NUTRIZIONE E DISRUPTORS ENDOCRINI

(ENDOCRINE DISRUPTORS CHEMICALS, EDCs)

OVAIO

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Conflitti di interesse

Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni non ho avuto rapporti diretti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario.

ENVIRONMENTAL FACTORS… THE SIDE EFFECTS OF CIVILIZATION

EDCs e …… NUTRIZIONE ⇒

~~EDCs e … FARMACI~~

~~EDCs e … 'MEDICAL/DENTAL DEVICES'~~

~~EDCs e … 'POLLUTANTS'~~

~~EDCs e … COSMETICI~~

(EFSA 2018)

AGENTI CHIMICI PRESENTI A VARIO TITOLO **ANCHE** NEI CIBI O IN MATERIALI CHE POSSONO VENIRE IN CONTATTO CON I CIBI

(BPA) POLICARBONATI:
bottiglie di plastica riciclabili, biberon, tazze, materiale x microonde, contenitori x cibi, piatti …

RESINE EPOSSIDICHE:
rivestimento interno di contenitori x cibi o bevande

FITOESTROGENI IN ALIMENTI:
soia, genisteina …

FOOD ADDITIVES:
dolcificanti, sodio monoglutamato, coloranti …

ALIMENTI:
zucchero, caffeina, alcool …

Endocrine disruption by dietary phyto-oestrogens: impact on dimorphic sexual systems and behaviours

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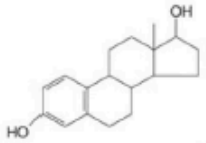
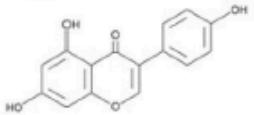
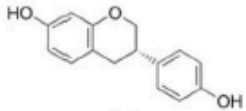
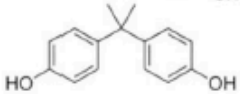
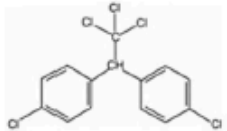
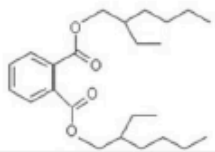
Proc Nutr Soc. 2017 May ; 76(2): 130–144

MOLECOLE ESTROGENO-SIMILI

INTERFERENZA CON RECETTORI ESTROGENICI O STEROIDOGENESI

Fig. 1.
Structures of some well-known anthropogenic and naturally occurring endocrine-disrupting compounds. BPA, bisphenol A; DDT, dichlorodiphenyltrichloroethane; DEPH, di(2-ethylhexyl)phthalate.

Compound	Structure	Classification
Estradiol		Endogenous Estrogen
Genistein		Soy Isoflavone
Equol		Metabolite of Daidzein
BPA		Plastics Component
DDT		Pesticide
DEHP		Phthalate

BISFENOLO A

A review of dietary and non-dietary exposure to bisphenol-A

Tinne Geens [a,k], Dominique Aerts [b,k], Carl Berthot [c,k], Jean-Pierre Bourguignon [d,k], Leo Goeyens [e,k], Philippe Lecomte [f,k], Guy Maghuin-Rogister [g,k], Anne-Madeleine Pironnet [h,k], Luc Pussemier [i,k], Marie-Louise Scippo [g,k], Joris Van Loco [j,k], Adrian Covaci [a,k,*]

Food and Chemical Toxicology 50 (2012) 3725–3740

si lega ai rececettori estrogenici con capacità 1000-5000 volte inferiore rispetto al 17-beta estradiolo (FASFC, 2009; Roy et al., 2009)

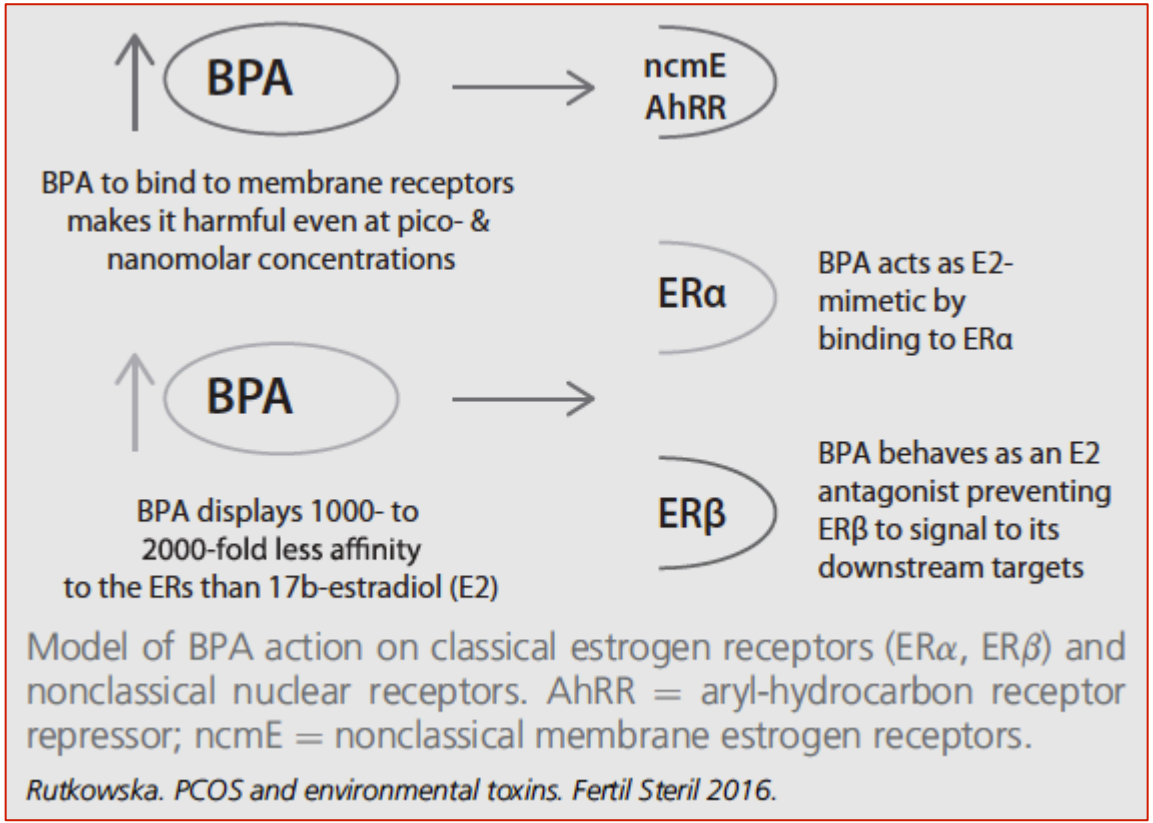
Estimated intake of BPA in children and adults.

	Age category	Estimation through dietary exposure (μg/kg bw/day)
Children		
EFSA (2006)	Infants (3–12 month)	0.2–13
	Children	5.3
Health Canada (2008)	1–4 years	0.26–1.98
	5–11 years	0.15–1.28
Chapin et al. (2008)	Infants-bottle fed	1–11
	Infants-breast fed	0.2–1
	Children (6–12 m)	1.7–13
	Children (2–6 years)	0.04–14.7
FDA (2009)	0–12 m	0.3–0.6
	12–24 m	0.5–1.1
	>2 years	0.1–0.3
ANSES (2010)	Infants (<36 m)	0.1–0.5
	Children (3–17 years)	0.2–0.6
WHO (2010)	Infants 0–6 m	0.01–4.5
	Infants 6–36 m	0.01–3.0
	Children > 3 years	0.2–1.9
Adults		
EFSA (2006)	Adults	1.5
Health Canada (2008)	12–19 years	0.09–0.73
	>20 years	0.07–0.60
Chapin et al. (2008)	Adults	0.008–1.5
FDA (2009)	>2 years	0.1–0.3
ANSES (2010)	Adults	0.1–0.3
WHO (2010)	Adults	0.4–4.2

Overview of BPA in canned food samples and canned beverages.

Country	Sample size	Detection freq. (%)	Range	Refs.
Canned food (ng/g)				
US	78	91	<2–730	Noonan et al. (2011)
US	97	59	<0.2–65	Schecter et al. (2010)
Canada	78	99	<0.6–534	Cao et al. (2010)
Japan	48	92	<1–842	Sajiki et al. (2007)
Korea	61	64	<3–136	Lim et al. (2009a)
Belgium	21	100	0.2–169	Geens et al. (2010)
Beverage cans (ng/mL)				
Spain	11	64	<0.05–0.61	Gallart-Ayala et al. (2010)
Canada	69	100	0.03–4.5	Cao et al. (2009a)
Belgium	45	91	<0.02–8.1	Geens et al. (2010)
Portugal	30	70	<0.01–4.7	Cunha et al. (2011)

BISFENOLO A



Model of BPA action on classical estrogen receptors (ERα, ERβ) and nonclassical nuclear receptors. AhRR = aryl-hydrocarbon receptor repressor; ncmE = nonclassical membrane estrogen receptors.

Rutkowska. PCOS and environmental toxins. Fertil Steril 2016.

BISFENOLO A

Body fluids		
Urine (Norway, pregnant women)	4.50 μg/dm³	Ye et al. (2009)
(Belgium, adults)	2.55 μg/dm³	Pirard et al. (2012)
(Germany, adults)	1.49 μg/dm³	Koch et al. (2012)
(USA, adults)	2.50 μg/dm³	Calafat et al. (2008)
(Denmark, children and adolescents)	1.49 μg/dm³	Frederiksen et al. (2013)
(USA, children)	4.50 μg/dm³	Calafat et al. (2008)
(USA, premature infants with intense medical care)	30.0 μg/dm³	Calafat et al. (2009)
Sweat	10–82 μg/dm³	Genuis et al. (2012)
Woman milk	1.1–3.4 μg/dm³	Fernandez et al. (2007)
Tissues		
Blood (unconjugated BPA)	0.2–20 ng/dm³	Sajki et al. (1999)
(Conjugated BPA, pregnant woman)	4.0 μg/dm³	Vandenberg et al. (2012)
(Conjugated BPA, non-pregnant women)	1.0 μg/dm³	Vandenberg et al. (2012)
Placenta	1.0–104 μg/kg	Sajki et al. (1999)
Adipose (adults)	3.19 μg/kg	Fernandez et al. (2007)
Liver (adults)	1.48 μg/kg	Geens et al. (2012)
Brain (adults)	0.91 μg/kg	Geens et al. (2012)
Drinking water		
Tap water (Europe, Asia, North America)	0.099–0.317 μg/dm³	Arnold et al. (2013)
Bottled water (France)	0.07–4.21 μg/dm³	Colin et al. (2013)
Food		
Cereals	1–3.8 μg/kg	Niu et al. (2012)
Meat	0.49–56 μg/kg	Shao et al. (2007)
Fish	7.1–102.7 μg/kg	Munguia-Lopez et al. (2005)
Vegetables and fruits	11–95.3 μg/kg	Yoshida et al. (2001)
Canned seafood	1–99.9 μg/kg	Cunha et al. (2012)
Canned vegetables and fruits	3.7–265.6 μg/kg	Cunha and Fernandes (2013)
Tinned soft drinks	0.032–4 μg/kg	Cao et al. (2009)
Milk	1.32–176 μg/kg	O'Mahony et al. (2013)

Bisphenol A – Sources, toxicity and biotransformation

ENVIRONMENTAL TOXICOLOGY AND PHARMACOLOGY 37 (2014) 738–758

Phthalates and diet: a review of the food monitoring and epidemiology data

Samantha E Serrano[1], Joseph Braun[2], Leonardo Trasande[3,4,5], Russell Dills[7] and Sheela Sathyanarayana[1,6,7*]

Serrano *et al. Environmental Health* 2014, **13**:43

FTALATI

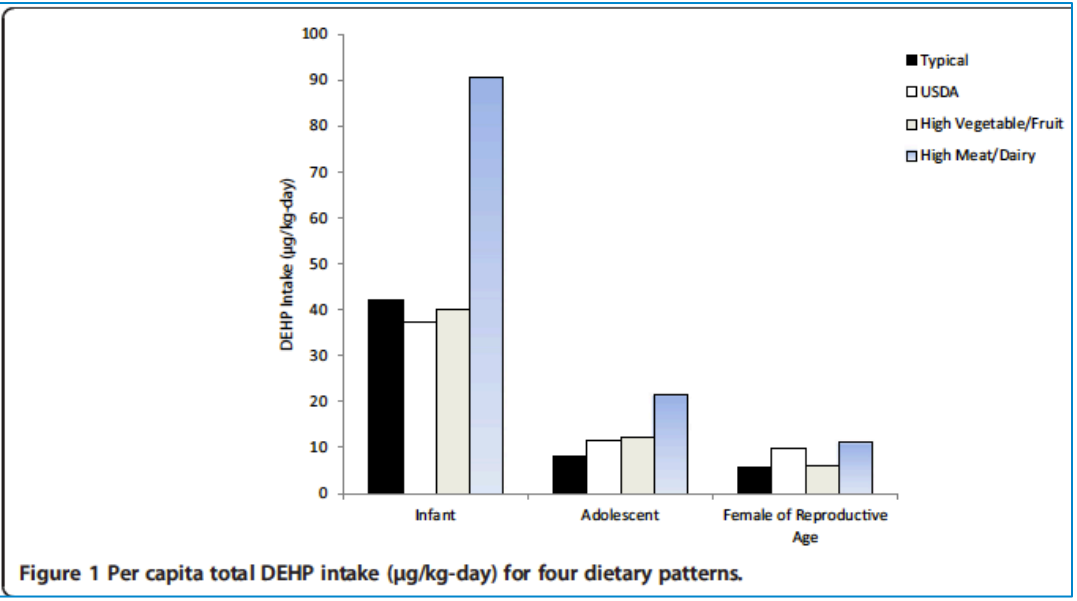


Figure 1 Per capita total DEHP intake (µg/kg-day) for four dietary patterns.

