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Prof. Ordinario di Pediatria

Gli interferenti endocrini nella catena alimentare

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2) DIFFUSIONE
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4) IMPATTO SULLA SALUTE
5) PREVENZIONE

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1) **DEFINIZIONE**
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DEFINIZIONE

Sostanza o materiale esogeno che possa alterare una o più funzioni del sistema endocrino e conseguentemente causare effetti avversi sulla salute di un organismo sano e della sua progenie

European Commission

Qualsiasi sostanza esogena in grado di interferire con la sintesi, la secrezione, il trasporto, il metabolismo, il legame recettoriale o l'escrezione di una sostanza endogena con azione ormonale normalmente in grado di garantire l'omeostasi, il normale sviluppo e la funzione riproduttiva di un individuo

U. S. Environmental Protection Agency

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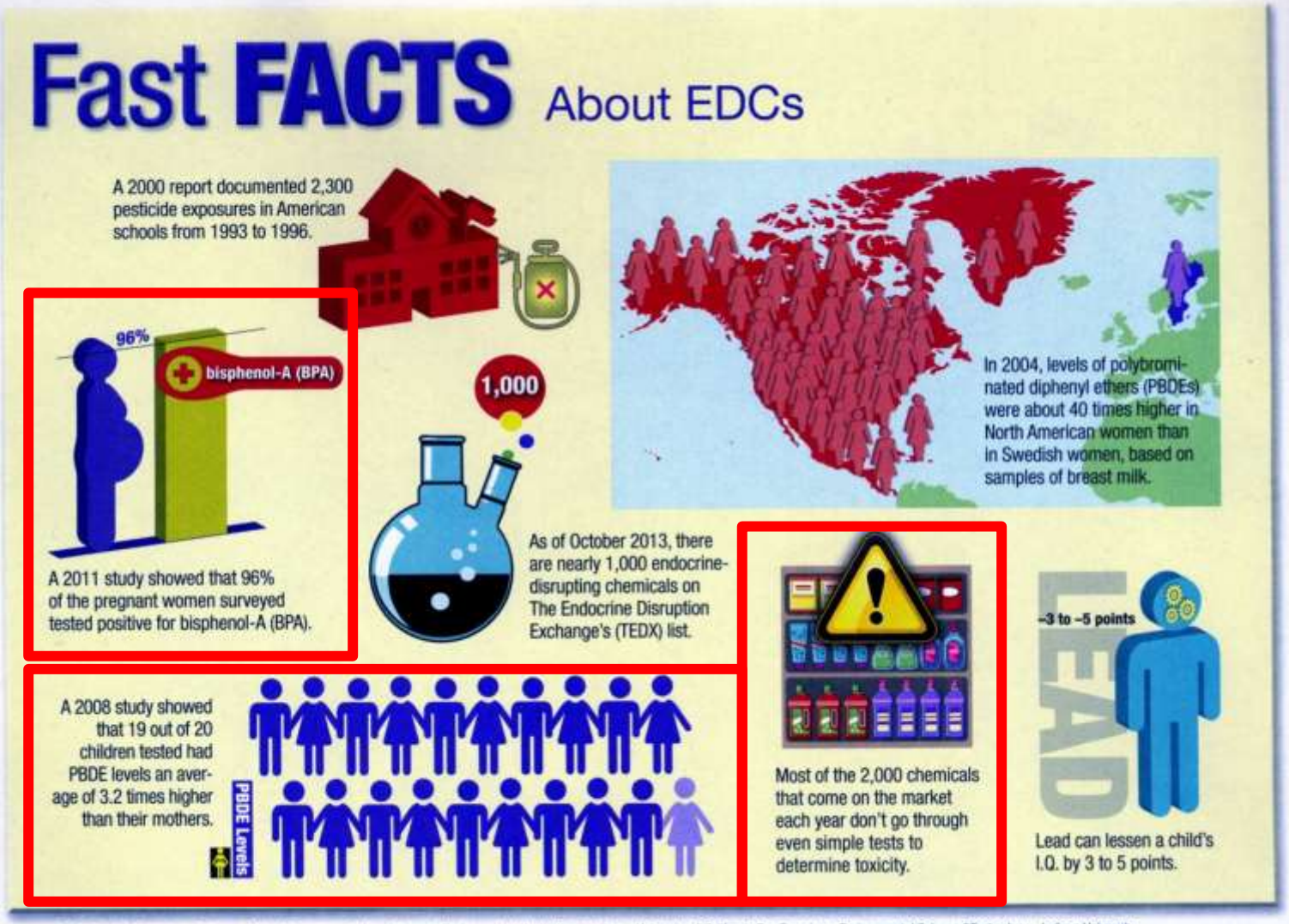
Dove si trovano gli ftalati?

Endocrine News April 2014



Dove si trovano gli ftalati?

What Are the Sources of Exposure to Eight Frequently Used Phthalic Acid Esters in Europeans?

Risk Analysis, Vol. 26, No. 3, 2006

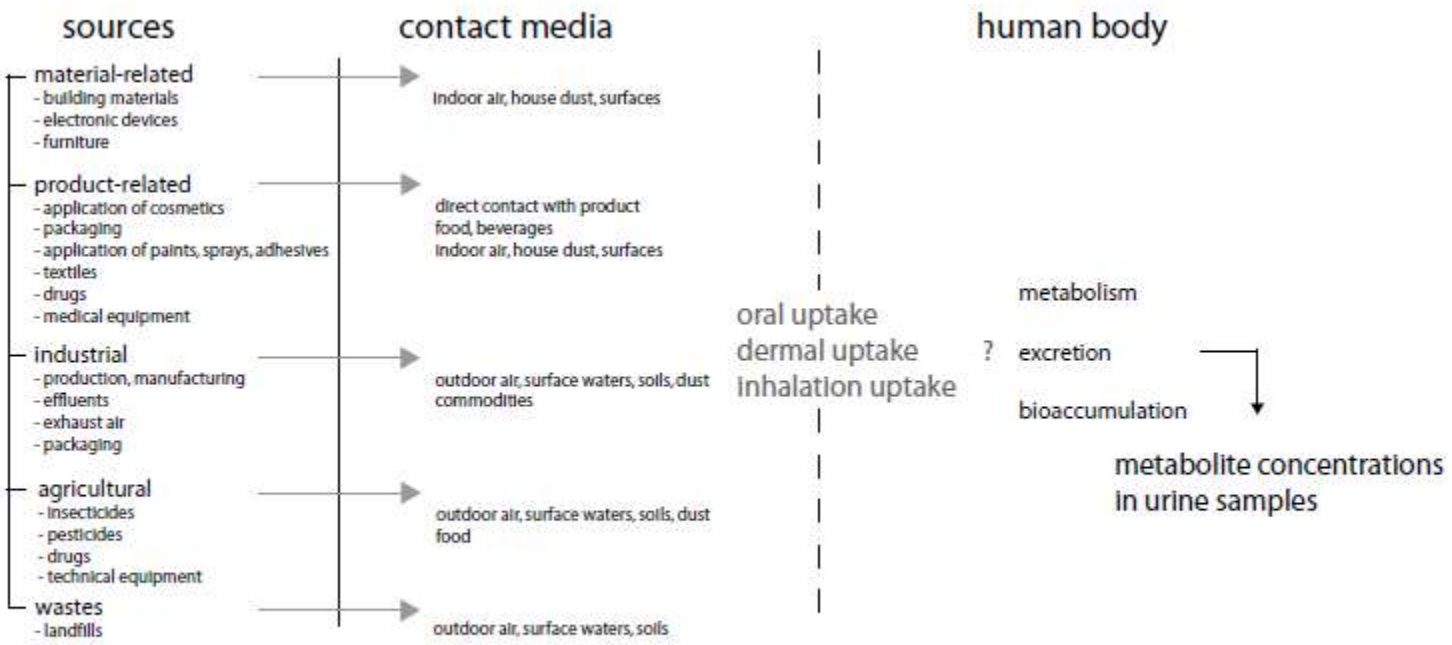
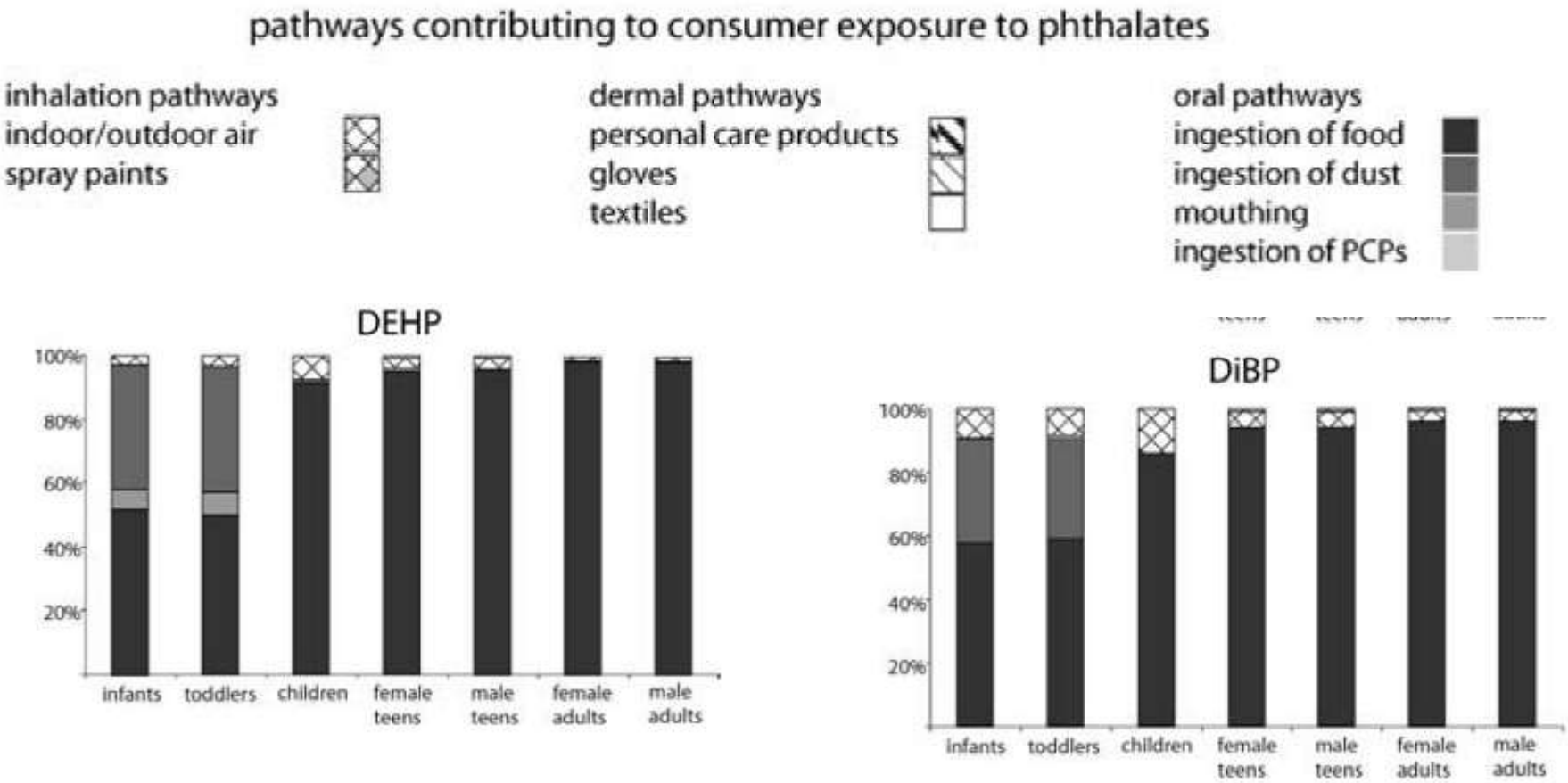


Fig. 1. Consumers are exposed to phthalates via different sources. Measurements of concentrations of phthalate metabolites in urine samples have demonstrated the ubiquitous consumer exposure to these plasticizers.

