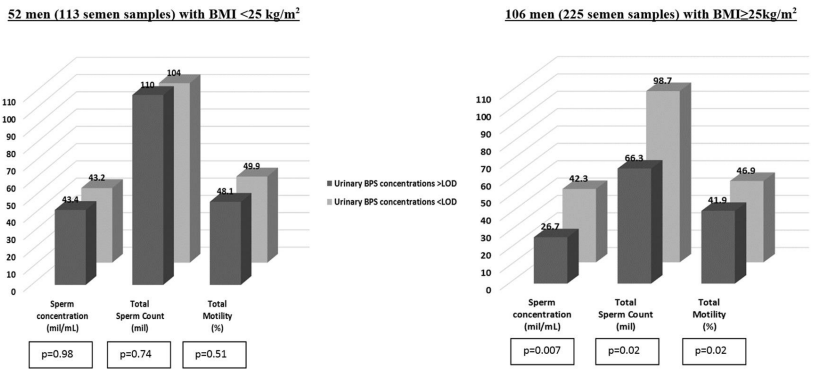
- Plasma levels of BPA, BPS and BPF were significantly higher compared to the control subjects.
  - BPA: median value: 9.95 ng/mL vs. 5.54 ng/mL, p<0.05.
  - BPS: median value: 3.93 ng/mL vs. 1.45 ng/mL, p<0.001.
  - BPF: median value: 3.56 ng/mL vs. 1.83 ng/mL, p<0.05.



Komarowska MD, Grubczak K, Czerniecki J, et al. Identification of the Bisphenol A (BPA) and the Two Analogues BPS and BPF in Cryptorchidism. Front Endocrinol (Lausanne). 2021 Jul 14;12:694669.

BPS Decreases Male Fertility

- Damaging effects primarily in overweight men



Ghayda RA, Williams PL, Chavarro JE, et al. Urinary bisphenol S concentrations: Potential predictors of and associations with semen quality parameters among men attending a fertility center. Environ Int. 2019 Oct;131:105050

BPA & Cardiovascular Disease

- Highest level of urinary BPA was associated with increased prevalence of myocardial infarction (MI) (OR = 1.73, 95% CI = 1.11-2.69) and stroke (OR = 1.61, 95% CI = 1.09-2.36),
- Per unit (μg/g creatinine) increment in ln-transformed BPA concentration was shown to be significantly associated with 19%, 19%, 25%, 29%, 20%, and 16% increased odds ratios of prevalence of congestive heart failure, coronary heart disease (CHD), angina pectoris, MI, stroke and total CVD among total participants, respectively

Cai S, Rao X, Ye J, Ling Y, Mi S, Chen H, Fan C, Li Y. Relationship between urinary bisphenol a levels and cardiovascular diseases in the U.S. adult population, 2003-2014. Ecotoxicol Environ Saf. 2020 Apr 1;192:110300.

Bisphenols & Depression

- U.S. National Health and Nutrition Examination Survey (NHANES)
  - In the general population, no significant association was observed between urinary BPA, BPS, and BPF and depressive symptoms
  - However, urinary BPS was positively associated with depressive symptoms in men (OR 2.9)
  - In elderly men (≥60 years old), urinary BPA and **BPS** were positively correlated with depressive symptoms with ORs of 5.53 and **28.89**, respectively.
  - Inverse association in elderly women

Hao K, Luo J, Sun J, et al. Associations of urinary bisphenol A and its alternatives bisphenol S and F concentrations with depressive symptoms among adults. Chemosphere. 2021 Sep;279:130573.

Bisphenols & Asthma

- 2013-2016 National Health and Nutrition Examination Survey (NHANES), 3,538 participants aged 12 years or older
- BPF, BPS, and BPA were detected in 57.1%, 88.4%, and 94.8% of the urine samples
- Urinary BPF detection was positively associated with current asthma (OR 1.54), and hay fever (OR 1.66).
- Urinary BPS was associated with increased odds of current asthma in men (OR 1.64) and urinary BPA was associated with increased odds of asthma without hay fever in children aged 6-11 years (OR 2.65).