- ✓ Metaboliti degli 8 principali ftalati si trovano nell'89-98% della popolazione degli USA (Zota et al., 2104)
- ✓ L'esposizione giornaliera stimata del DEHP (2-etil-exil-ftalato) media è 3-30 mcg/kg/die (Hannon & Flaws 2015)

FTALATI

Table 3 Per capita total DEHP dietary intake for eight major food groups in average diets of US infants, adolescents and females of reproductive age[a]

Food group	Conc.[b] (μg/kg)	Young infants (1–2 years)		Adolescents (13–19 years)		Females of reproductive age (13–49)	
		Food consumption[c] (g/kg-day)	Daily intake (%) (μg/kg-day)	Food consumption[c] (g/kg-day)	Daily intake (%) (μg/kg-day)	Food consumption[c] (g/kg-day)	Daily intake (%) (μg/kg-day)
Total dairy	712.4	43.2	30.8 (73.1)	5.5	3.9 (47.9)	3.8	2.7 (47.2)
Total meat	209.6	4	0.8 (2.0)	2	0.4 (5.1)	1.6	0.3 (5.8)
Total egg	21.1	1.40[d, e]	0.03 (0.1)	0.25[d, f]	0.01 (0.1)	0.23[d, g]	0.01 (0.1)
Total fish	180.4	0.26	0.05 (0.1)	0.13[h]	0.02 (0.3)	0.19	0.03 (0.6)
Total grain	187.4	6.4	1.2 (2.8)	2.4	0.5 (5.5)	1.9	0.04 (6.2)
Total vegetable	131.9	6.7	0.9 (2.1)	2.3	0.3 (3.7)	2.5	0.3 (5.8)
Total fruit	115.6	7.8	0.9 (2.1)	0.9	0.1 (1.3)	1	0.1 (2.0)
Total fat	1851.7	4	7.4 (17.6)	1.6[h, i]	3.0 (36.2)	1[i, j]	1.9 (32.3)
Total dietary intake	3409.7	73.76	42.1 (100)	15.08	8.2 (100)	12.22	5.7 (100)

[a](Concentration in Food/1000) *Daily Food Consumption = Daily Intake.
[b]Weighted average of all available mean concentrations in foods corresponding to one of the eight food categories. Calculated by taking the sum of each average concentration multiplied by individual number of samples and diving by total number of samples: ((avg.conc.dairy1 * n) + (avg.conc.dairy2 * n)…)/∑n.
[c]Source NHANES 2003–2006.
[d]Source USDA CSFII 1994–1996, 1998.
[e]Calculated for a 11.4 kg infant.
[f]Calculated for adolescent under 19 years old and 56.8 kg.
[g]Calculated for female 20 and over and 70 kg.
[h]11 to <21 years.
[i]Source NHANES 2007.
[j]Females 21 to <41 years.

Environmental influences on ovarian dysgenesis — developmental windows sensitive to chemical exposures

Hanna Katarina Lilith Johansson[1], Terje Svingen[1], Paul A. Fowler[2], Anne Marie Vinggaard[1] and Julie Boberg[1]

VOLUME 13 | JULY 2017 | 410

NATURE REVIEWS | ENDOCRINOLOGY

BPA

-esposizione media:

USA ed Europa: 0.03-0.04 mcg/kg/die in adulti; 5% della popolazione: 0.15

EFSA (European Food Safety Autority): 0.1-0.4 mcg/kg/die

- effetti su sviluppo ovarico in studi animali: ~20 mcg/kg/die

-no-effect level: ~20 mcg/kg/die

DEHP (dietil-exil-ftalato)

-esposizione media:

Europa: ~ 1.5 mcg/kg/die in adulti; 5% popolazione: > 4.4

USA: ~ 4 mcg/kg/die; 5% popolazione: > 34

- effetti su sviluppo ovarico in studi animali: 20 e 40 mcg/kg/die

-no-effect level: < 20 mcg/kg/die

FITOESTROGENI NELLA DIETA COME EDCs

Endocrine disruption by dietary phyto-oestrogens: impact on dimorphic sexual systems and behaviours

Heather B. Patisaul
Department of Biological Sciences, Center for Human Health and the Environment, NC State University, Raleigh, NC

Proc Nutr Soc. 2017 May ; 76(2): 130–144

SOIA

Proteina completa, no colesterolo e lattosio, ricca di fibre e carboidrati complessi, anti-ossidanti e acidi grassi liberi, … abbondanza di fitoestrogeni, quindi ormonalmente attiva

Le conseguenze sono in genere minime o potenzialmente benefiche, ma non sempre

EQUOL

Metabolita della dazdeina, più attivo degli altri metaboliti o di composti similari

Strutturalmente simili agli EDCs chimici, comportamento analogo su target molecolari e cellulari. Rischio per alcuni gruppi, feto, neonati …

Phyto-oestrogens are naturally occurring plant compounds that are structurally and/or functionally similar to mammalian oestrogens and their active metabolites.

There are several phyto-oestrogen classes, but the most hormonally active are the phenolic compounds of which the isoflavones and coumestans are the most widely studied groups. Isoflavones are most abundant in soyabeans and other legumes but also found in berries, wine, grains, nuts and soya-fortified foods.

Although present as inactive glycoside conjugates (containing glucose or carbohydrate moieties) and unconjugated (aglycone) forms in food, only the latter are bioactive. Fermented soya, such as tem-peh or miso, typically contains higher aglycone levels than other soya-based foods.

Once consumed, isoflavones are rapidly metabolised and absorbed, entering systemic circulation predominantly as conjugates with limited bioavailability and bioactivity, leaving only a tiny fraction of the ‘free’ bioactive form in systemic circulation.

Soya-based infant formula: 25% del mercato USA

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EFFETTI DEGLI ISOFLAVONI

- interferenza con gli estrogeni
- si legano a ER alfa e ER beta (maggiore affinità), azione come agonisti parziali
- binding maggiore rispetto a BFA, minore rispetto a dietilstilbestrolo
- effetto su steroidogenesi (11-beta idrossisteroidodeidrogenasi, 5-alfa reduttasi)
- effetto locale, non variazioni dei livelli di ormoni circolanti
- alterazione di sintesi e biodisponibilità di SHBG
- effetti probabili: pubertà anticipata/precoce

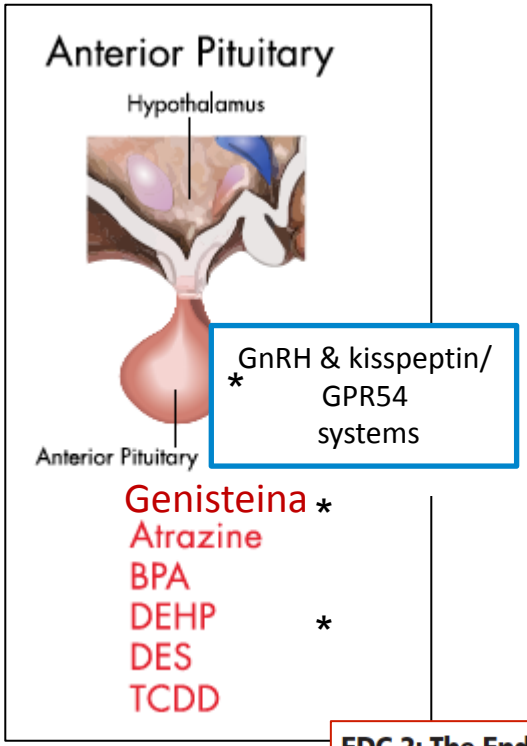
How much is too much: human isoflavone intake, metabolism and excretion

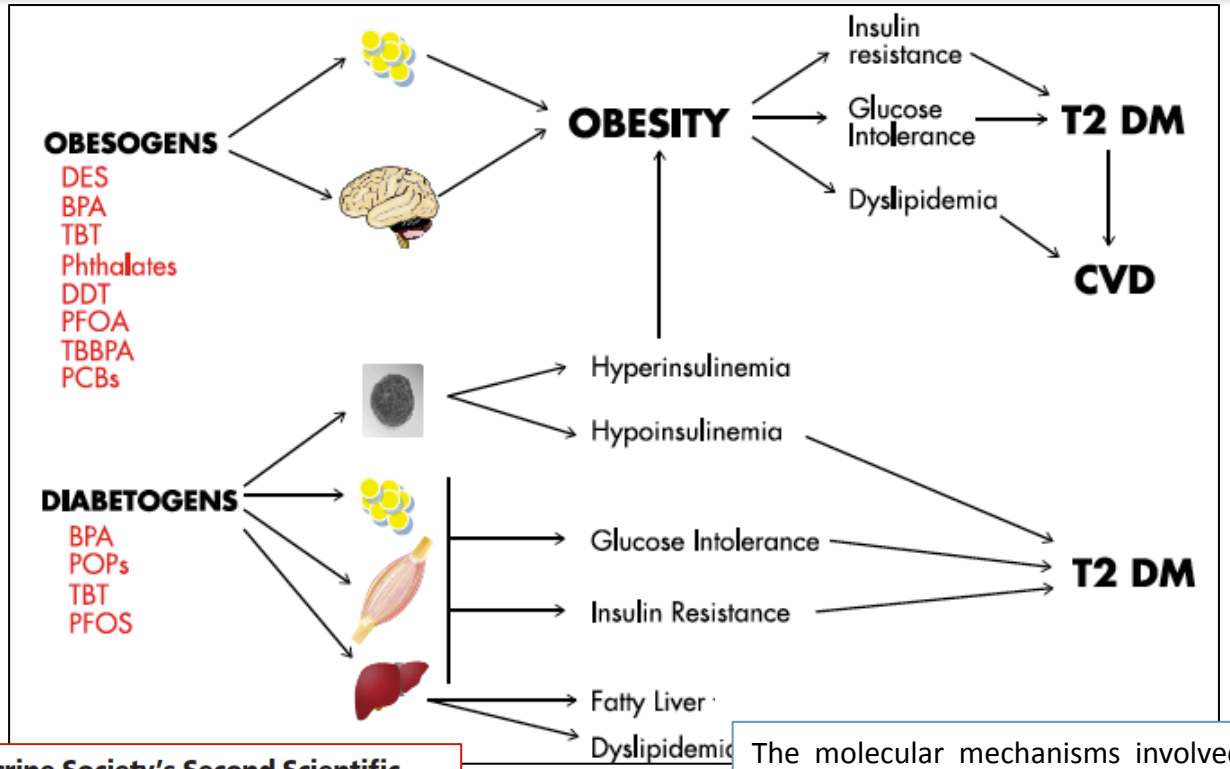
There is no ‘typical’ level of isoflavone intake as consumption patterns vary widely across populations, and geographic regions. For Asians, vegetarians and other groups in which soya is foundational to the diet, isoflavone consumption can be as high as 100 mg/d (intake range is about 0·3–1·5 mg/kg body weight). Western diet intake estimates range from 1 to 3 mg/d. For their weight, infants exclusively fed soya-based formula have the highest mean daily consumption of total isoflavones, ranging from 6 to 9 mg/kg body weight per d in 4-month-old infants, an amount that is up to seven times higher than Asians consuming a traditional soya-based diet.