Dove si trovano gli ftalati?



Risk Analysis, Vol. 26, No. 3, 2006

What Are the Sources of Exposure to Eight Frequently Used Phthalic Acid Esters in Europeans?

Matthias Wormuth,[1] Martin Scheringer,[1*] Meret Vollenweider,[1] and Konrad Hungerbühler[1]

Dove si trovano gli ftalati?

Temporal Trends in Phthalate Exposures: Findings from the National Health and Nutrition Examination Survey, 2001–2010
Ami R. Zota,[1,2] Antonia M. Calafat,[3] and Tracey J. Woodruff[2]

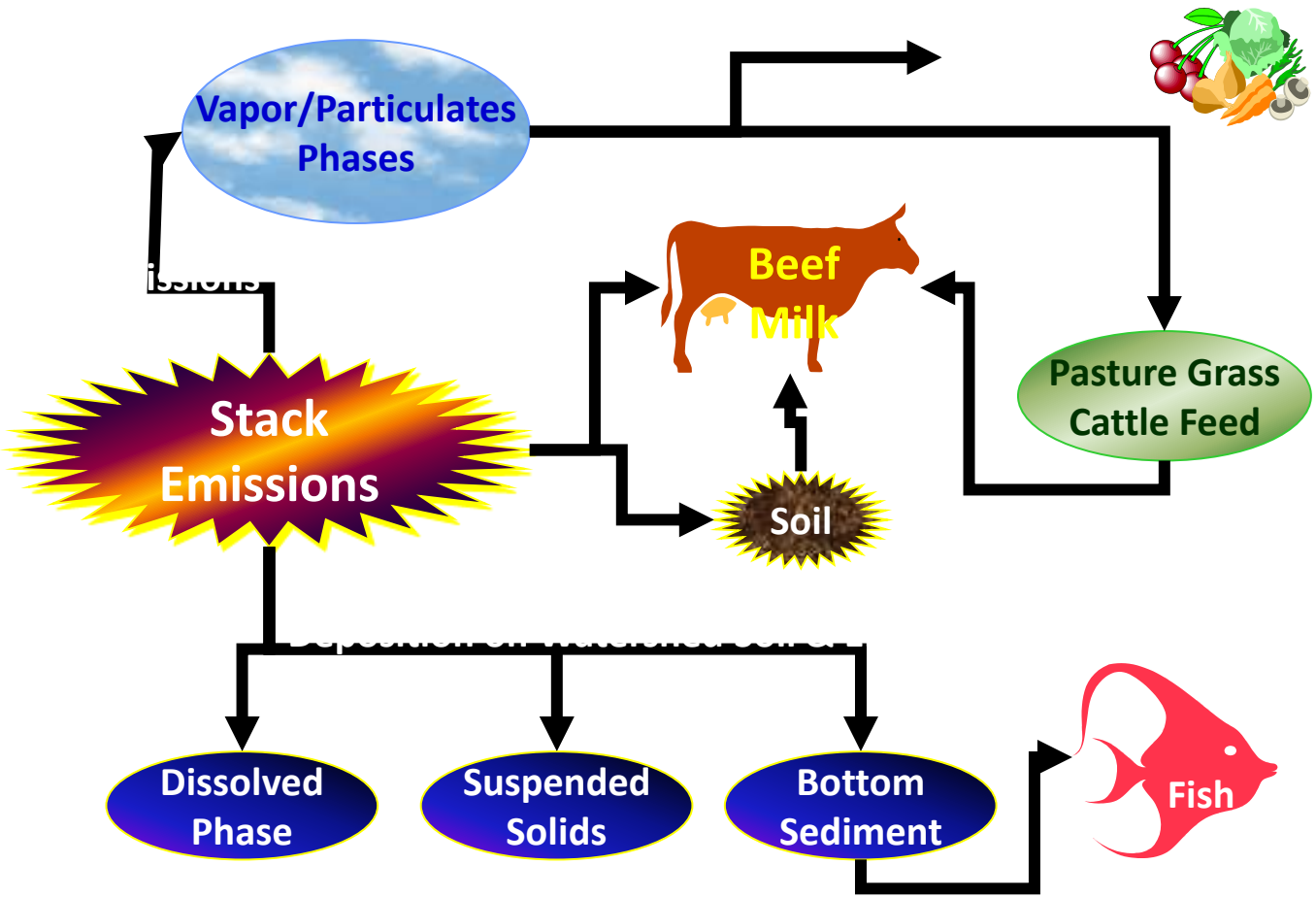
Environmental Health Perspectives • VOLUME 122 | NUMBER 3 | March 2014

Table 1. Phthalates and urinary metabolites measured in the NHANES biomonitoring program.

Phthalate	Abbrev	Level of restriction in the U.S.[a]	MW[b]	Urinary metabolites	Abbrev	Common sources
Dimethyl phthalate	DMP	—	194.2	Monomethyl phthalate	MMP	Insect repellent, plastic bottles, food[c,d]
Diethyl phthalate	DEP	—	222.2	Monoethyl phthalate	MEP	Fragrance, cosmetics, medications[e,f,g]
Di-*n*-butyl phthalate	DnBP	++	278.4	Mono-*n*-butyl phthalate	MnBP	Cosmetics, medications, food packaging, food, PVC applications[e,g,h,i,j,k]
Diisobutyl phthalate	DiBP	—	278.3	Monoisobutyl phthalate	MiBP	Cosmetics, food, food packaging[e,f,h,i]
Butylbenzyl phthalate	BBzP	++	312.4	Monobenzyl phthalate Monobutyl phthalate (minor)	MBzP	PVC flooring, food, food packaging[h,l]
Dicyclohexyl phthalate	DCHP	—	330.4	Monocyclohexyl phthalate	MCHP	Food, food packaging[h]
Di(2-ethylhexyl) phthalate	DEHP	++	390.6	Mono(2-ethylhexyl) phthalate Mono(2-ethyl-5-hydroxyhexyl) phthalate Mono(2-ethyl-5-oxohexyl) phthalate Mono(2-ethyl-5-carboxypentyl) phthalate	MEHP MEHHP MEOHP MECPP	PVC applications, toys, cosmetics, food, food packaging[e,f,h,i,j,k,m]
Di-*n*-octyl phthalate	DnOP	+	390.6	Mono(3-carboxypropyl) phthalate Monooctyl phthalate	MCPP[n] MOP	PVC applications, food, food packaging[h,i,j]
Diisononyl phthalate	DiNP	+	418.6	Monoisononyl phthalate Monocarboxyoctyl phthalate	MiNP MCOP	PVC applications, toys, flooring, wall covering[i,m,o]
Diisodecyl phthalate	DiDP	+	446.4	Monocarboxynonyl phthalate	MCNP	PVC applications, toys, wire and cables, flooring[i,m,o]

Abbreviations: —, no use restrictions; +, moderate use restrictions; ++, most use restrictions; abbrev, abbreviation.
[a]Indicates degree of risk management activities by federal and state governments in the United States (U.S. EPA 2012). [b]We classified DMP, DEP, DnBP, and DiBP as low-molecular-weight phthalates, and BBzP, DCHP, DEHP, DnOP, DiNP, and DiDP high-molecular-weight phthalates. [c]Karunamoorthi and Sabesan (2010). [d]Al-Saleh et al. (2011). [e]Koniecki et al. (2011). [f]Dodson et al. (2012). [g]Kelley et al. (2012). [h]Fierens et al. (2012). [i]Schecter et al. (2013). [j]Kawakami et al. (2011). [k]Cirillo et al. (2013). [l]Kavlock et al. (2002). [m]Stringer et al. (2000). MCPP is also a nonspecific metabolite of several high-molecular-weight phthalates. [n]European Chemicals Agency (2012).