Mendy A, Salo PM, Wilkerson J, et al. Association of urinary levels of bisphenols F and S used as bisphenol A substitutes with asthma and hay fever outcomes. Environ Res. 2020 Apr;183:108944.

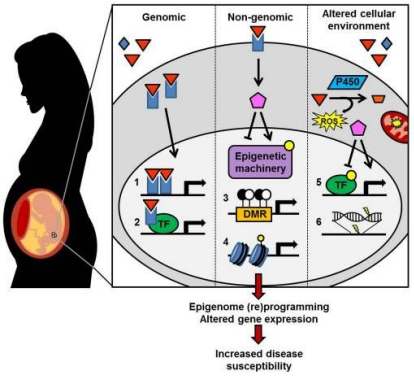
Bisphenols & IQ

- Swedish Environmental Longitudinal Mother and Child, Asthma and Allergy (SELMA) study
- ~800 children followed for 7 years
- All three bisphenols were detected in over 90% of the women
- Prenatal BPF exposure was associated with decreased full scale IQ (β = -1.96), as well as with a decrease in all four sub scales covering verbal comprehension, perceptual reasoning, working memory and processing speed.
- This association corresponded to a 1.6-point lower IQ score for an inter-quartile-range (IQR) change in prenatal BPF exposure

Bornehag CG, Engdahl E, Unenge Hallerbäck M, et al. Prenatal exposure to bisphenols and cognitive function in children at 7 years of age in the Swedish SELMA study. Environ Int. 2021 May;150:106433.

Transgenerational Effects

- BPA was shown to alter DNA methylation in primordial germ cells and cultured oocytes
- Two examples in mice:
  - Exposure in the F0 pregnant mouse altered behavior up to the F4 generation, and the transgenerational phenotype was accompanied by altered expression of the *Avp* and *Oxt* genes, which encode for neuropeptides involved in social recognition
  - Altered DNA methylation was observed in F1 and F2 male mice at a differentially methylated region (DMR) that regulates expression of the imprinted *Igf2* gene, a critical fetal growth-promoting factor with roles in metabolic homeostasis

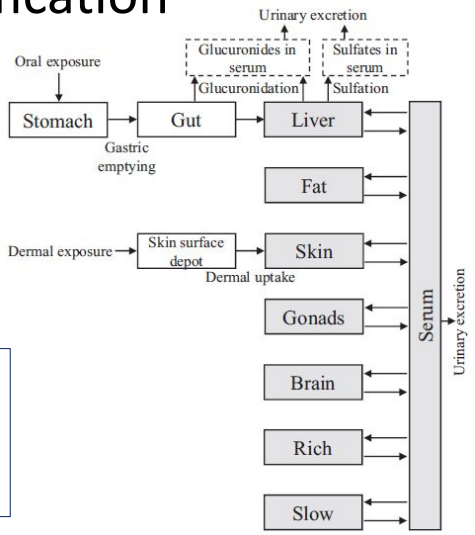


Wolstenholme JT, Goldsby JA, Rissman EF. Transgenerational effects of prenatal bisphenol A on social recognition. Horm Behav. 2013 Nov;64(5):833-9.
Xin F, Susiarjo M, Bartolomei MS. Multigenerational and transgenerational effects of endocrine disrupting chemicals: A role for altered epigenetic regulation? Semin Cell Dev Biol. 2015 Jul;43:66-75.