I potenziali ‘disruptors’ ovarici possono teoricamente agire:

- direttamente sull’ovaio: molti diversi processi possono essere alterati (differenziazione/sviluppo, follicologenesi, steroidogenesi, …)

- indirettamente
  - a livello ipotalamico e ipofisario, alterando la secrezione di gonadotropine
  - tramite effetto su omeostasi lipidica e glicidica, fattori di rischio per disordini metabolici (obesità, …)



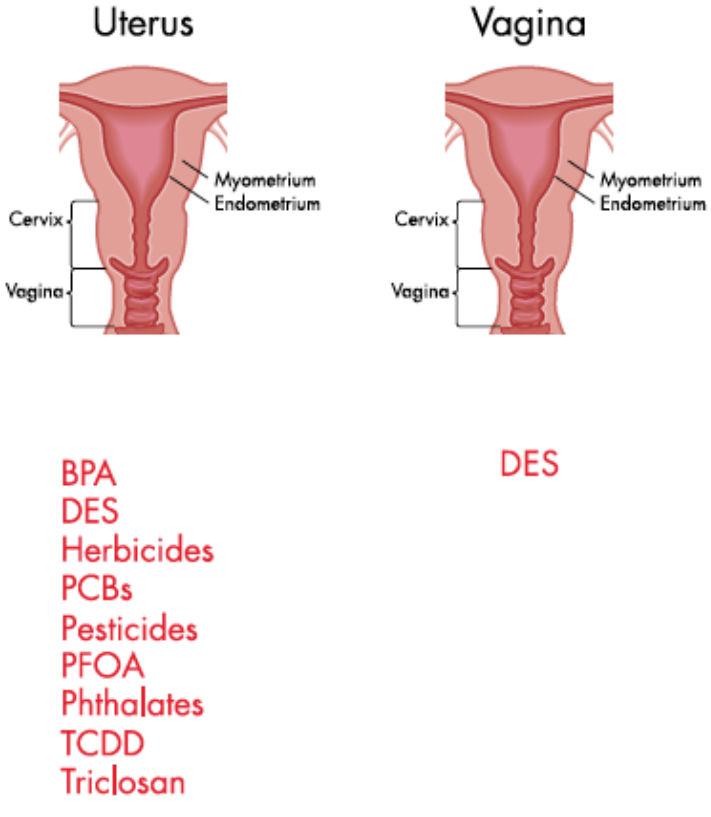


EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals

A. C. Gore, V. A. Chappell, S. E. Fenton, J. A. Flaws, A. Nadal, G. S. Prins, J. Toppari, and R. T. Zoeller Endocrine Reviews 36: E1–E150, 2015

The molecular mechanisms involved are still largely unknown, but alteration of gene expression after binding to the AhR, PPAR, and ERs seems to play a role.

- ✓ Numerosi studi indicano che gli EDCs possono interferire negativamente oltre che su ovaio, anche su tube, struttura e funzione uterina, vagina.
- ✓ L'esperienza del dietilstilbestrolo …



- ✓ La maggior parte delle informazioni deriva da studi nel ratto
- ✓ Gli uomini sono continuamente esposti a numerosi EDCs in ogni determinato periodo della vita, mentre gli esperimenti negli animali tipicamente coinvolgono esposizione a singoli composti chimici in specifiche finestre temporali

- ✓ Il 'timing' dell'esposizione a EDCs gioca un ruolo fondamentale; infatti l'esposizione durante finestre critiche di suscettibilità nel corso dell'embriogenesi interferisce con lo sviluppo ghiandolare ma può anche alterare la funzione ovarica nell'età adulta mediante interferenze sulla steroidogenesi.

- ✓ In molti studi i disordini sono causati da esposizione cronica a *basse dosi* di EDCs, o a *combinazione* di differenti classi di sostanze. È verosimile che anche i disordini dell'uomo siano i risultati additivi di esposizione cronica a basse quantità di miscele di EDCS.

Hormones and Endocrine-Disrupting Chemicals: Low-Dose Effects and Nonmonotonic Dose Responses

Laura N. Vandenberg, Theo Colborn, Tyrone B. Hayes, Jerrold J. Heindel, David R. Jacobs, Jr., Duk-Hee Lee, Toshi Shioda, Ana M. Soto, Frederick S. vom Saal, Wade V. Welshons, R. Thomas Zoeller, and John Peterson Myers

Endocr Rev. 2012 Jun; 33(3): 378–455.

Environmental epigenomics: Current approaches to assess epigenetic effects of endocrine disrupting compounds (EDC's) on human health

Natalia Tapia-Orozco[a], Gerardo Santiago-Toledo[b,c], Valeria Barrón[d], Ana María Espinosa-García[d], José Antonio García-García[d], Roeb García-Arrazola[a,*]

[a] Departamento de Alimentos y Biotecnología, Facultad de Química, Universidad Nacional Autónoma de México, Circuito Escolar s/n Ciudad Universitaria, Distrito Federal, Mexico
[b] Department of Biochemical Engineering, University College London, Torrington Place, London WC1E 7JE, UK
[c] Abraxas Biolabs SAPI de CV, Donato Guerra 9, Álvaro Obregón, Distrito Federal, Mexico
[d] Unidad de Medicina Genómica, Hospital General de México, Dr Balmis 148, Distrito Federal, Mexico

Environmental Toxicology and Pharmacology 51 (2017) 94–99

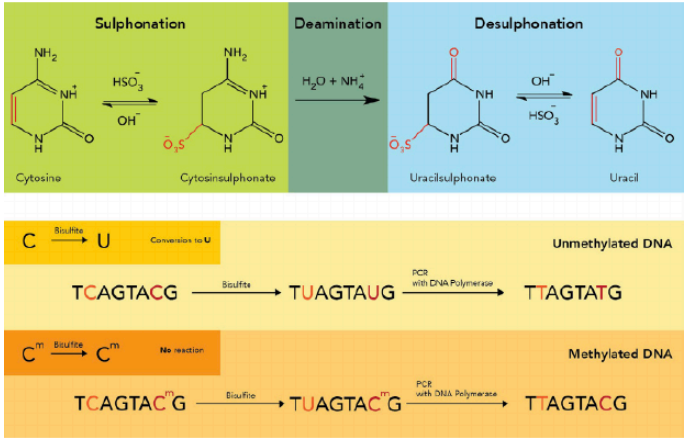
Epigenetics research includes a variety of events, such as messenger RNA (mRNA) silencing through microRNAs (miRNAs), chromatin remodeling, histone modifications, and DNA methylation. Histone modification and DNA methylation are heritable events, but they do not involve DNA changes or mutations (Jaenisch and Bird, 2003).

Conventional detection of EDCs is based on chemical structure and concentration sample analysis.

However, substantial evidence has emerged, suggesting that cell exposure to EDCs leads to epigenetic changes, independently of its chemical structure with non-monotonic low-dose responses.

Consequently, a paradigm shift in toxicology assessment of EDCs is proposed based on a comprehensive review of analytical techniques used to evaluate the epigenetic effects.

DNA methylation analysis is a viable method for assessing endocrine disruptors beyond the conventional study approach of chemical structure and concentration analysis.



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Endocrine Reviews 36: E1–E150, 2015

Table 2. Mode of Action for EDCs

EDC	Mechanism	Mode of Action
Bisfenolo A	uclear receptor	ER agonist (359, 1246); strong affinity for ERRγ (860, 1247); antiandrogen (1248); increased PR expression (477, 1249); hPXR agonist (1250)
	ER-mediated nongenomic pathway	Activates membrane-associated ERα, ERβ signaling cascades through PI3K-pAkt and MAPK-pErk and GPER-pErk pathways (960, 1251–1255)
	Nonsteroidal receptor	Antagonist of ThR (1095); binds to GPR30 (861)
	Ion channels	Activates membrane ERβ-Ca^{2+} pathway; activates ERβ-KATP and Ca^{2+} mobilization (293); up-regulation of Ca^{2+} ion channel gene and protein, Orai1 (966, 326, 1256, 1257)
	Uninhibited growth	Alters MaSC gene expression and induces early neoplastic lesions (348); induces beaded ducts and increases hyperplasia (362, 1258, 1259)
	Inflammation	Induces proinflammatory cytokines and chemokines (1260)
Diclorodifenil-dicloroetano	Nuclear receptor	Binds and transactivates ERα and ERβ (1246, 1261); DDE binds AR and represses transcription (1262)
	Microenvironment/stroma	Induced estrogenic microenvironment in breast adipose tissue (865)
Dietilstilbestrolo	lear receptor	ERα agonist (1246, 1263); AR binding (1264); suppresses activation of ERR α, β, and γ (1265)
	mediated non-genomic pathway	Activates MAPK and PI3K and induces phosphorylation of ERK (1266, 1267)
	Epigenetic	Hypermethylation of HOXA10 (1268); DNA methylation (1269)
Diossine	Nonsteroidal receptor	Binds to AhR (1270)
	Coactivator recruitment	Recruitment of coactivator p300 (1270)
Bifenili policlorinati	oid hormone biosynthesis	Inhibits sulfotransferase (1271), inhibits aromatase (1272); increases T_4 glucuronidation, competes with thyroid hormone binding proteins (1273)
	Nuclear receptor	Weak binding to ER (1246), weak binding to AR (1264)
Acido perfluoroctanoico	ear receptor	Binds to ER and EREs (845, 846)
	teroidal receptor	PPARα agonist (157, 1274)
	Uninhibited growth	Increased hyperplasia and stromal density (853)
Ftalati	Nuclear receptor	DBP weak affinity for ER (874) (d-n-butil-ftalato)
	Microenvironment/stroma	MEHP induced PPARβ in adipose (1274)

Abbreviations: EREs, estrogen response elements; ERR, estrogen-related receptor; PI3K, phosphatidylinositol-3-kinase.

EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals

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Endocrine Reviews 36: E1–E150, 2015

Table 4. Summary of the Main Effects of EDCs on the Female Reproductive System

Organ or Condition	Category	BPA (BISFENOLO A)	Phthalates	Pesticides	Environmental Contaminants	DES (DIETILSTILBERST
Ovary	Ovarian development			Decreased ovarian weight	Delayed ovarian development	
	Germ cell nests	Decreased germ cell nest breakdown				Decreased germ cell nest breakdown
	Atresia	Increased atresia	Increased atresia		Increased atresia	Increased atresia
	Oocytes	Increased number of multioocyte follicles, interference with meiosis	Decreased no. of viable oocytes		Decreased oocyte quality	
	Primordial follicles	Decreased number of primordial follicles	Increased primordial follicle recruitment	Increased activation of primordial follicles		
	Follicle growth	Decreased antral follicle growth	Decreased antral follicle growth	Decreased antral follicle growth	Decreased follicle growth	
	Steroidogenesis	Altered steroidogenesis	Altered steroidogenesis	Altered steroidogenesis	Decreased steroidogenesis	
	Gene expression	Altered gene expression	Altered gene	Altered gene	Altered gene expression	

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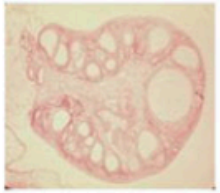
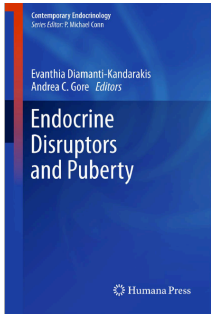
Organ or Condition	Category	BPA	Phthalates	Pesticides	Environmental Contaminants	DES
Uterus	Structure	Development of endometrial-like structures		Altered uterine weight	Shorter fundi and uterine lengths, fewer uterine glands	
	Proliferation/hyperplasia/ carcinoma	Impaired proliferation				Endometrial hyperplasia, uterine adenocarcinoma
	Immune function	Increased immune responsiveness			Chronic active inflammation	
	Receptivity		Compromised uterine receptivity, decreased implantation sites	Decreased implantation sites		
Vagina	Gene expression Carcinoma	Altered gene expression			Altered gene expression	Altered gene expression Carcinoma Altered gene expression

Effects of developmental exposure to selected endocrine disruptors in ovarian physiology. Stimulatory (+) and inhibitory (–) effects of the environmental endocrine disruptors.