Meccanismi di trasferimento



Meccanismi di trasferimento

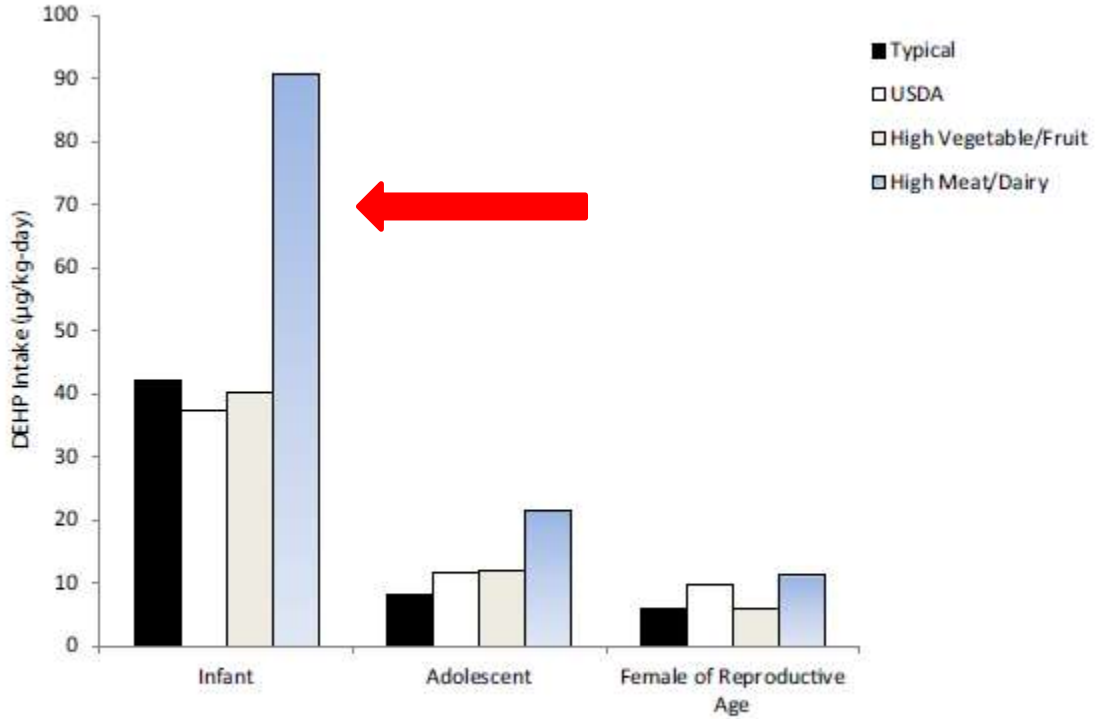


Figure 1 Per capita total DEHP intake (µg/kg-day) for four dietary patterns.

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*]

Environmental Health 2014, **13**:43

Meccanismi di trasferimento

Children's Exposure to Di(2-ethylhexyl)phthalate and Dibutylphthalate Plasticizers from School Meals

J. Agric. Food Chem. 2011, 59, 10532–10538

Teresa Cirillo,*[,†] Evelina Fasano,[†] Enrica Castaldi,[†] Paolo Montuori,[‡] and Renata Amodio Cocchieri[†]

Table 3. DEHP Concentrations in Ready Courses before (n = 60) and after Packaging at Consuming Time (n = 60)

	DEHP (ng/g ww)			
	before packaging		after packaging	
course	mean ± SD (min−max)	median	mean ± SD (min−max)	median
first[a]	146.6 ± 99.7 (37.9−379.4)	112.6	311.4 ± 255.1 (36.6−1050.8)	224.6
second	182.4 ± 100.3 (24.6−329.5)	154.8	250.4 ± 163.4 (43.6−497.2)	253.3
vegetables	117.0 ± 70.0 (22.6−365.0)	111.4	183.0 ± 140.4 (21.3−365.0)	127.0

[a] First course values showed statistically significant differences between before and after packaging (p = 0.02).

since 2005 the European Food Safety Authority (EFSA) has set tolerable daily intakes (TDIs) of 0.05 mg/kg body weight (bw) for DEHP and 0.01 mg/kg bw for DBP.[20−22]

Meccanismi di trasferimento

Exposure to Di-2-Ethylhexyl Phthalate, Di-*N*-Butyl Phthalate and Bisphenol A through Infant Formulas

Teresa Cirillo,[*,†] Giuseppe Latini,[‡] Maria Antonietta Castaldi,[§] Lucia Dipaola,[‡] Evelina Fasano,[†] Francesco Esposito,[†] Gelsomina Scognamiglio,[†] Fabio Di Francesco,[‡,∥] and Luigi Cobellis[§]

DOI: 10.1021/jf505563k
J. Agric. Food Chem. 2015, 63, 3303−3310

Table 2. Concentrations of Di(2-ethylhexyl)phthalate (DEHP), di-*n*-butylphthalate (DnBP) and Bisphenol A (BPA) in Liquid Milk Samples and Type of Packaging

type	packaging	DEHP (μg/g dry weight)	DnBP (μg/g dry weight)	BPA (μg/g dry weight)
infant formula	Tetrapak	0.696	0.075	0.003
		1.831	0.067	0.003
infant formula	PET	0.092	0.082	0.030
		0.219	0.084	0.020
		0.633	0.142	0.009
		2.067	0.0075	0.003
		1.456	0.287	0.003
		0.301	0.067	0.003
		2.099	0.624	0.003
		0.784	0.482	0.058
		0.606	0.216	0.014
		1.877	0.787	0.003
		1.202	0.351	0.003
		0.923	0.899	0.017
		0.256	0.14	0.018
		0.929	0.088	0.003
		2.919	1.624	0.169
		0.852	0.423	0.030
		1.428	0.384	0.003
		0.796	0.807	0.003
		1.137	0.272	0.003
		1.371	0.548	0.003

Meccanismi di trasferimento

Exposure to Di-2-Ethylhexyl Phthalate, Di-*N*-Butyl Phthalate and Bisphenol A through Infant Formulas

Teresa Cirillo,[*,†] Giuseppe Latini,[‡] Maria Antonietta Castaldi,[§] Lucia Dipaola,[‡] Evelina Fasano,[†] Francesco Esposito,[†] Gelsomina Scognamiglio,[†] Fabio Di Francesco,[‡,∥] and Luigi Cobellis[§]

DOI: 10.1021/jf505563k
J. Agric. Food Chem. 2015, 63, 3303−3310

Table 3. Concentrations of Di(2-ethylhexyl)phthalate (DEHP), Di-*n*-butylphthalate (DnBP) and Bisphenol A (BPA) in Powder Milk Samples in Aluminium Packaging

type	DEHP (μg/g dry weight)	DnBP (μg/g dry weight)	BPA (μg/g dry weight)
infant formula	1.408	0.321	0.003
	1.134	0.199	0.003
	0.702	0.155	0.003
	0.871	0.212	0.028
	1.274	0.161	0.008
	0.883	0.137	0.003
	3.552	0.809	0.011
	2.909	0.765	0.100
	1.023	0.101	0.009
	1.142	0.356	0.022
	0.981	0.392	0.003
	1.024	0.161	0.003
	0.922	0.337	0.043
	1.052	0.709	0.054
	1.018	0.575	0.026
	2.341	0.187	0.012
	0.982	0.123	0.003
	1.723	0.118	0.016
	1.899	0.704	0.003
	1.175	0.148	0.035
	2.409	0.349	0.041
infant formula for gastrointestinal problems	1.213	0.301	0.003
	1.897	0.812	0.108
	1.821	0.201	0.018
rice milk formula	1.723	0.211	0.003
	2.871	0.321	0.003
	0.951	0.184	0.046
premature formula	0.997	0.201	0.003

Meccanismi di trasferimento

Exposure to Di-2-Ethylhexyl Phthalate, Di-*N*-Butyl Phthalate and Bisphenol A through Infant Formulas

Teresa Cirillo,[*,†] Giuseppe Latini,[‡] Maria Antonietta Castaldi,[§] Lucia Dipaola,[‡] Evelina Fasano,[†] Francesco Esposito,[†] Gelsomina Scognamiglio,[†] Fabio Di Francesco,[‡,∥] and Luigi Cobellis[§]

DOI: 10.1021/jf505563k
J. Agric. Food Chem. 2015, 63, 3303−3310

Table 5. Worst Case, Estimated Daily Dietary Intake of Di(2-ethylhexyl)phthalate (DEHP), di-*n*-butylphthalate (DnBP) and Bisphenol A (BPA) in Newborns Fed with Liquid or Powder Formulae, According to the 50th and 97th of Infant Weight Growth Curve by WHO (2006)

	infant's average weight (kg)		milk assumption (g dry weight/day)		DEHP intake (μg/kg bw day)		DnBP intake (μg/kg bw day)		BPA intake (μg/kg bw[b] day)	
age (days)	50th pctl[a]	97th pctl	50th pctl	97th pctl	50th pctl	97th pctl	50th pctl	97th pctl	50th pctl	97th pctl
15	3.70	4.75	67.61	76.06	45.74	40.07	14.64	12.82	1.06	0.93
30	4.25	5.45	92.96	101.41	54.68	46.52	17.50	14.89	1.27	1.08
45	4.76	6.20	101.41	109.86	53.32	44.33	17.06	14.19	1.24	1.03
60	5.41	6.84	98.59	105.63	45.60	38.61	14.59	12.35	1.06	0.90
75	5.76	7.26	105.63	112.68	45.85	38.83	14.67	12.42	1.06	0.90
90	6.10	7.65	112.68	126.76	46.18	41.43	14.78	13.26	1.07	0.96
120	6.70	8.35	114.08	129.58	42.57	38.80	13.62	12.41	0.99	0.90

[a]pctl, percentile. [b]kg bw, kg body weight.

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MECCANISMO D'AZIONE

frontiers in NEUROSCIENCE

REVIEW ARTICLE
published: 03 March 2015
doi: 10.3389/fnins.2015.00057

Bisphenol A and phthalate endocrine disruption of parental and social behaviors

*Cheryl S. Rosenfeld**

Bond Life Sciences Center, Genetics Area Program, Biomedical Sciences, University of Missouri, Columbia, MO, USA

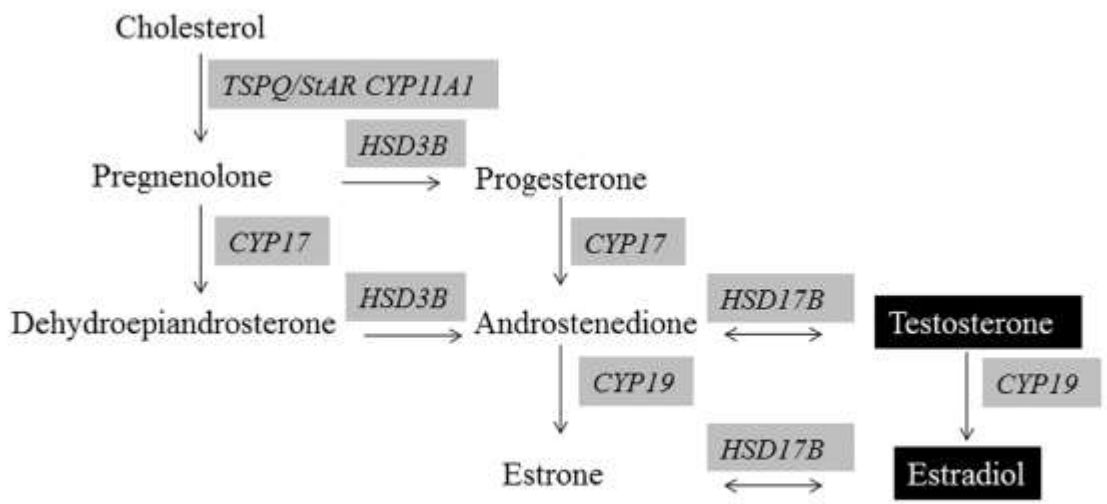

FIGURE 1 | Steroidogenesis of androgens and estrogens. Evidence exists that all of the shaded enzymes required in the synthesis of these hormones are altered by BPA and/or phthalate exposure.