Bisphenol Detoxification

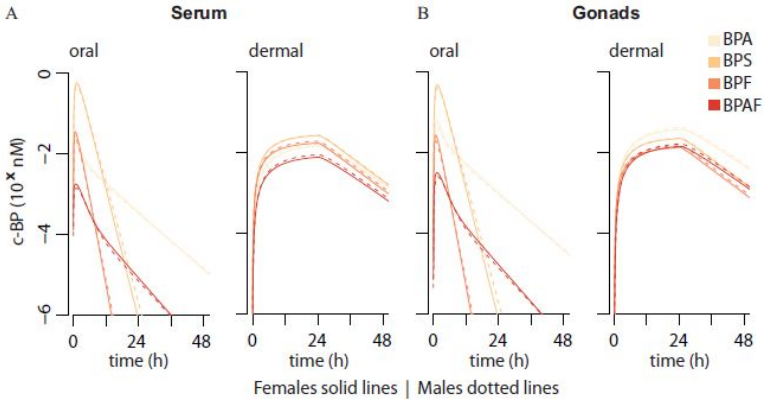
Bisphenol Detoxification

- Non-persistent.
- ½ lives 0.5–4.0 days.



Karrer C, Roiss T, von Goetz N, Gramec Skledar D, *et al*. Physiologically Based Pharmacokinetic (PBPK) Modeling of the Bisphenols BPA, BPS, BPF, and BPAF with New Experimental Metabolic Parameters: Comparing the Pharmacokinetic Behavior of BPA with Its Substitutes. Environ Health Perspect. 2018 Jul 10;126(7):077002PMID: 29995627

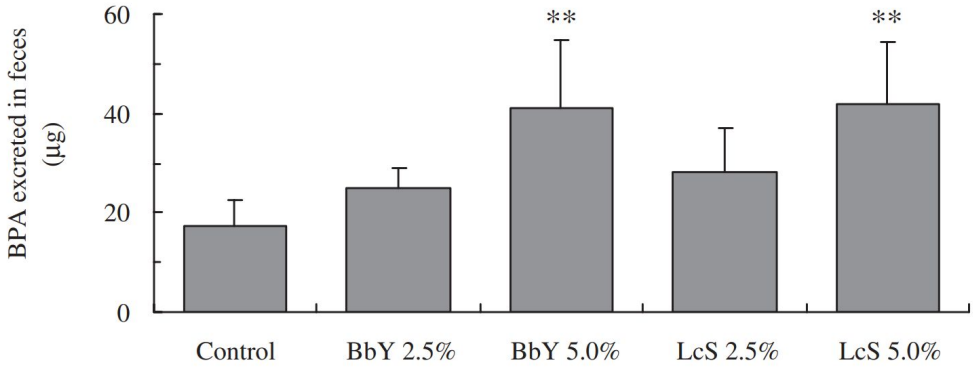
Bisphenol Half-Lives



Karrer C, Roiss T, von Goetz N, Gramec Skledar D, *et al.* Physiologically Based Pharmacokinetic (PBPK) Modeling of the Bisphenols BPA, BPS, BPF, and BPAF with New Experimental Metabolic Parameters: Comparing the Pharmacokinetic Behavior of BPA with Its Substitutes. Environ Health Perspect. 2018 Jul 10;126(7):077002PMID: 29995627