OVARY

BPA bisphenol A
DES diethylstilbestrol
DDE 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene,
DCB , MXC methoxychlor,
HPTE 2,2-bis(phydroxyphenyl)-1,1,1 trichloroethane,
ER b estrogen receptor b
ER a estrogen receptor a
AMH anti-Mullerian hormone
VEGF vascular endothelial growth factor
IGF-1 insulin growth factor 1
E2 estradiol, P4 progesterone
Symbols : ↓: decreased



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Ovarian organization/ morphology	↓ Ovarian size/weight (Genistein,MXC) Ovarian cysts (BPA, DES) Multioocyte follicles (BPA, Genistein) Hypertrophy of interstitial tissuse (DES, vinclozolin)
Folliculogenesis	(+/–) initial follicle maturation (DES) (+/–) late preantral stage (MXC,BPA) (–) copora lutea formation (anovulation) (BPA,Genistein DES)
Steroidogenesis	(+/–) E2 production (Genistein, DDE,HPTE) (+/–) P4 production (Genistein, DDE,HPTE)
Ovarian cellular/molecular phenomena (gene induction/expression) Oocyte chromosomal abnormalitiess	Induction of ectopic expression of ER α in granulosa cells (Genistein) (–) ER β expression (DDE) Aneuploidy (BPA)
Intraovarian local factors production	(+) AMH production (MXC,HPTE) (–) VEGF and IGF– 1 production (DDE) (–) Activin expression (DES)

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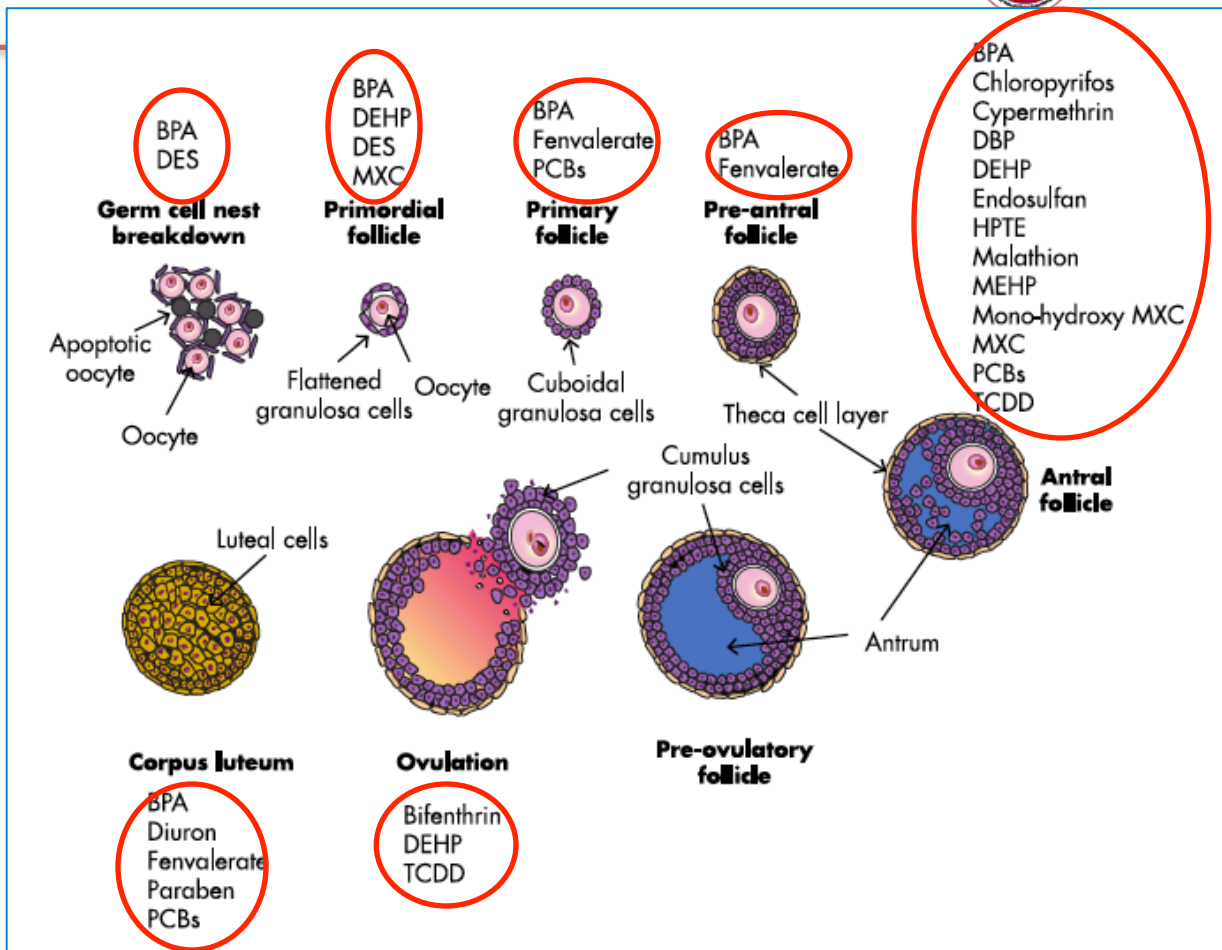
Fig. 1 - Normal developmental stages of ovarian follicles beginning with germ cell nest breakdown around birth, formation of primordial follicles, and their growth to primary follicles, preantral follicles, antral follicles, and finally, preovulatory follicles.

Ovulation and the formation of the corpus luteum.

Examples of EDCs that adversely affect the ovary are listed in red font above or below their likely site of action.



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The effects of phthalates on the ovary

*Patrick R. Hannon and Jodi A. Flaws**

Department of Comparative Biosciences, University of Illinois at Urbana-Champaign, Urbana, IL, USA

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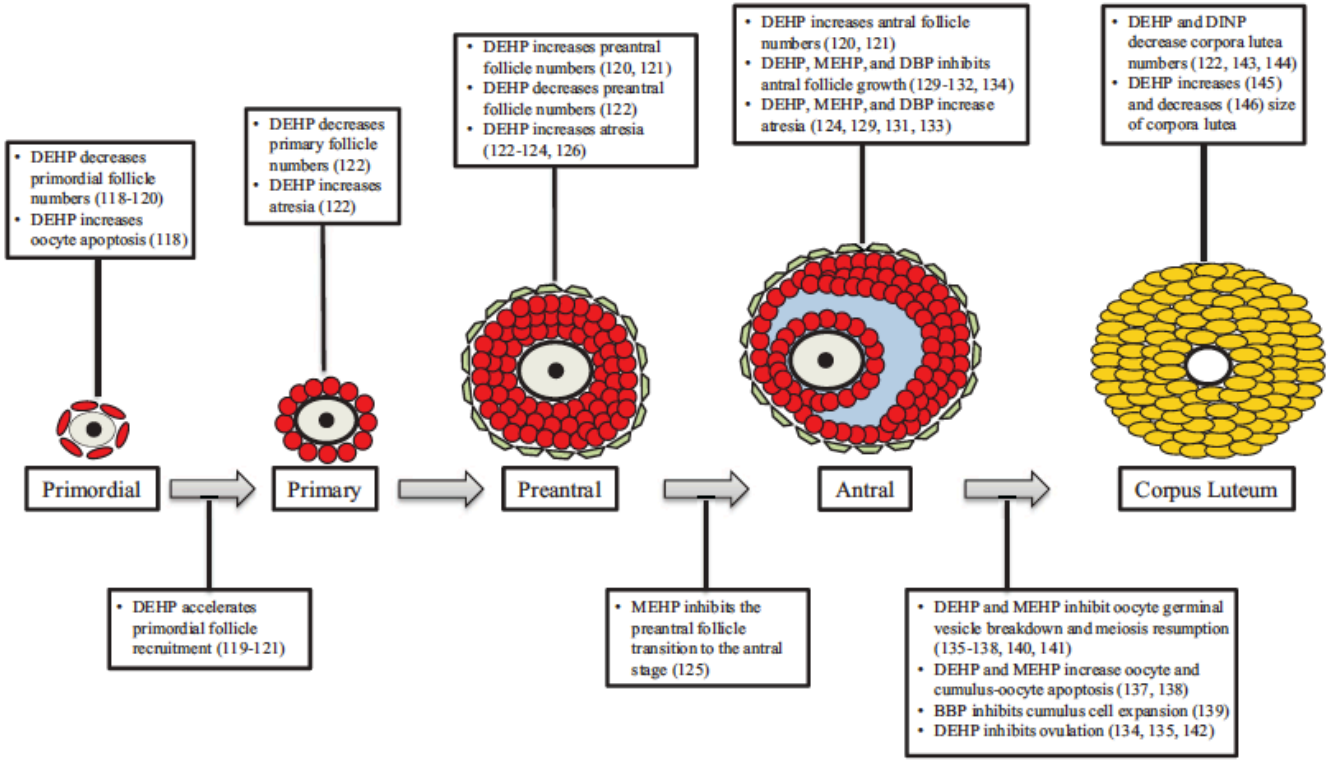

FIGURE 4 | Phthalates disrupt folliculogenesis. This figure is a summation of the major findings on the effects of phthalates on folliculogenesis. Text boxes above a particular follicle type outline the major effects of phthalates at that stage of development, while text boxes below transition arrows outline the major effects of phthalates on that developmental transition.

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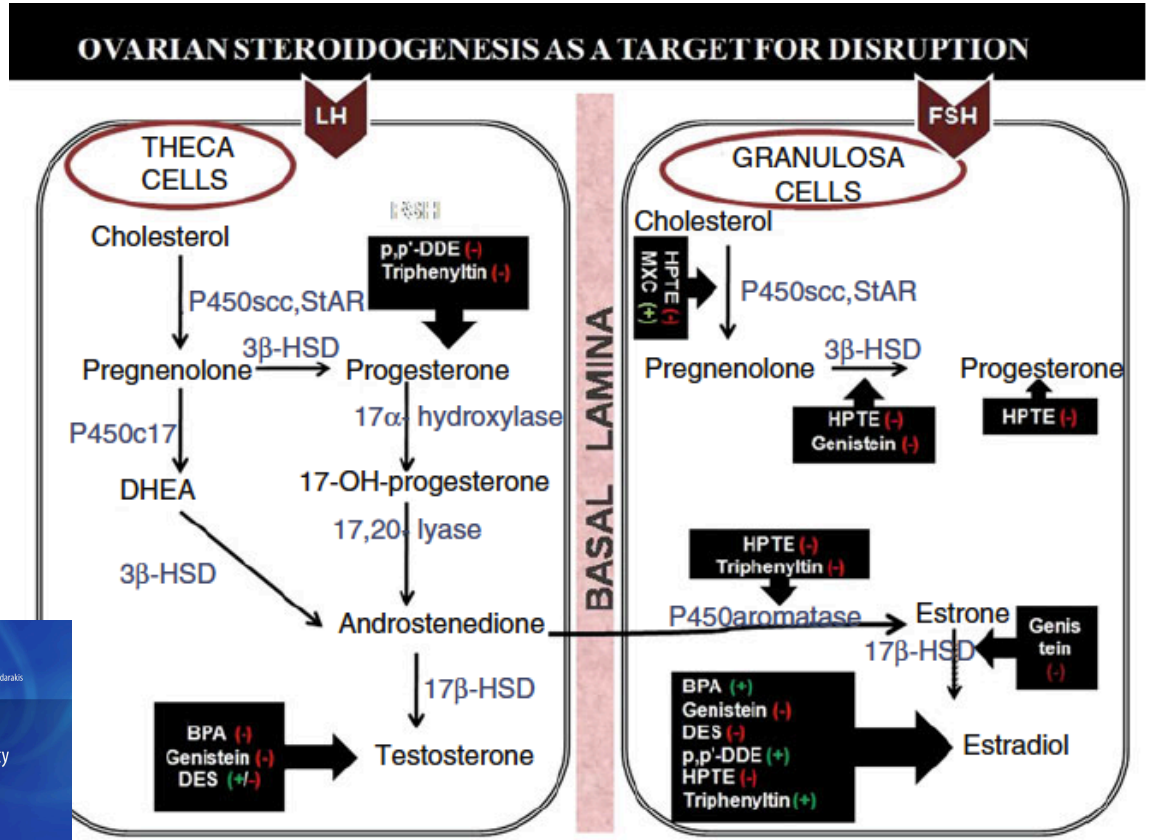
Table 1 | Genes associated with folliculogenesis that are altered by phthalate exposure.