MECCANISMO D'AZIONE

Sex-specific *Esr2* mRNA expression in the rat hypothalamus and amygdala is altered by neonatal bisphenol A exposure

Jinyan Cao[1], Linwood Joyner[1], Jillian A Mickens[1], Stephanie M Leyrer[1] and Heather B Patisaul[1,2]

Table 2 *Esr2* mRNA expression in postnatal (PND 0 to PND 2) rat brain with neonatal BPA exposure.

		Vehicle	EB	LBPA	HBPA
BNSTp	PND 4	F=M	F=M	F=M	F=M
	PND 10	F=M	↓F=M	F>M⇓	↓F<M
PVN	PND 4	F=M	↓F=M⇓	F=M	F=M⇓
	PND 10	F<M	↓F=M⇓	F>M⇓	F=M
MeA	PND 4	F=M	↓F=M	↓F=M	↓F=M
	PND 10	F=M	F=M	NA	F=M⇓
SON	PND 4	F<M	F=M	F=M⇓	F=M⇓
	PND 10	F=M	F=M	F=M	↓F=M⇓

'↓' and '⇓' represent signal significantly decreased compared with vehicle control or PND 0 female and male respectively. *P=0.07 from t-test between female and male on PND 19. NA, analysis is not available.

MECCANISMO D'AZIONE

Stimulation of the pituitary–adrenal axis and of adrenocortical steroidogenesis *ex vivo* by administration of di-2-ethylhexyl phthalate to prepubertal male rats

Vichit Supornsilchai, Olle Söder and Konstantin Svechnikov

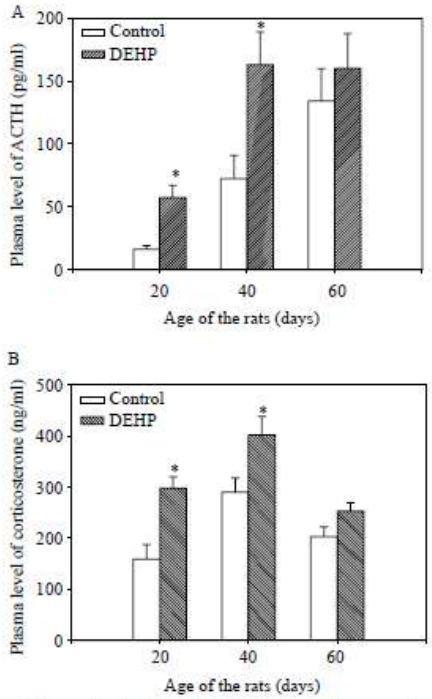

Figure 1 Plasma levels of (A) ACTH and (B) corticosterone in male rats of different ages exposed to DEHP (500 mg/kg at 20 days of age and 750 mg/kg at the ages of 40 and 60 days). DEHP was administered in corn oil by oral gavage for 4 days, while control animals received corn oil alone. Each bar (treated group and controls) represents the mean±S.E.M. (n=8, 20 days; n=12, 40 days; n=15, 60 days). *P<0·05 compared with the corresponding control values.

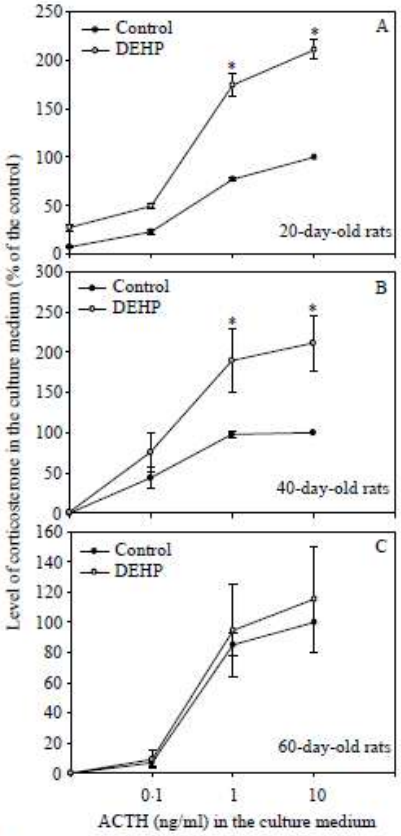

Figure 2 Effects of ACTH on corticosterone production by cultures of adrenocortical cells isolated from DEHP-treated and control male rats aged (A) 20, (B) 40, and (C) 60 days. Following incubation of these cells with varying concentrations of ACTH for 6 h, the concentrations of corticosterone in the culture media were determined by RIA. The results presented are the means±S.E.M. of three independent preparations of adrenocortical cells. *P<0·05 compared with the corresponding control values.

MECCANISMO D'AZIONE

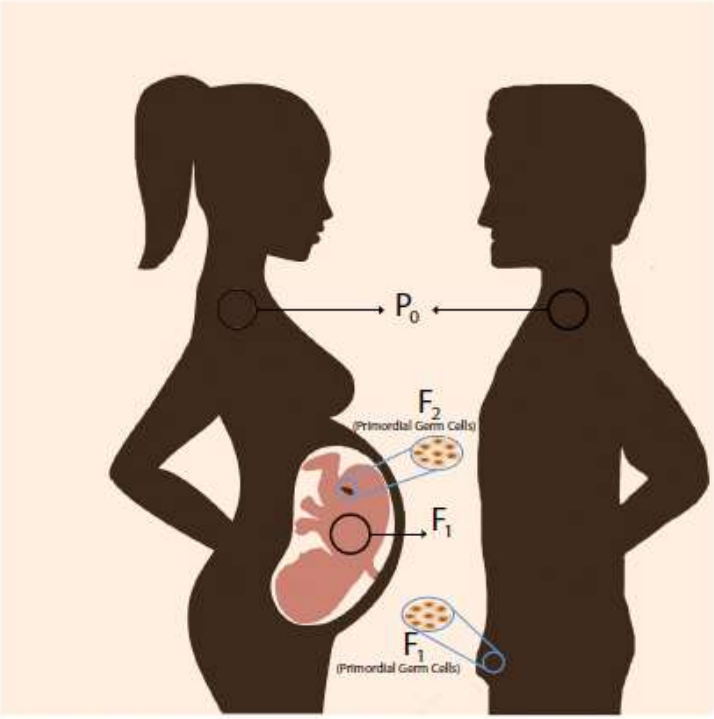

Figure 1. A cartoon of the multiple generations comprising transgenerational inheritance. A pregnant woman (P0) carries genetic and epigenetic information for up to the F2 generation. Her fetus (F1) and its germ cells (F2) may be affected by environmental exposures such as EDCs. For any changes in the F1 phenotype or epigenetic state to be considered transgenerational, the aberrant epigenetic state has to be sustained until at least the F3 generation. In contrast to females, EDC exposure in males (P0) will potentially change his germ cells, which will be the F1 generation. However, because the F2 germ cells are not exposed, any phenotypic or epigenetic changes noted in F2 can be considered transgenerational.

Minireview: Transgenerational Epigenetic Inheritance: Focus on Endocrine Disrupting Compounds

Emilie F. Rissman and Mazhar Adli

Endocrinology, August 2014, 155(8):2770–2780

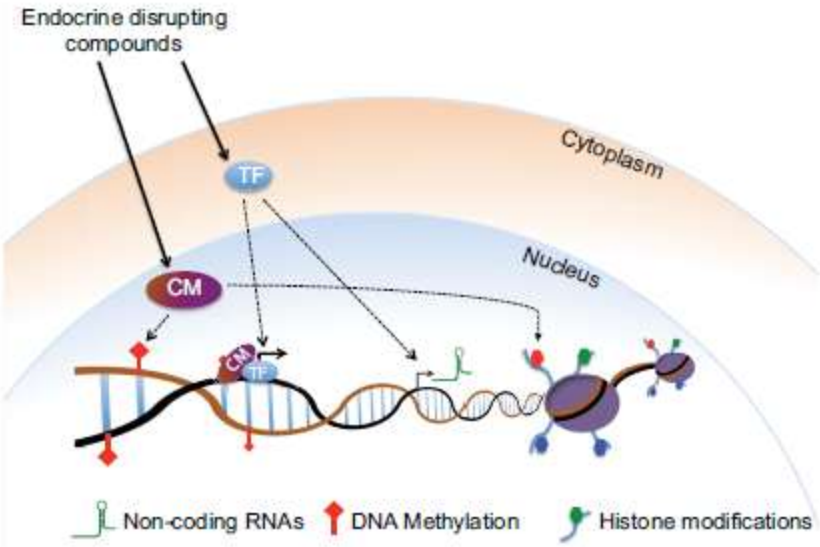

Figure 3. A general model depicting epigenetic alterations upon exposure to EDCs. EDCs bind to steroid receptors, and other TFs, thereby changing the local chromatin states and expression of various chromatin modifiers (CM) such as histone and DNA modifiers or ncRNAs. Moreover, EDCs can change the composition or the activity of epigenetic chromatin regulator complexes and thereby act directly on the global epigenome.