Probiotics Decrease BPA Load

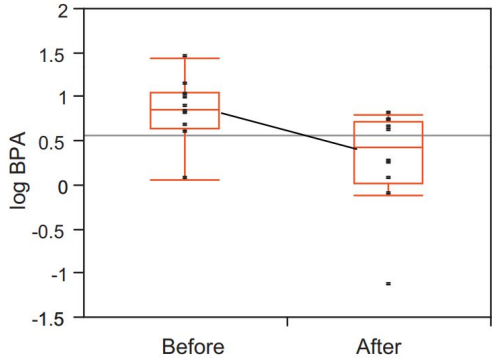
- Rat study



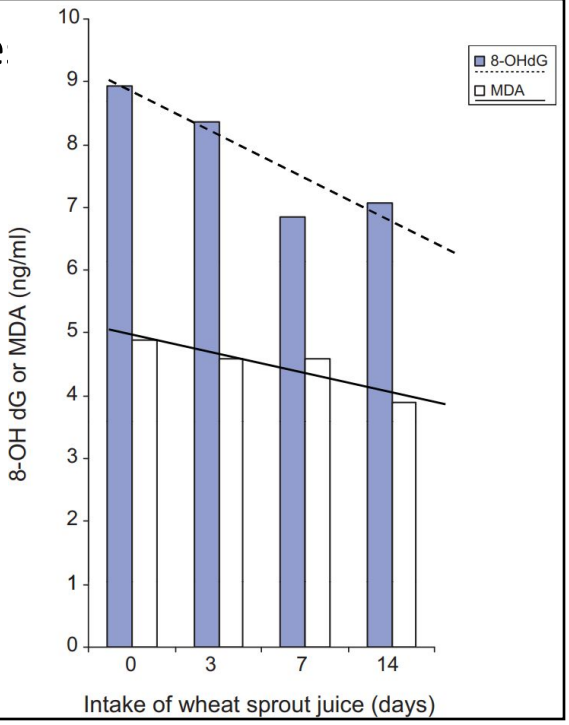
Oishi K, Sato T, Yokoi W, Yoshida Y, Ito M, Sawada H. Effect of probiotics, Bifidobacterium breve and Lactobacillus casei, on bisphenol A exposure in rats. *Biosci Biotechnol Biochem*. 2008;72(6):1409-1415.

Wheat Sprout Juice Decreases BPA and DNA Damage

- All benefit could be reduced exposure

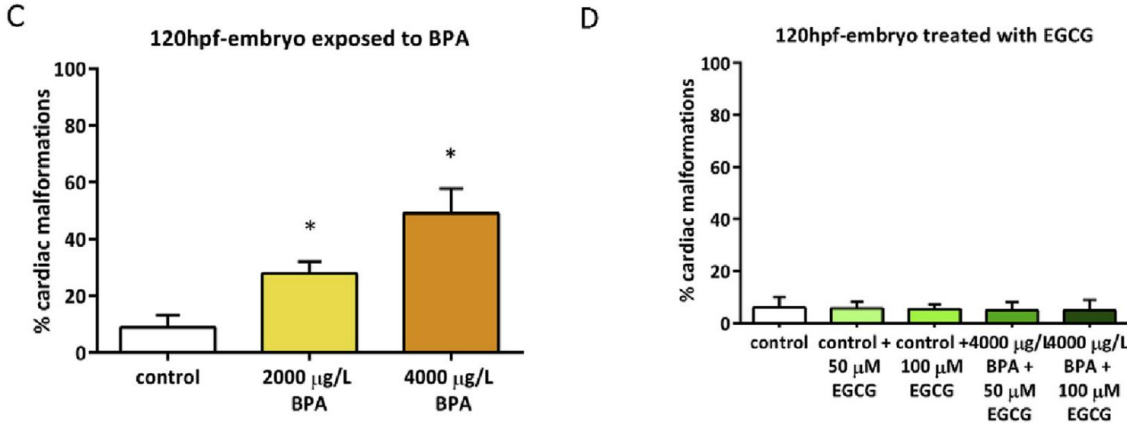


Yi B, Kasai H, Lee HS, Kang Y, Park JY, Yang M. Inhibition by wheat sprout (Triticum aestivum) juice of bisphenol A-induced oxidative stress in young women. *Mutat Res*. 2011;724(1-2):64-68



ECGC Totally Protects Against BPA Heart Damage

- Zebra embryo study



Lombó M, González-Rojo S, Fernández-Díez C, Herráez MP. Cardiogenesis impairment promoted by bisphenol A exposure is successfully counteracted by epigallocatechin gallate. *Environ Pollut*. 2019;246:1008-1019

Assessment and Intervention

BPA Assessment

- Total bisphenols preferred, but not commercially available
- Urinary bisphenols
  - The lower the better!

Clinical Application

- Non-persistent toxins
- Avoidance primary strategy
  - Must avoid ALL bisphenols
- Antioxidants and other natural molecules help increase detoxification and protect from damage