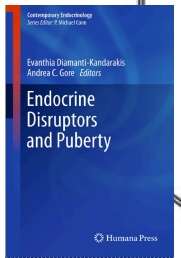
Phthalate (dose)	Model (duration of exposure)	Effect on gene (reference)	Gene name
DEHP (0.02–40 μg/l)	Adult zebrafish (21 days)	Decreased *Ptgs2* (135)	Prostaglandin-endoperoxide synthase 2
DEHP (100 μg/ml)	Mouse antral follicles (96 h)	Decreased *Ccnd2* (132)	Cyclin D2
		Decreased *Cdk4* (132)	Cyclin-dependent kinase 4
		Decreased *Sod1* (130)	Cu–Zn superoxide dismutase 1
DEHP (10–100 μM)	Neonatal mouse (72 h)	Increased *Bax* (118)	BCL-2-associated X protein
		Decreased *Lhx8* (118)	LIM homeobox 8
		Decreased *Figla* (118)	Factor in the germline alpha
		Decreased *Sohlh2* (118)	Spermatogenesis and oogenesis helix-loop-helix
		Decreased *Nobox* (118)	Newborn ovary homeobox
DEHP (20 μg/kg/day–750 mg/kg/day)	Adult mouse (10 or 30 days)	Increased *Pdpk1* (119)	3-phosphoinositide-dependent protein kinase-1
		Increased *Mtorc1* (119)	Mammalian target of rapamycin complex 1
		Decreased *Pten* (119)	Phosphatase and tensin homolog
		Decreased *Tsc1* (119)	Tuberous sclerosis 1
DEHP (40 μg/kg/day)	Fetal and prepubertal mouse, *in utero* (length of gestation)	Decreased methylation of *Igf2r* (115)	Insulin-like growth factor 2 receptor
		Decreased methylation of *Peg3* (115)	Paternally expressed gene 3
MEHP (1–100 μg/ml)	Mouse antral follicles (24–96 h)	Decreased *Ccnd2* (131)	Cyclin D2
		Decreased *Ccne1* (131)	Cyclin E1
		Decreased *Cdk4* (131)	Cyclin-dependent kinase 4
		Increased *Bax* (131)	BCL-2-associated X protein
		Increased *Aifm1* (133)	Apoptosis-inducing factor, mitochondrion-associated, 1
		Decreased *Bcl2* (131)	B-cell leukemia/lymphoma 2
		Decreased *Bcl2l10* (133)	Bcl2-like 10
		Decreased *Gpx* (131)	Glutathione peroxidase
		Decreased *Sod1* (131)	Cu–Zn superoxide dismutase 1
MEHP (10–4 M)	Human fetus (72 h)	Increased *LXRα* (117)	Liver X receptor alpha
		Increased *SREBP* members (117)	Sterol regulatory element-binding protein
MEHP (250–500 μM)	Fetal mouse oocytes (24 h)	Decreased *Nd1* (113)	Mitochondrial respiratory chain protein
		Increased *Sod1* (113)	Cu–Zn superoxide dismutase 1
MEHP (50 μM)	Bovine oocytes (22–24 h)	Decreased *CCNA2* (137)	Cyclin A2
		Decreased *ASAH1* (137)	Acid ceramidase 1
		Decreased *POU5F1* (137)	POU domain, class 5, transcription factor 1
DBP (1–1000 μg/ml)	Mouse antral follicles (24–168 h)	Decreased *Ccnd2* (129)	Cyclin D2
		Decreased *Ccne1* (129)	Cyclin E1
		Decreased *Ccna2* (129)	Cyclin A2
		Decreased *Ccnb1* (129)	Cyclin B1
		Increased *Cdkn1a* (129)	Cyclin-dependent kinase inhibitor 1A

Ovarian synthesis of steroid hormones is subject to direct inhibitory (−) and/or stimulatory (−/+) modulation by several environmental chemicals.

Key ovarian steroidogenic enzymes also represent a target for disruption.

BPA bisphenol A
DES diethylstilbestrol
HPTE, DDE, 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene
MXC methoxychlor
P450scc cholesterol side-chain cleavage cytochrome P450
StAR steroidogenic acute regulatory protein
3 b -HSD 3 b -hydroxysteroid dehydrogenase
17 b -HSD 17 b –hydroxysteroid dehydrogenase
P450c17 17 a -hydroxylase/C17–20 lyase cytochrome P450
DHEA dehydroepiandrosterone





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The effects of phthalates on the ovary

Patrick R. Hannon and Jodi A. Flaws*

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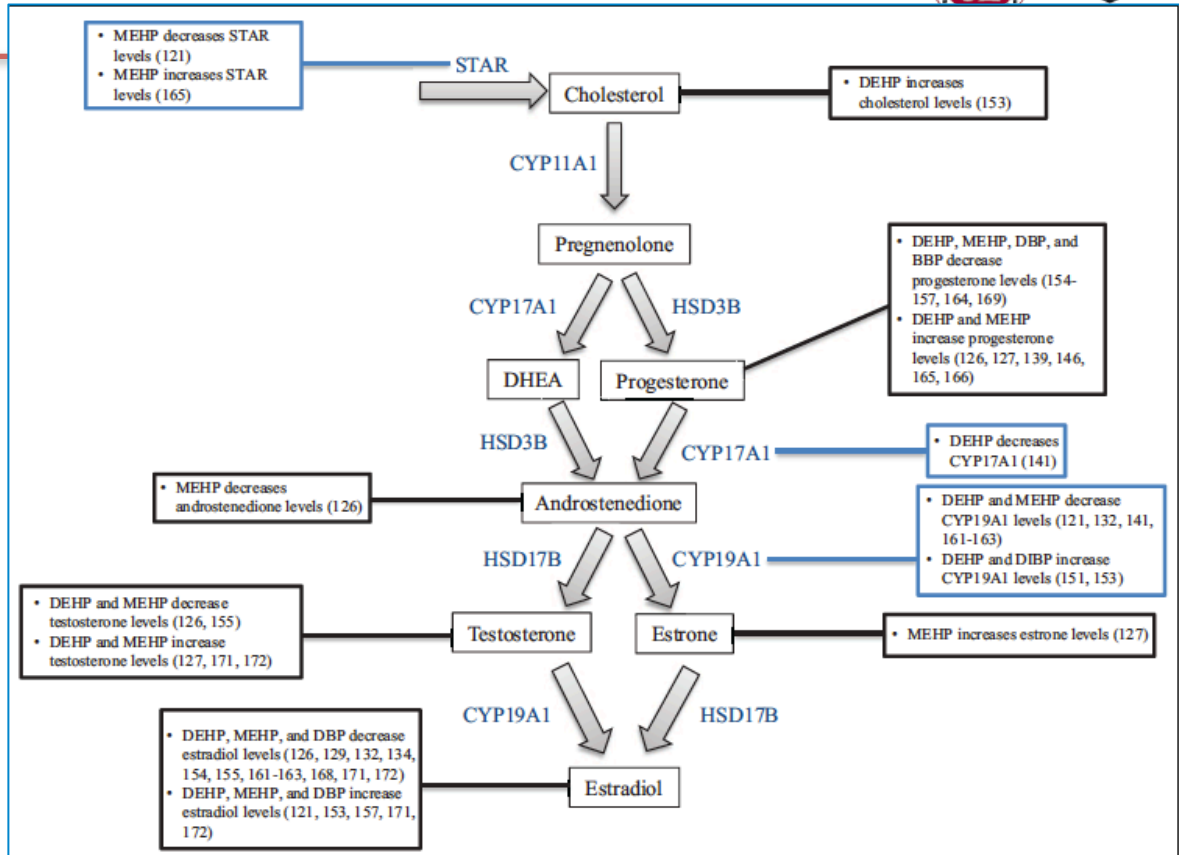

FIGURE 5 | Phthalates alter steroidogenesis. This figure is a summation of the major findings on the effects of phthalates on steroidogenesis. Black text boxes connected to hormones outline the major effects of phthalates on the levels of that hormone. Blue text boxes connected to steroidogenic enzymes outline the major effects of phthalates on the mRNA and/or protein levels of that enzyme.

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Table 2 | Genes associated with steroidogenesis that are altered by phthalate exposure.

Phthalate (dose)	Model (duration of exposure)	Effect on gene (reference)	Gene name
DEHP (0.05–5 mg/kg/day)	Adult mouse, *in utero* (length of gestation–weaning)	Decreased *Cyp19a1* (141) Decreased *Cyp17a1* (141) Decreased *Pgr* (141) Decreased *Fshr* (141) Decreased *Lhr* (141)	Cytochrome-P450 aromatase Cytochrome-P450 steroid 17-α-hydroxylase 1 Progesterone receptor FSH receptor LH receptor
DEHP (100 μg/ml)	Mouse antral follicles (96 h)	Decreased *Cyp19a1* (132)	Cytochrome-P450 aromatase
DEHP (25 mg/m^3)	Prepubertal rat (63 days)	Increased *Cyp19a1* (158)	Cytochrome-P450 aromatase
MEHP (10 μg/ml)	Mouse antral follicles (96 h)	Decreased *Cyp19a1* (132)	Cytochrome-P450 aromatase
MEHP (100–1000 mg/kg/day)	Adult mouse, *in utero* (gestational day 17–19)	Decreased *Star* (121) Decreased *Cyp19a1* (121)	Steroidogenic acute regulatory protein Cytochrome-P450 aromatase
MEHP (50–200 μM)	Rat granulosa cells (48 h)	Decreased *Cyp19a1* (166–168)	Cytochrome-P450 aromatase
BBP (1 μM)	HO23 cells (24 h)	Increased *AHR* (175) Increased *ARNT* (175) Increased *CYP1B1* (175)	Aryl hydrocarbon receptor Aryl hydrocarbon receptor nuclear translocator Cytochrome-P450 1B1
DIBP (600 mg/kg/day)	Prepubertal rat, *in utero* (gestational day 7–21)	Increased *Cyp19a1* (156)	Cytochrome-P450 aromatase

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Table 4. Summary of the Main Effects of EDCs on the Female Reproductive System

Organ or Condition	Category	BPA	Phthalates	Pesticides	Environmental Contaminants	DES
Anterior pituitary	Gonadotropins	Increased gonadotropin mRNA	Increased ability to produce gonadotropins	Altered gonadotropin release	Altered gonadotropin levels	Decreased LH-secreting gonadotropes
Reproductive cycles	Puberty			Altered vaginal opening	Altered onset of puberty	
Pathophysiological reproductive conditions	Fertility	Reduced fertility	Reduced fertility	Reduced fertility	Reduced fertility	
	Early menopause/premature reproductive failure	Early menopause/ premature ovarian failure	Early menopause	Early menopause	Early menopause	Early menopause
	Fibroids	Increased risk of fibroids	Increased risk of fibroids		Increased risk of fibroids	Increased risk of fibroids
	Endometriosis		Increased risk of endometriosis	Increased risk of endometriosis	Increased risk of endometriosis	
Pregnancy and birth outcomes	Adverse birth outcomes	Increased risk of adverse birth outcomes	Increased risk of adverse birth outcomes	Increased risk of adverse birth outcomes	Increased risk of adverse birth outcomes	
	Gene expression	Altered gene expression	Altered gene expression	Altered gene expression	Altered gene expression	

Sugar-sweetened beverage consumption and age at menarche in a prospective study of US girls

J.L Carwile[1], W.C Willett[1,2,3], D. Spiegelman[1,3,4], E. Hertzmark[3,4], J. Rich-Edwards[1,3,5], A.L Frazier[3,6], and K.B Michels[1,3,7,*]

[1]Department of Epidemiology, Harvard School of Public Health, Boston, MA 02115, USA. [2]Department of Nutrition, Harvard School of Public Health, Boston, MA 02115, USA [3]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA [4]Department of Biostatistics, Harvard School of Public Health, Boston, MA 02115, USA [5]Connors Center for Women's Health and Gender Biology, Brigham and Women's Hospital, Boston, MA 02115, USA [6]Department of Pediatric Oncology, Dana-Farber/Children's Hospital Cancer Center, Boston, MA 02115, USA [7]Obstetrics and Gynecology Epidemiology Center, Department of Obstetrics, Gynecology and Reproductive Biology, Brigham and Women's Hospital, Harvard Medical School, 221 Longwood Avenue, Boston, MA 02115, USA

Human Reproduction, Vol.30, No.3 pp. 675–683, 2015

STUDY QUESTION: Is sugar-sweetened beverage (SSB) consumption associated with age at menarche?