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IMPATTO SULLA SALUTE

Review

Bisphenol A and human health: A review of the literature

Johanna R. Rochester*

Reproductive Toxicology 42 (2013) 132–155

Reproduction
2.1.1. Fertility
2.1.2. Male sexual function
2.1.3. Reduced sperm quality
2.1.4. Sex hormone concentrations
2.1.5. Polycystic ovary syndrome
2.1.6. Endometrial disorders
2.1.7. Breast cancer
2.1.8. Miscarriage
2.1.9. Premature deliveries
Development
2.2.1. Birth weight
2.2.2. Male genital abnormalities
2.2.3. Childhood behavior/neurodevelopment
2.2.4. Childhood asthma/wheeze
Metabolic disease
2.3.1. Type-2 diabetes
2.3.2. Cardiovascular disease, hypertension, and cholesterol levels
2.3.3. Liver function
2.3.4. Obesity
Other health effects
2.4.1. Thyroid function
2.4.2. Immune function
2.4.3. Albuminuria
2.4.4. Oxidative stress and inflammation
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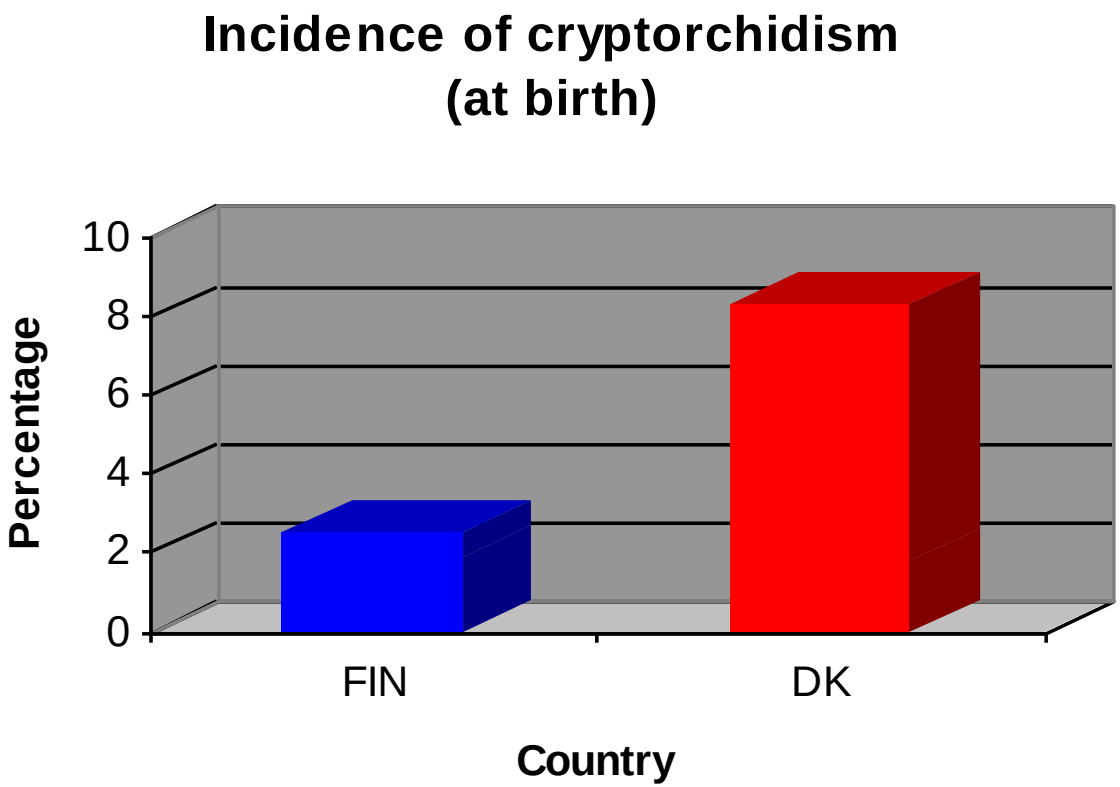
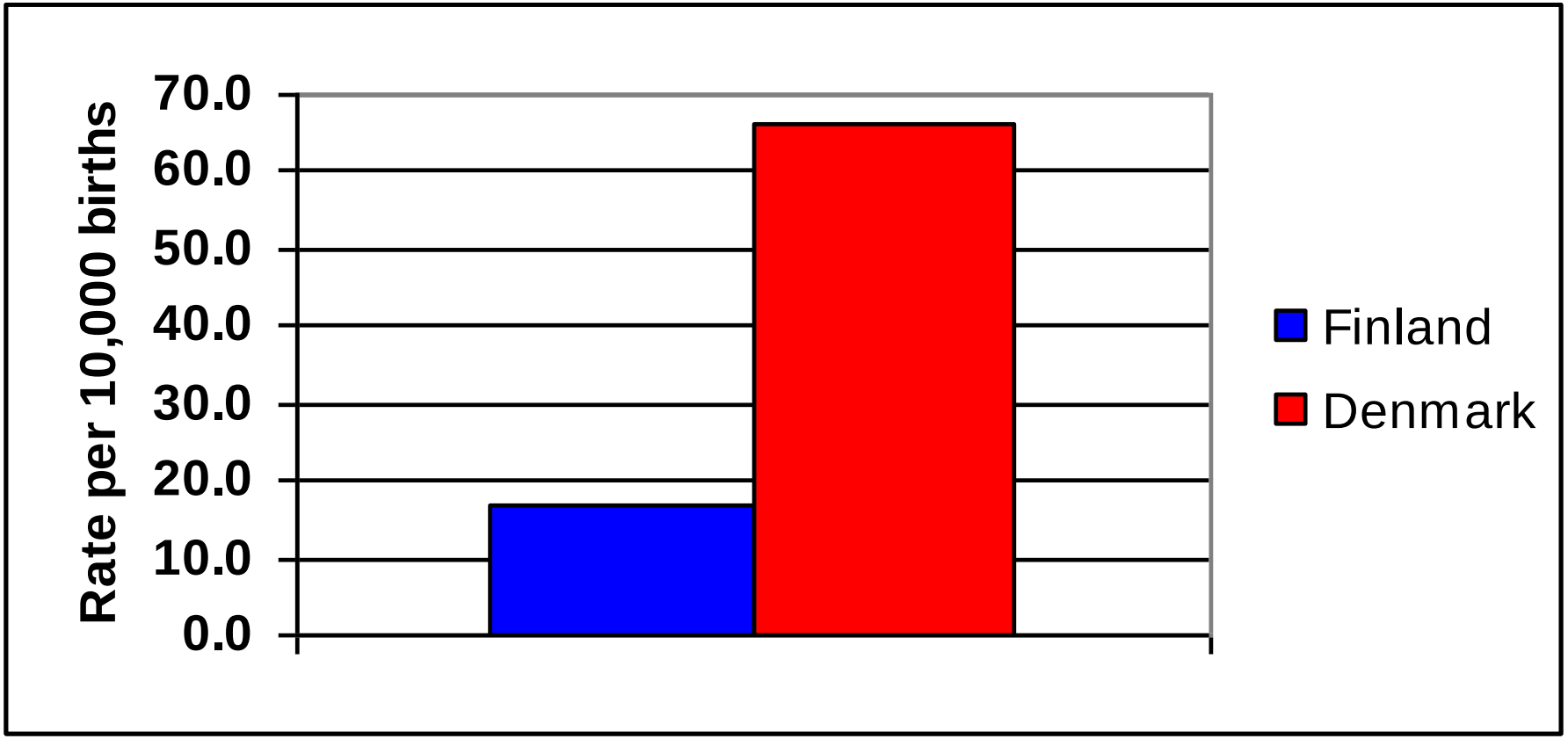
Dati epidemiologici