SUMMARY ANSWER: More frequent SSB consumption was associated with earlier menarche in a population of US girls.

WHAT IS KNOWN ALREADY: SSB consumption is associated with metabolic changes that could potentially impact menarcheal timing, but direct associations with age at menarche have yet to be investigated.

STUDY DESIGN, SIZE, DURATION: The Growing up Today Study, a prospective cohort study of 16 875 children of Nurses' Health Study II participants residing in all 50 US states. This analysis followed 5583 girls, aged 9–14 years and premenarcheal at baseline, between 1996 and 2001. During 10 555 person-years of follow-up, 94% ($n = 5227$) of girls reported their age at menarche, and 3% ($n = 159$) remained premenarcheal in 2001; 4% ($n = 197$) of eligible girls were censored, primarily for missing age at menarche.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Cumulative updated SSB consumption (composed of non-carbonated fruit drinks, sugar-sweetened soda and iced tea) was calculated using annual Youth/Adolescent Food Frequency Questionnaires from 1996 to 1998. Age at menarche was self-reported annually. The association between SSB consumption and age at menarche was assessed using Cox proportional hazards regression.

MAIN RESULTS AND THE ROLE OF CHANCE: More frequent SSB consumption predicted earlier menarche. At any given age between 9 and 18.5 years, premenarcheal girls who reported consuming >1.5 servings of SSBs per day were, on average, 24% more likely [95% confidence interval (CI): 13, 36%; *P*-trend: <0.001] to attain menarche in the next month relative to girls consuming ≤2 servings of SSBs weekly, adjusting for potential confounders induding height, but not BMI (considered an intermediate). Correspondingly, girls consuming >1.5 SSBs daily had an estimated 2.7-month earlier menarche (95% CI: −4.1, −1.3 months) relative to those consuming ≤2 SSBs weekly. The frequency of non-carbonated fruit drink (*P*-trend: 0.03) and sugar-sweetened soda (*P*-trend: 0.001), but not iced tea (*P*-trend: 0.49), consumption also predicted earlier menarche. The effect of SSB consumption on age at menarche was observed in every tertile of baseline BMI. Diet soda and fruit juice consumption were not associated with age at menarche.

LIMITATIONS, REASONS FOR CAUTION: Although we adjusted for a variety of suspected confounders, residual confounding is possible. We did not measure SSB consumption during early childhood, which may be an important window of exposure.

WIDER IMPLICATIONS OF THE FINDINGS: More frequent SSB consumption may predict earlier menarche through mechanisms other than increased BMI. Our findings provide further support for public health efforts to reduce SSB consumption.

Energy-containing beverages: reproductive hormones and ovarian function in the BioCycle Study[1–3]

Karen C Schliep, Enrique F Schisterman, Sunni L Mumford, Anna Z Pollack, Neil J Perkins, Aijun Ye, Cuilin J Zhang, Joseph B Stanford, Christina A Porucznik, Ahmad O Hammoud, and Jean Wactawski-Wende

Background: Energy-containing beverages are widely consumed among premenopausal women, but their association with reproductive hormones is not well understood.

Objective: The objective was to assess the association of energy-containing beverages, added sugars, and total fructose intake with reproductive hormones among ovulatory cycles and sporadic anovulation in healthy premenopausal women.

Design: Women ($n = 259$) in the BioCycle Study were followed for up to 2 menstrual cycles; they provided fasting blood specimens during up to 8 visits/cycle and four 24-h dietary recalls/cycle.

Results: Women who consumed ≥1 cup (1 cup = 237 mL) sweetened soda/d had 16.3% higher estradiol concentrations compared with women who consumed less sweetened soda (86.5 pg/mL compared with 74.4 pg/mL, $P = 0.01$) after adjustment for age, BMI, race, dietary factors, and physical activity. Similarly elevated estradiol concentrations were found for ≥1 cup cola/d and noncola soda intake. Neither artificially sweetened soda nor fruit juice intake ≥1 cup/d was significantly associated with reproductive hormones. Added sugar above the average US woman's intake (≥73.2 g/d) or above the 66th percentile in total fructose intake (≥41.5 g/d) was associated with significantly elevated estradiol but not consistently across all models. No associations were found between beverages, added sugars, or total fructose intake and anovulation after multivariate adjustment.

Conclusions: Even at moderate consumption amounts, sweetened soda is associated with elevated follicular estradiol concentrations among premenopausal women but does not appear to affect ovulatory function. Further research into the mechanism driving the association between energy-containing beverages and reproductive hormones, and its potential implications for women's health, is warranted. *Am J Clin Nutr* 2013;97:621–30.

Dati contrastanti, per campionamento inadeguato per numero, fase del ciclo..

Chavarro JE, Rich-Edwards JW, Rosner BA, Willett WC. Caffeinated and alcoholic beverage intake in relation to ovulatory disorder infertility. Epidemiology 2009;20:374–81.

Schliep KC, Schisterman EF, Mumford SL, Pollack AZ, Zhang C, Ye A, Stanford JB, Hammoud AO, Porucznik CA, Wactawski-Wende J. Caffeinated beverage intake and reproductive hormones among premenopausal women in the BioCycle Study. Am J Clin Nutr 2012;95: 488–97.

Nagata C, Kabuto M, Shimizu H. Association of coffee, green tea, and caffeine intakes with serum concentrations of estradiol and sex hormonebinding globulin in premenopausal Japanese women. Nutr Cancer 1998 30:21–4.

Lucero J, Harlow BL, Barbieri RL, Sluss P, Cramer DW. Early follicular phase hormone levels in relation to patterns of alcohol, tobacco, and coffee use. Fertil Steril 2001;76:723–9.

Consumption of caffeinated and artificially sweetened soft drinks is associated with risk of early menarche[1,2]

Noel T Mueller,[3,4] David R Jacobs Jr,[5] Richard F MacLehose,[5] Ellen W Demerath,[5] Scott P Kelly,[6] Jill G Dreyfus,[5] and Mark A Pereira[5]*

[3]Department of Epidemiology, Mailman School of Public Health and [4]Institute of Human Nutrition and Department of Medicine, College of Physicians and Surgeons, Columbia University Medical Center, New York, NY; [5]Division of Epidemiology & Community Health, School of Public Health, University of Minnesota, Minneapolis, MN; and [6]Department of Epidemiology and Biostatistics, George Washington University, Washington, DC

Background: Early menarche has been linked to risk of several chronic diseases. Prospective research on whether the intake of soft drinks containing caffeine, a modulator of the female reproductive axis, is associated with risk of early menarche is sparse.

Objective: We examined the hypothesis that consumption of caffeinated soft drinks in childhood is associated with higher risk of early menarche.

Design: The National Heart, Lung, and Blood Institute Growth and Health Study recruited and enrolled 2379 (1213 African American, 1166 Caucasian) girls aged 9–10 y (from Richmond, CA; Cincinnati, OH; and Washington, DC) and followed them for 10 y. After exclusions were made, there were 1988 girls in whom we examined prospective associations between consumption of caffeinated and noncaffeinated sugar- and artificially sweetened soft drinks and early menarche (defined as menarche age <11 y). We also examined associations between intakes of caffeine, sucrose, fructose, and aspartame and early menarche.

Results: Incident early menarche occurred in 165 (8.3%) of the girls. After adjustment for confounders and premenarcheal percentage body fat, greater consumption of caffeinated soft drinks was associated with a higher risk of early menarche (RR for 1 serving/d increment: 1.47; 95% CI: 1.22, 1.79). Consumption of artificially sweetened soft drinks was also positively associated with risk of early menarche (RR for 1 serving/d increment: 1.43; 95% CI: 1.08, 1.88). Consumption of noncaffeinated soft drinks was not significantly associated with early menarche (RR for 1 serving/d increment: 0.88; 95% CI: 0.62, 1.25); nor was consumption of sugar-sweetened soft drinks (RR for 1 serving/d increment: 1.15; 95% CI: 0.95, 1.39). Consistent with the beverage findings, intakes of caffeine (RR for 1-SD increment: 1.22; 95% CI: 1.08, 1.37) and aspartame (RR for 1-SD increment: 1.20; 95% CI: 1.10, 1.31) were positively associated with risk of early menarche.

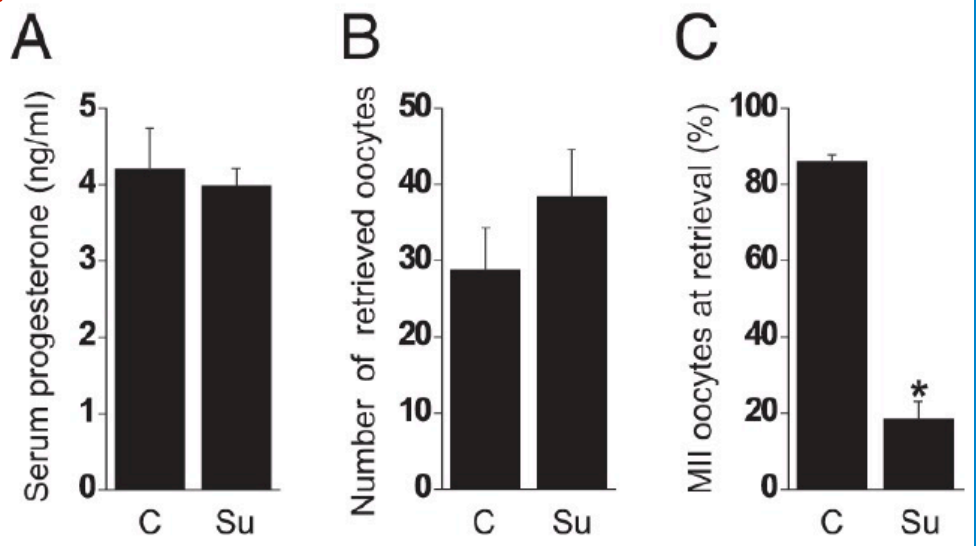
Conclusion: Consumption of caffeinated and artificially sweetened soft drinks was positively associated with risk of early menarche in a US cohort of African American and Caucasian girls. *Am J Clin Nutr* 2015;102:648–54.

Dietary Sugar in Healthy Female Primates Perturbs Oocyte Maturation and In Vitro Preimplantation Embryo Development

Charles L. Chaffin,[⊠] Keith E. Latham, Namdori R. Mtango, Uros Midic, and Catherine A. VandeVoort

Endocrinology. 2014 Jul; 155(7): 2688–2695.