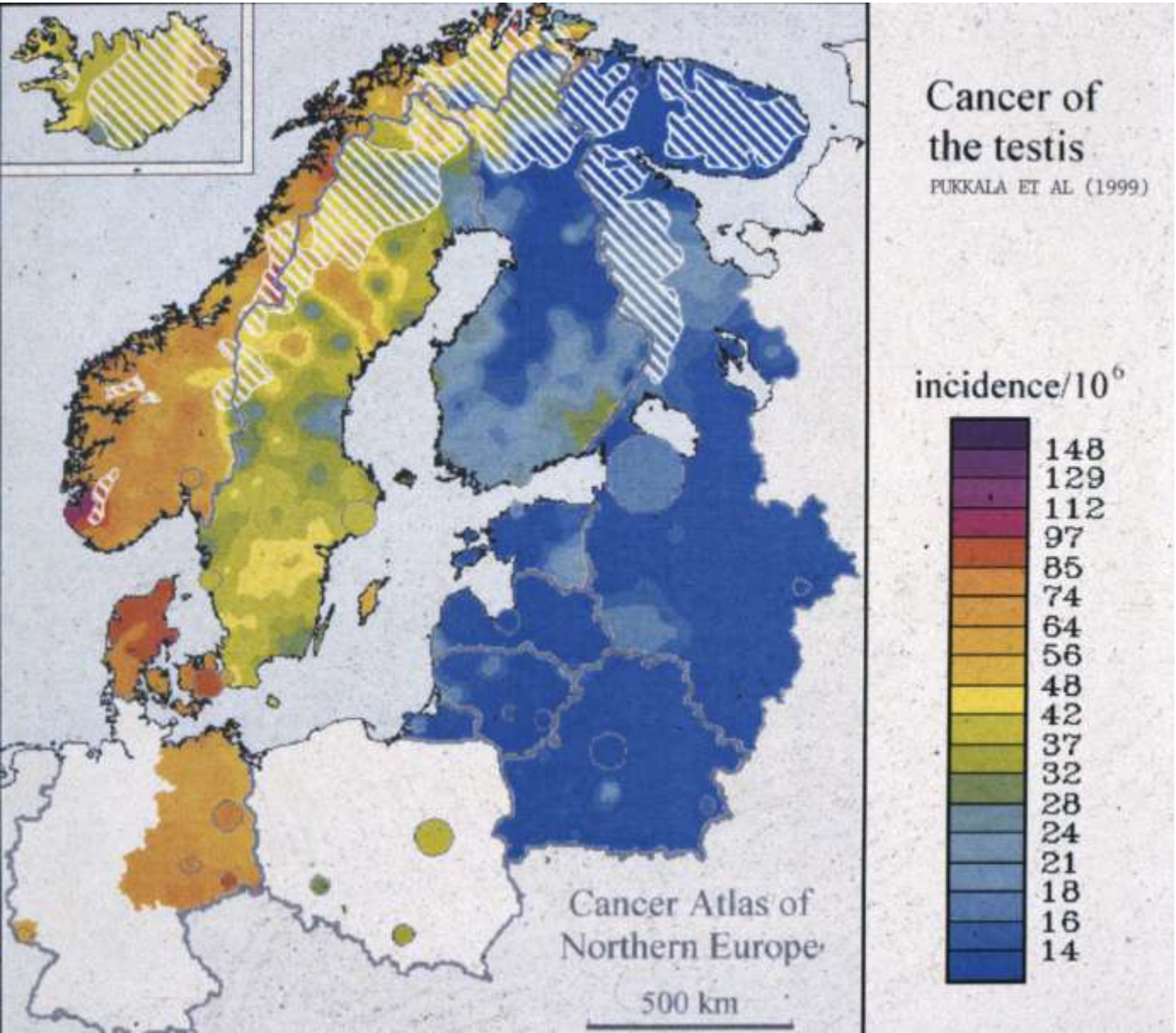


Dati epidemiologici

Birth rate of hypospadias 1997-2000



Dati epidemiologici

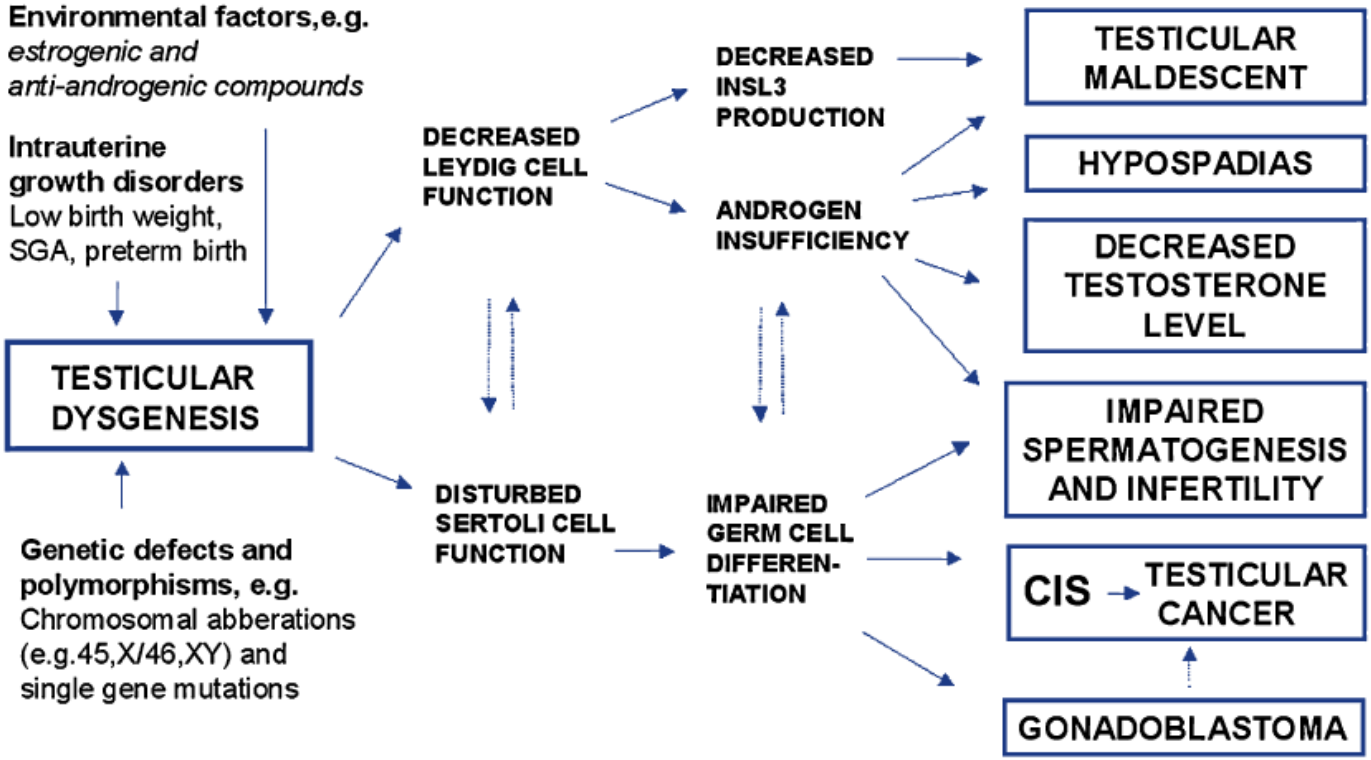


Dati epidemiologici

Environment, testicular dysgenesis and carcinoma in situ testis

Best Practice & Research Clinical Endocrinology & Metabolism
Vol. 21, No. 3, pp. 462–478, 2007

Testicular Dysgenesis Syndrome



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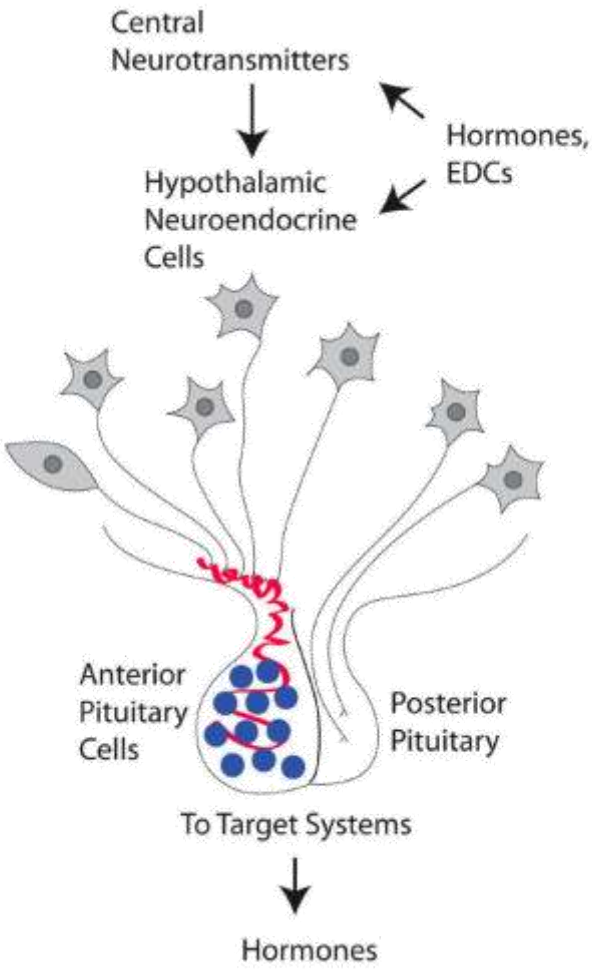
Ricerche su animali



Ruolo del sistema Kiss1/Kisspeptine sul corretto sviluppo dell'apparato riproduttivo:

- Gene kiss1 codifica per i peptidi kisspeptine, recentemente identificati come fattori chiave nell'attività del GnRH pulse ipotalamico

- **Studi nel topo hanno dimostrato come l'esposizione precoce a xeno-estrogeni come il BPA determina una riduzione dei** livelli di Kiss1 mRNA e della densità delle fibre kisspetinergiche dell'ipotalamo

- Alterazione della funzione del GnRH pulse ipotalamico e del conseguente sviluppo puberale

Tena Sempere, Int J Androl 2010
Navarro et al, Endocrinology 2009

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3) MECCANISMO D'AZIONE
4) **IMPATTO SULLA SALUTE**
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   - ricerche su animali
   - **espressione genica**

Espressione genica

Evidence for Epigenetic Abnormalities of the Androgen Receptor Gene in Foreskin from Children with Hypospadias

J Clin Endocrinol Metab, December 2011, 96(12):E1953–E1962

A. Vottero, R. Minari, I. Viani, F. Tassi, F. Bonatti, T. M. Neri, L. Bertolini, S. Bernasconi, and L. Ghizzoni

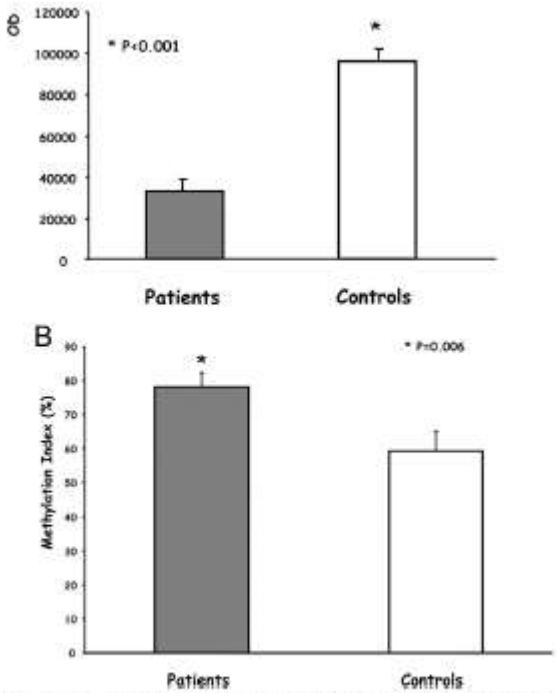


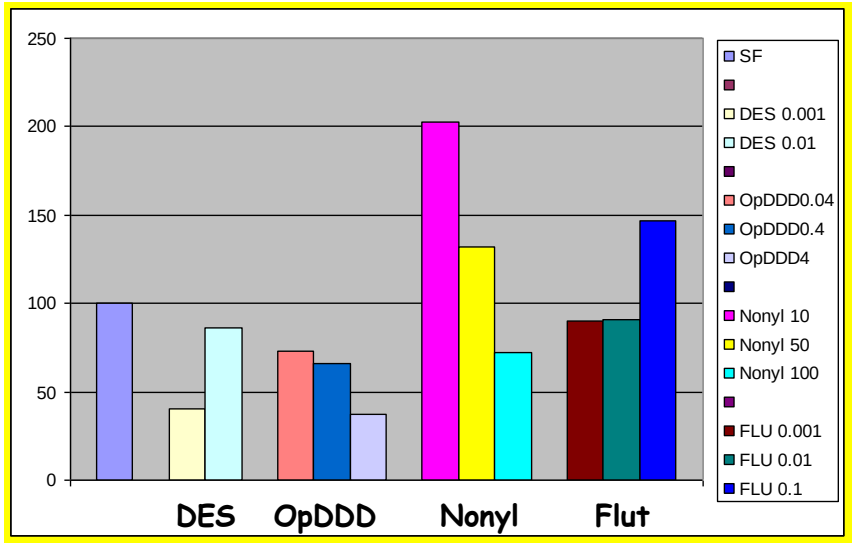
FIG. 2. A, *AR* gene expression (molecular mass 110 kDa) analyzed by Western blotting in foreskin tissue from patients with hypospadias and normal children (mean ± SE, $P < 0.001$). B, *AR* gene methylation in foreskin tissue from patients with hypospadias and normal children (methylation index, mean ± SE, $P < 0.006$).

AR gene in foreskin tissue of **hypospadic patients** is more methylated, and thus less active, than in normal children of the same age

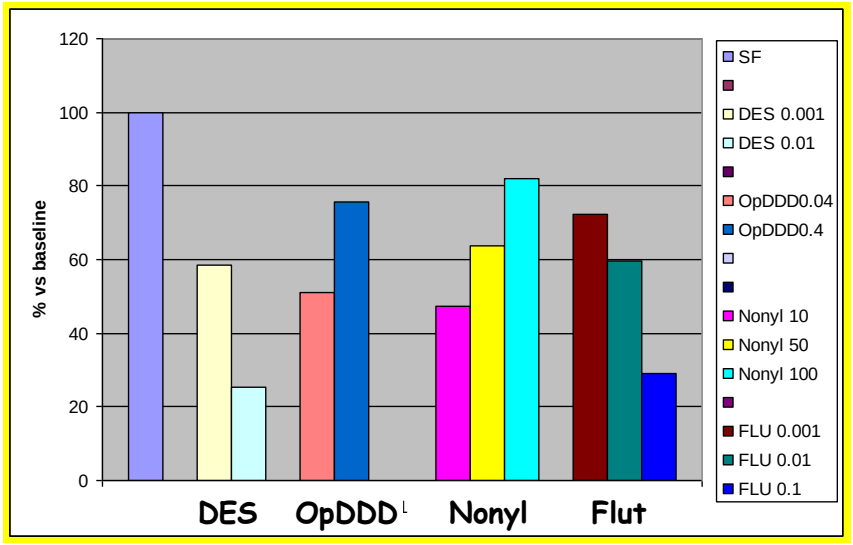
Hypospadic patients present a reduced expression of AR in comparison to controls

Espresione genica

Androgen receptor gene methylation



Androgen receptor gene expression



DES: Diethylstilbesterol
OpDDD: o,p'-Diclorodiphenyldichloroethane
Nonyl: Nonylphenol
Flut: Flutamide

DES and Flutamide: AR gene methylation

AR gene expression

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   - espressione genica
   - **ricerche sull'uomo**

Ricerche sull'uomo

Identification of Phthalate Esters in the Serum of Young Puerto Rican Girls with Premature Breast Development

Ivelisse Colón,[1] Doris Caro,[1] Carlos J. Bourdony,[2,3] and Osvaldo Rosario[1]

Environ Health Perspect 2000

Figure 1. Twenty-three-month-old Puerto Rican girl with premature breast development (thelarche).

Phthalate esters were consistently detected at significant concentration levels (ranging from tens of parts per billion to units of parts per million) in 28 of 41 (68%) serum samples obtained from the thelarche patients.

Ricerche sull'uomo

Prenatal Phthalate Exposures and Anogenital Distance in Swedish Boys

Carl-Gustaf Bornehag,[1] Fredrik Carlstedt,[2] Bo AG. Jönsson,[3] Christian H. Lindh,[3] Tina K. Jensen,[4] Anna Bodin,[2] Carin Jonsson,[2] Staffan Janson,[1] and Shanna H. Swan[5]

Environmental Health Perspectives • VOLUME 123 | NUMBER 1 | January 2015

Table 6. Association between AGD (short, medium, and long) and log-transformed concentrations of phthalate metabolites in prenatal urine calculated in an adjusted[a] logistic regression model [OR (95% CI)].

		AGDas			AGDap		
Phthalate	Metabolite	Short 1st quartile	Medium 2nd–3rd quartile	Long 4th quartile (ref)	Short 1st quartile	Medium 2nd–3rd quartile	Long 4th quartile (ref)
DBP	MBP	1.84 (0.43, 7.91)	0.73 (0.21, 2.60)	1.0	1.83 (0.37, 9.02)	0.84 (0.23, 3.01)	1.0
DEP	MEP	1.06 (0.47, 2.40)	0.84 (0.32, 2.16)	1.0	2.23 (0.80, 6.24)	1.11 (0.47, 2.62)	1.0
BBzP	MBzP	1.92 (0.74, 5.00)	0.75 (0.33, 1.79)	1.0	1.49 (0.53, 4.17)	1.21 (0.52, 2.81)	1.0
DEHP	MEHP	1.71 (0.52, 5.64)	1.04 (0.37, 2.93)	1.0	1.98 (0.51, 7.66)	4.01 (1.32, 12.20)	1.0
	oh-MEHP	1.85 (0.50, 6.95)	0.89 (0.27, 2.92)	1.0	2.62 (0.58, 11.78)	3.05 (0.91, 10.16)	1.0
	oxo-MEHP	1.47 (0.40, 5.37)	0.72 (0.22, 2.32)	1.0	2.23 (0.50, 9.87)	3.05 (0.93, 10.07)	1.0
	cx-MEPP	1.76 (0.46, 6.70)	0.98 (0.30, 3.28)	1.0	1.76 (0.38, 8.27)	2.80 (0.82, 9.57)	1.0
	ΣDEHP	1.82 (0.47, 7.06)	0.88 (0.26, 3.00)	1.0	2.44 (0.51, 11.72)	3.36 (0.96, 11.82)	1.0
DiNP	oh-MMeOP	2.61 (1.24, 5.48)	1.08 (0.55, 2.09)	1.0	1.47 (0.67, 3.22)	1.17 (0.61, 2.24)	1.0
	oxo-MMeOP	2.99 (1.28, 7.00)	1.17 (0.54, 2.53)	1.0	1.73 (0.70, 4.23)	1.28 (0.61, 2.70)	1.0
	cx-MMeHP	3.11 (1.27, 7.66)	1.21 (0.52, 2.78)	1.0	1.77 (0.67, 4.65)	1.41 (0.62, 3.21)	1.0
	ΣDiNP	3.02 (1.28, 7.09)	1.16 (0.52, 2.56)	1.0	1.69 (0.68, 4.20)	1.32 (0.61, 2.84)	1.0

ref, reference.
[a]Adjusted for age (months), gestational week for urine sampling, weight for age percentile, and creatinine.

Ricerche sull'uomo

RESEARCH ARTICLE

Di-(2-Ethylhexyl) Phthalate Metabolites in Urine Show Age-Related Changes and Associations with Adiposity and Parameters of Insulin Sensitivity in Childhood

PLOS ONE | DOI:10.1371/journal.pone.0117831 February 23, 2015

Arianna Smerieri[1], Chiara Testa[2,3,4], Pietro Lazzeroni[1], Francesca Nuti[2,3,4], Enzo Grossi[5], Silvia Cesari[1], Luisa Montanini[1], Giuseppe Latini[6,7], Sergio Bernasconi[1], Anna Maria Papini[2,3,4], Maria E. Street[1,8]*

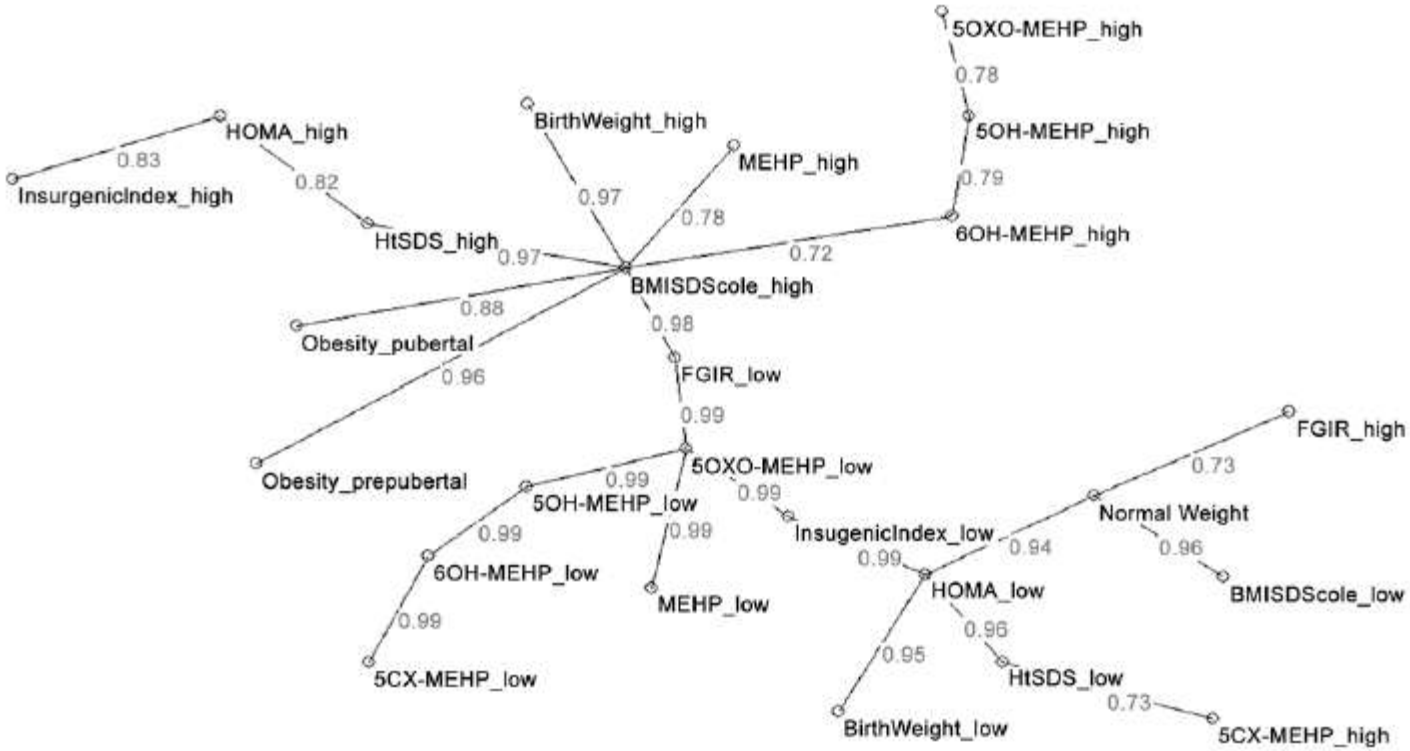

Fig 4. Semantic Connectivity Map linking DEHP metabolites. Analysis with auxological parameters and measurements of insulin sensitivity in normal-weight and obese children and adolescents. Values ranging from 0 (no association) to 1 (the strongest association) express the strength of association.

doi:10.1371/journal.pone.0117831.g004

Periodi critici per l'esposizione

- Periodo fetale
- Periodo neonatale
- Infanzia
- Pubertà

L'esposizione agli EDCs di un soggetto in una fase attiva e vivace dello sviluppo determina una peculiare modulazione dell'espressione genica con la possibilità di sviluppo di una condizione patologica anche dopo anni dall'esposizione.