- ✓ Sucrose administered to healthy primates at doses and routes relevant to human consumption results in a reduced percentage of mature oocytes after an ovulatory hCG bolus.
- ✓ In both mural granulosa and cumulus cells, a limited number of genes were altered by sucrose, whereas >1000 were changed in the blastocyst.
- ✓ Because sucrose treatments were stopped before the administration of an hCG injection, the treatment effects were carried from the immature oocyte to the blastocyst, most likely through changes in oocyte DNA methylation.
- ✓ These data provide evidence for the first time that dietary sugar consumption has profound consequences to the oocyte and early embryo in nonhuman primates



Long-term treatment of healthy primates with sucrose inhibits meiotic resumption. A, Oral sucrose (Su) treatment did not alter the total number of oocytes recovered after controlled ovarian stimulation and hCG administration compared with that for controls (labeled C), but significantly reduced the percentage of oocytes that resumed meiosis (B). C, Circulating concentrations of progesterone after an ovulatory stimulus were not altered by sucrose. Values are means ± SEM (n = 6 or 7 for control and sucrose) *, Significantly different from control.

Gli effetti diretti sull'ovaio costituiscono un aspetto significativo delle interferenze degli EDCs sui disordini dell'apparato riproduttivo:

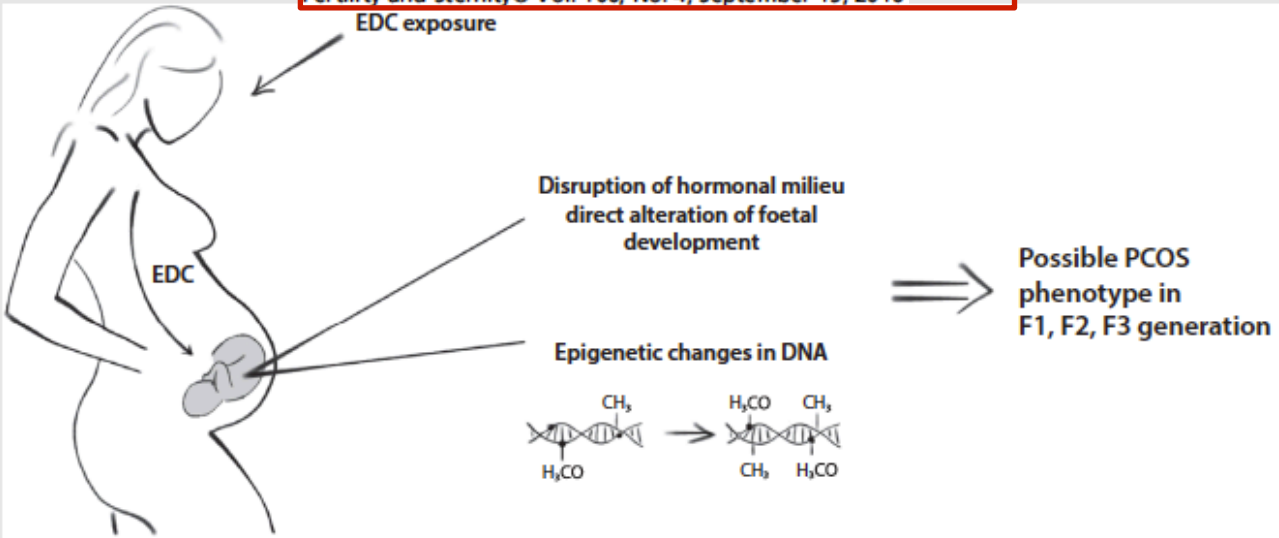
- *Pubertà precoce*
- *Alterazioni del ciclo mestruale*
- *PCOS*
- *Infertilità*
- *Insufficienza ovarica prematura/ menopausa*
- *Endometriosi*
- *Complicanze in corso di gravidanza*
- *Cancro*

Martino-Andrade AJ et al., Mol Nutr Food Res 2010
Craig ZR et al., Reproduction 2011
Hunt PA et al., PNAS 2012
Balabanic B et al., Reprod fertil Dev 2011
Uzumcu M et al., Reprod Domestic Anim 2012
Meeker JD, Arch Pediatr Aldolesc 2012
Kay VR et al., Crit. Rev Toxicol 2013
Caserta D et al., Reprod Biol Endocrinol 2014
Wang F et al., Toxicol Appl Pharmacol 2014
Weinberger B et al., J Matern Fetal Neon Med 2014
……..

Polycystic ovary syndrome and environmental toxins

Aleksandra Zofia Rutkowska, Ph.D.,[a] and Evanthia Diamanti-Kandarakis, M.D., Ph.D.[b]

Fertility and Sterility® Vol. 106, No. 4, September 15, 2016



The possible impact of EDCs on the developing fetus. Exposure of a mother (F0 generation) to EDCs may result in direct impact of these chemicals on fetal development (F1 generation) or in EDCs-dependent disruption of the hormonal balance crucial for proper growth and differentiation of the fetus. Additionally, the impact of EDCs on epigenetic changes in fetal DNA (F1 generation) may be inherited, and adverse health effects (also PCOS phenotype) may occur not only in F1 but also in F2 and F3 generations.

Rutkowska. PCOS and environmental toxins. Fertil Steril 2016.

EDCs PCOS

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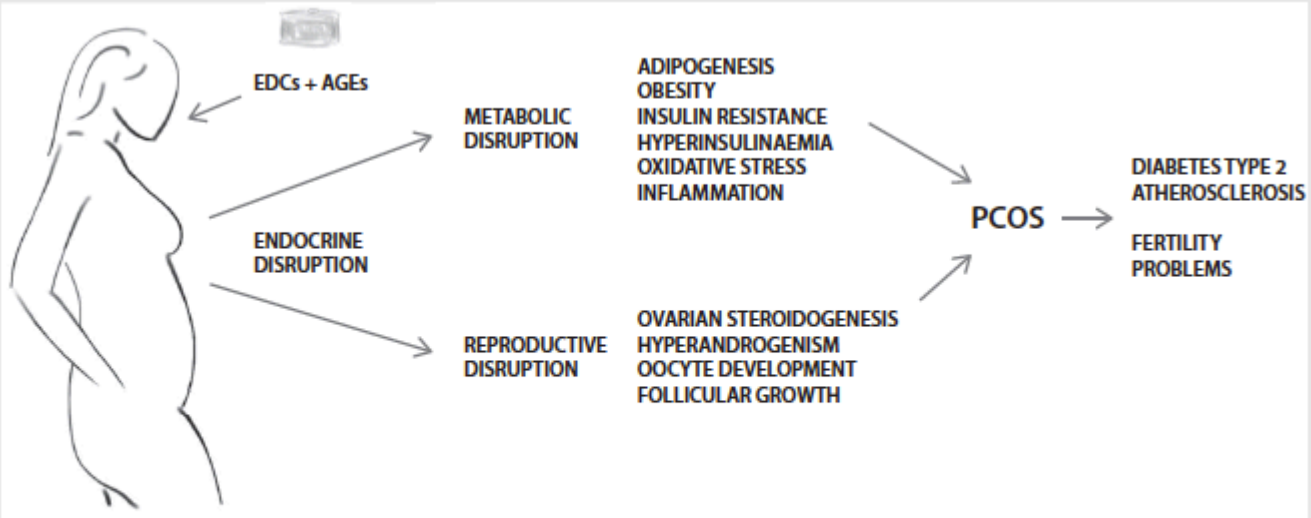

Potential results of environmental factors exposure that may be linked to PCOS and its consequences. Processed, canned, and especially animal-derived foods are examples of sources of high exposure to both suspected environmental toxins, EDCs and AGEs, which may lead to endocrine, metabolic, and reproductive disruption, resulting in PCOS phenotypes and adverse health effects.

Rutkowska. PCOS and environmental toxins. Fertil Steril 2016.

AGEs advanced glycation end products

EDCs PCOS

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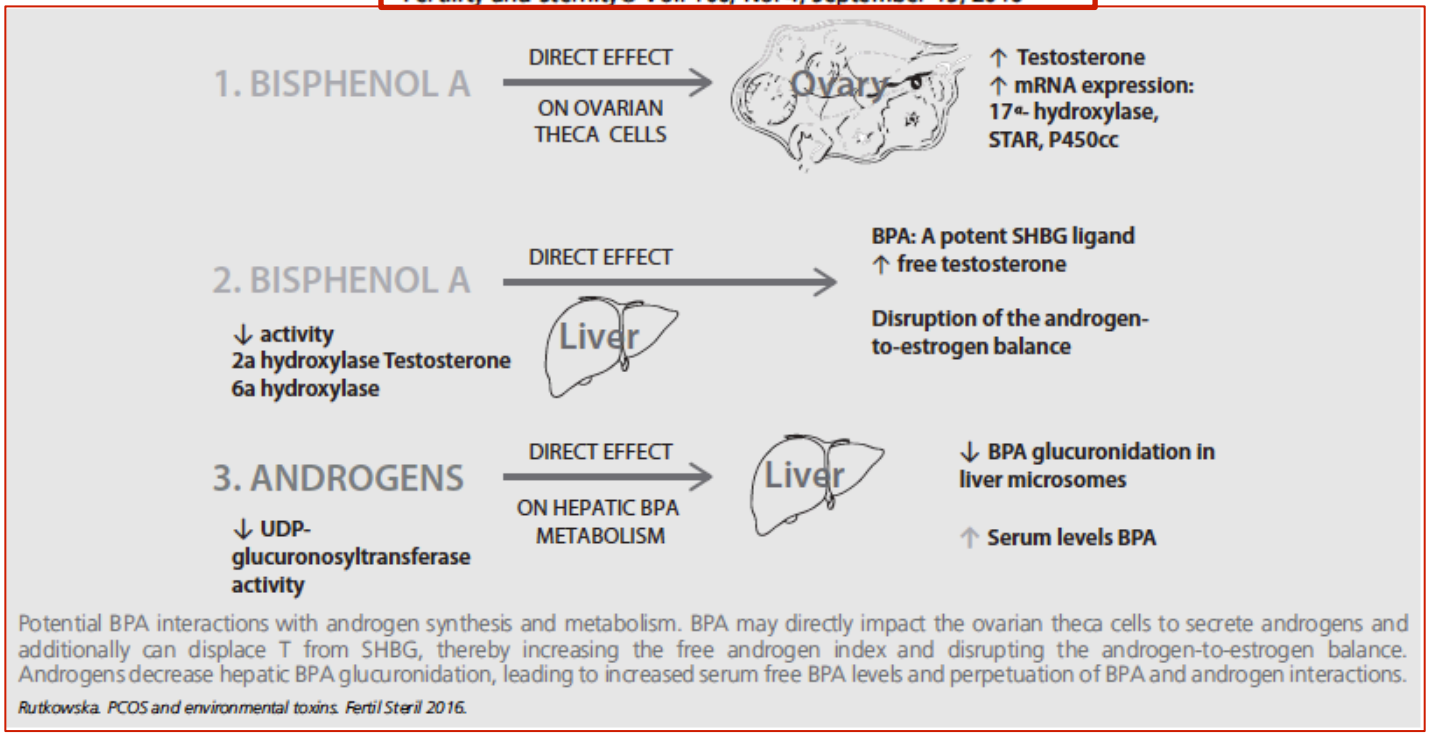

Potential BPA interactions with androgen synthesis and metabolism. BPA may directly impact the ovarian theca cells to secrete androgens and additionally can displace T from SHBG, thereby increasing the free androgen index and disrupting the androgen-to-estrogen balance. Androgens decrease hepatic BPA glucuronidation, leading to increased serum free BPA levels and perpetuation of BPA and androgen interactions.

Rutkowska. PCOS and environmental toxins. Fertil Steril 2016.

Polycystic ovary syndrome and environmental toxins

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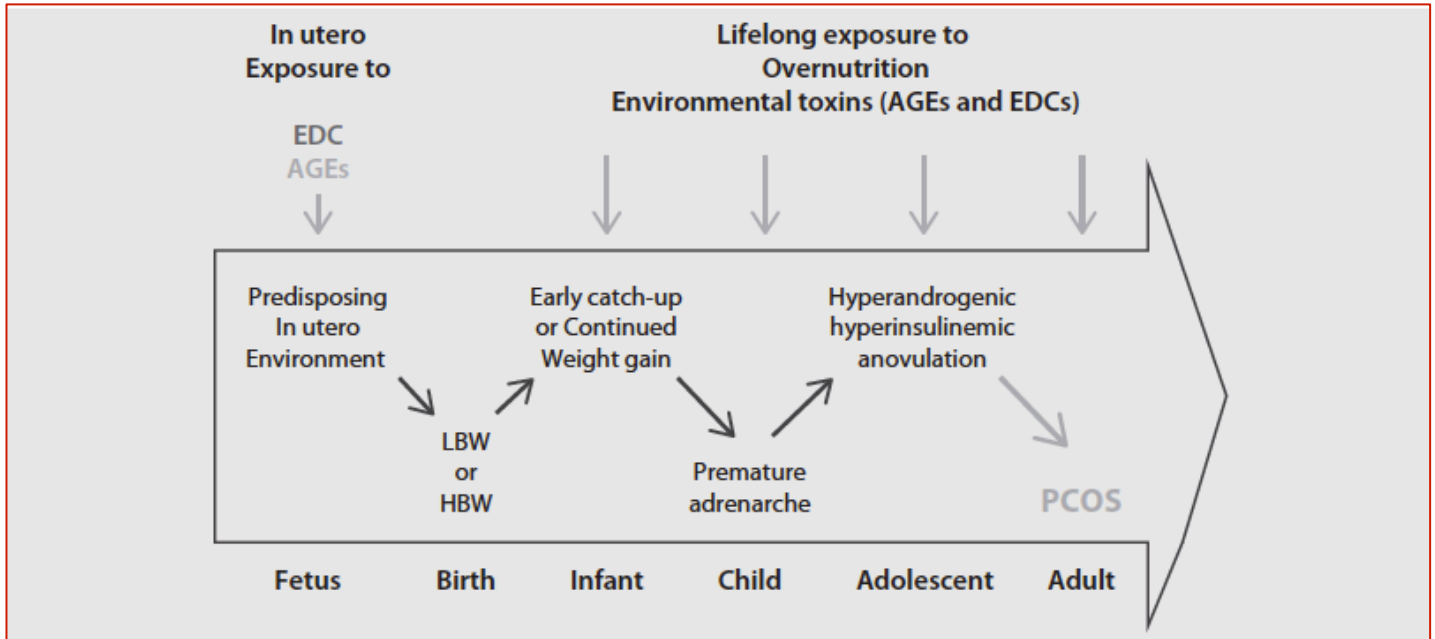


PCOS and environmental toxin exposure across the life cycle. Schematic of developmental and adult windows of vulnerability to AGEs and EDCs, common environmental factors, in the pathogenesis of and pathophysiology of PCOS.

Rutkowska. PCOS and environmental toxins. Fertil Steril 2016.

Nat Rev Endocrinol. 2017 Jul;13(7):400-414. doi: 10.1038/nrendo.2017.36. Epub 2017 Apr 28.

Environmental influences on ovarian dysgenesis - developmental windows sensitive to chemical exposures.

Johansson HKL[1], Svingen T[1], Fowler PA[2], Vinggaard AM[1], Boberg J[1].

Ovarian malignant germ cell tumors: cellular classification and clinical and imaging features.

Shaaban AM[1], Rezvani M, Elsayes KM, Baskin H Jr, Mourad A, Foster BR, Jarboe EA, Menias

Radiographics. 2014 May-Jun;34(3):777-801

Non è dimostrato un chiaro rapporto fra esposizione precoce a EDCs e cancro degli organi riproduttivi

- ✓ Another class of cancers, malignant ovarian germ cell tumours, is of special interest in the light of exposure to EDCs, as these tumours are believed to originate from fetal pluripotent germ cells.
- ✓ These cancers share much of their aetiology with the equivalent cancer in men, testicular germ cell tumours, which arise from genetic aberrations, but the development of these tumours is probably also influenced by environmental factors during early developmental stages.
- ✓ In fact, patients with disorders of sex development have an increased risk of developing germ cell tumours, which attests to the importance of the somatic environment, and not only of intrinsic factors, in the regulation of germ cell development.

EDCs-CANCRO ORGANI RIPRODUTTIVI

The molecular mechanisms of action of the endocrine disrupting chemical bisphenol A in the development of cancer

Ayman Shafei[a], Maggie M. Ramzy[b,*], Abdelhares I. Hegazy[c], Ahmed K. Husseny[c], Usama G. El-hadary[c], Mazen M. Taha[c], Ali A. Mosa[c]

Gene 647 (2018) 235–243

Endocrine Disrupting Chemicals Promote the Growth of Ovarian Cancer Cells via the ER-CXCL12-CXCR4 Signaling Axis

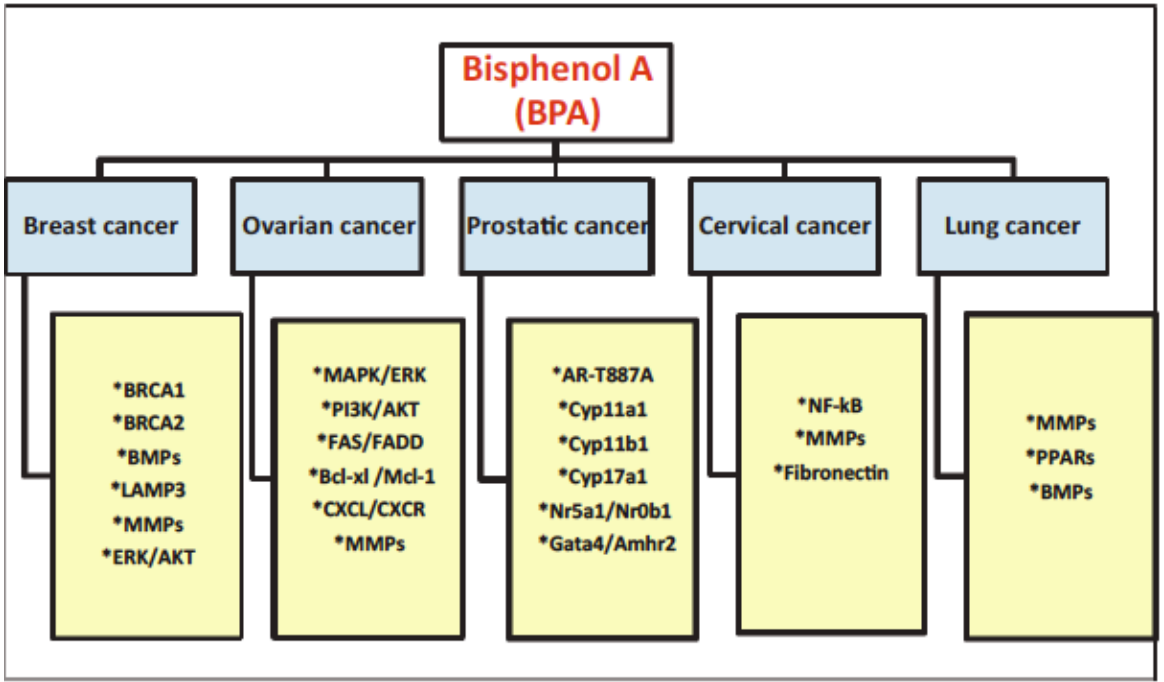
Julie M. Hall[1] and **Kenneth S. Korach**[2]

[1]Campbell University, College of Pharmacy and Health Sciences, Buies Creek, NC 27506

[2]Receptor Biology Section, Laboratory of Reproductive and Developmental Toxicology, The National Institutes of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC 27709

Mol Carcinog. 2013 September ; 52(9): 715–725.

BPA
GENISTEINA
HPTE



BPA

- regola l'espressione di una batteria di geni nel tessuto ovarico, alcuni dei quali associati con signaling oncogenico, proliferazione cellulare e inibizione dell'apoptosi o sviluppo di cancro ovarico
- stimola l'espressione da parte di cellule della granulosa di metallo-proteinasi 9 (MMP-9), associata con la progressione del k ovarico

Bisphenol A and Hormone-Associated Cancers: Current Progress and Perspectives

Hui Gao, MD, Bao-Jun Yang, MD, Nan Li, MD, Li-Min Feng, MD, Xiao-Yu Shi, MS, Wei-Hong Zhao, MD, and Si-Jin Liu, PhD

Medicine • Volume 94, Number 1, January 2015

Non è chiaro se gli effetti del BPA sullo sviluppo ovarico pre-natale e neonatale possano aumentare il rischio di cancro ovarico in età adulta.

Nel topo adulto CD-1 l'esposizione per lungo termine (18 mesi) a BPA induce un aumento significativo di cisti ovariche e iperplasia cistica dell'endometrio, lesioni considerate pre-maligne (Diamanti-Karandakis et al.. Phenotypes and environmental factors: their influence in PCOS. Curr Pharm Des 2012, 18-270-282).

Mancano comunque ancora dati epidemiologici sulla correlazione fra esposizione a BPA e cancro ovarico.

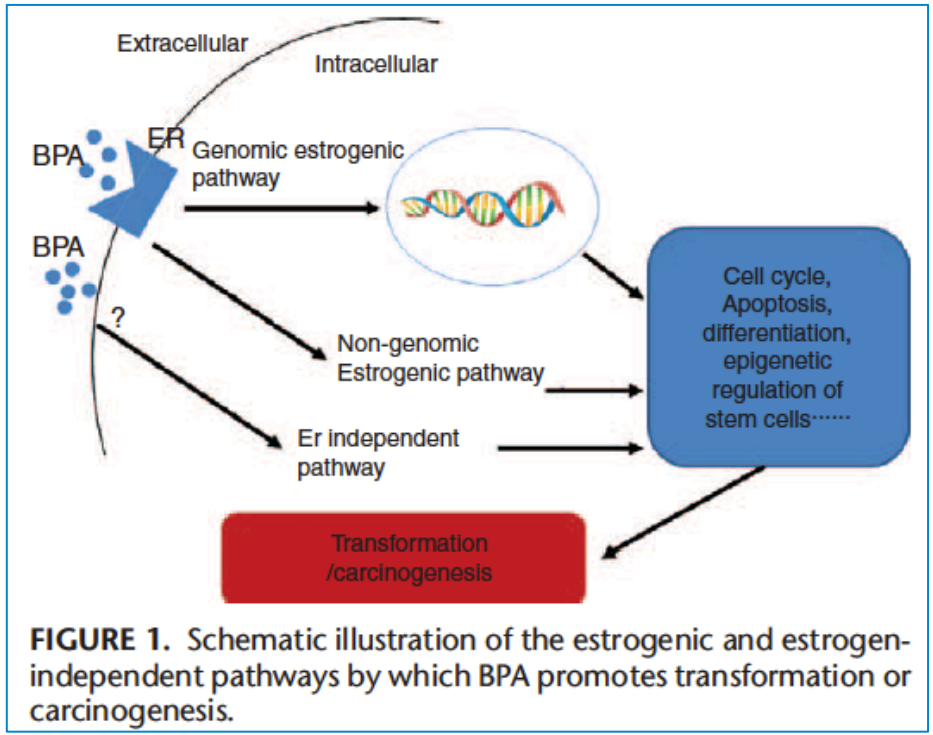


FIGURE 1. Schematic illustration of the estrogenic and estrogen-independent pathways by which BPA promotes transformation or carcinogenesis.

- Sulla base di esperimenti sull'animale è dimostrato che l'esposizione ad agenti chimici, incluso ECDs può interferire con lo sviluppo e la funzione ovarica.

- Gli studi sull'animale possono chiarire le relazioni fra esposizione precoce ed effetti nel corso della vita adulta.

- Tuttavia gli studi epidemiologici nell'uomo in questo campo sono difficili da interpretare, per il 'time lag' fra esposizione durante lo sviluppo e manifestazione degli effetti avversi nella vita adulta.

- Inoltre pattern di esposizione complessi possono distorcere le informazioni, contribuendo alla difficoltà di interpretazione.

- Una valutazione integrata degli studi sull'animale e sull'uomo conferma comunque che la salute della funzione riproduttiva femminile nella vita adulta può essere compromessa da fattori ambientali, compresa l'esposizione a ECDs durante la vita fetale.