The developmental basis of adult disease
Barker, European Journal of epidemiology, 2003

Susceptibility of Children to Environmental Pollutants

Peter D. Sly and Felicity Flack

Ann. N.Y. Acad. Sci. 1140: 163–183 (2008).
doi: 10.1196/annals.1454.017

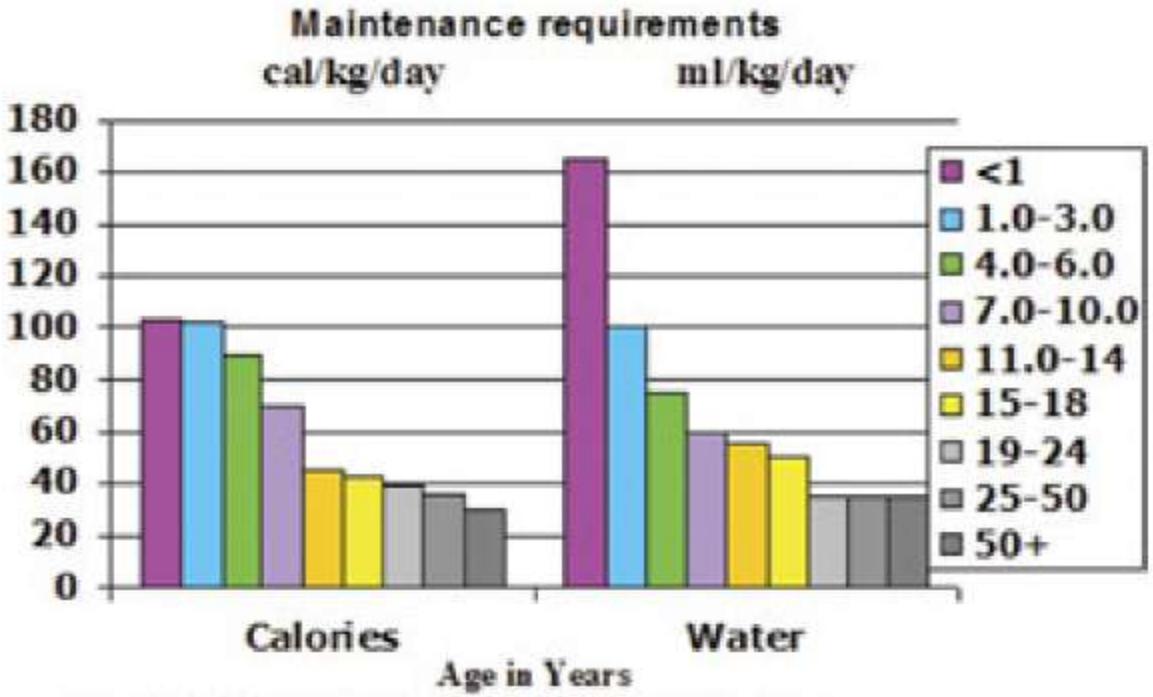

Figure from WHO Training Module: Children are not little adults

Figure 4. Caloric and water requirements versus age in years. (In color in *Annals* online.)

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

Environmental Health 2014, **13**:43

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

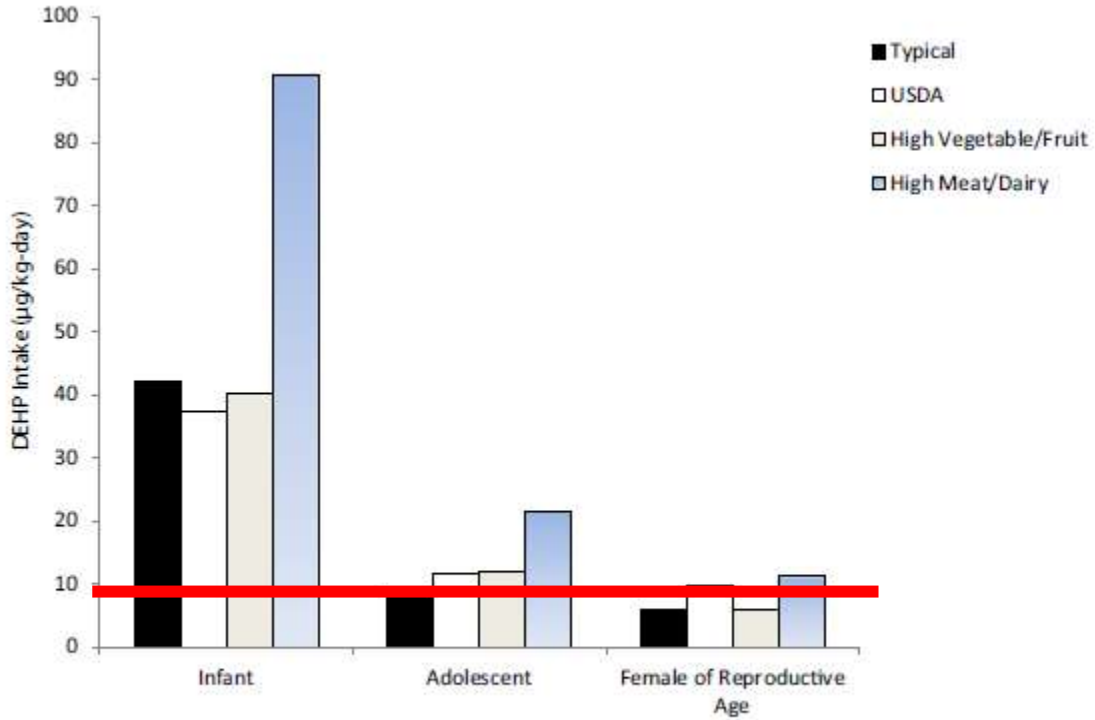

Figure 1 Per capita total DEHP intake (µg/kg-day) for four dietary patterns.

THE ENDOCRINE SOCIETY®

POSITION STATEMENT

ENDOCRINE-DISRUPTING CHEMICALS
JUNE 2009

- Policy should be developed and revised under the direction of a collaborative group comprising endocrinologists, toxicologists, epidemiologists, and policymakers. The same group should identify knowledge gaps and recommend research directions to fill those gaps.

- **Until such time as conclusive scientific evidence exists to either prove or disprove harmful effects of substances, a precautionary approach should be taken in the formulation of EDC policy.**

- The federal government should develop a public awareness campaign to inform the public of the risks and potential risks related to the presence of EDCs in the environment and in the food supply.

- The federal government should support further research into EDCs, including the development of high-throughput assays that would allow the testing of many chemicals for EDC activity at a full range of concentrations

Ud'A

National Toxicology Program

Headquartered at the National Institute of Environmental Health Sciences NIH-HHS

Bisphenol A (BPA)

What is BPA?

Bisphenol A, more commonly known as BPA, is a chemical widely used to make polycarbonate plastics and epoxy resins.

Where is BPA found?

Polycarbonate plastics have many applications including use in some food and drink packaging such as water and baby bottles, compact discs, impact-resistant safety equipment, and medical devices including those used in hospital settings.[1] Epoxy resins are used to coat metal products such as food cans, bottle tops, and water supply pipes. BPA can also be found in certain thermal paper products, including some cash register and ATM receipts. Some dental sealants and composites may also contribute to BPA exposure.

How does BPA get into the body?

BPA can leach into food from the epoxy resin lining of cans and from consumer products such as polycarbonate tableware, food storage containers, water bottles, and baby bottles. Additional traces of BPA can leach out of these products when they are heated at high temperatures. Recent studies also suggest that the public may be exposed to BPA by handling cash register receipts.[2] More research is needed to determine how much BPA from a receipt's coating enters the body and how it gets there. The National Institute of Environmental Health Sciences expects to support more research to determine if BPA in receipts poses a risk to human health.

Why are people concerned about BPA?

One reason people may be concerned about BPA is because human exposure to BPA is widespread. The 2003-2004 National Health and Nutrition Examination Survey (NHANES), conducted by the Centers for Disease Control and Prevention (CDC), found detectable levels of BPA in 93% of Americans six years and older. Another reason for concern, especially for parents, may be because some laboratory animal studies report subtle developmental effects in fetuses and newborns exposed to low doses of BPA.

Why did the National Toxicology Program (NTP) evaluate BPA?

The NTP Center for the Evaluation of Risks to Human Reproduction (CERHR) conducted the BPA evaluation. BPA was selected for evaluation because of the following factors:

- Widespread human exposure from use and occurrence in the environment
- Growing public concern
- Amount of BPA produced
- Extensive database of animal studies on reproductive and developmental effects

What did the NTP conclude about BPA?

The NTP has *"some concern"* for BPA's effects on the brain, behavior, and prostate gland in fetuses, infants, and children at current exposure levels.

The NTP has *"minimal concern"* for effects on the mammary gland and an earlier age for puberty in females, fetuses, infants, and children at current exposure levels.

The NTP has *"negligible concern"* that exposure of pregnant women to BPA will result in fetal or neonatal mortality, birth defects, or reduced birth weight and growth in their offspring.

The NTP has *"negligible concern"* that exposure to BPA will cause reproductive effects in non-occupationally exposed adults and *"minimal concern"* for workers exposed to higher levels in occupational settings.

NTP conclusions regarding the possibilities that human development or reproduction might be adversely affected by exposure to bisphenol A. The NTP uses a five-level scale of concern:

- **SERIOUS Concern** *for adverse effects*
- **CONCERN** *for adverse effects*
- Developmental toxicity for fetuses, infants, and children (effects on the brain, behavior, and prostate gland) → **SOME Concern** *for adverse effects*
- Developmental toxicity for fetuses, infants, and children (effects on the mammary gland and early puberty in females, and reproductive toxicity in workers) → **MINIMAL Concern** *for adverse effects*
- Reproductive toxicity in adult men and women and malformations in newborns → **NEGLIGIBLE Concern** *for adverse effects*

The NIEHS and NTP are supporting research to better understand the potential health effects of exposure to BPA.

PO Box 12233 • Research Triangle Park, NC 27709
Phone: 919-541-3345 • http://ntp.niehs.nih.gov

August 2010

Printed on recycled paper

DIFFERENTI IPOTESI SCIENTIFICHE

Scientifically unfounded precaution drives European Commission's recommendations on EDC regulation, while defying common sense, well-established science and risk assessment principles

Chemico-Biological Interactions 205 (2013) A1–A5

Daniel R. Dietrich, Editor-in-Chief, Chemico Biological Interactions
Sonja von Aulock, Editor-in-Chief, ALTEX
Hans Marquardt, Editor-in-Chief, Toxicology
Bas Blaauboer, Editor-Europe, Toxicology in Vitro
Wolfgang Dekant, Editor-in-Chief, Toxicology Letters
James Kehrer, Editor-in-Chief, Toxicology Letters
Jan Hengstler, Editor-in-Chief, Archives of Toxicology
Abby Collier, Section Editor, Chemico Biological Interactions
Gio Batta Gori, Editor-in-Chief, Regulatory Pharmacology and Toxicology
Olavi Pelkonen, Editor-in-Chief, Frontiers in Predictive Toxicology
Florian Lang, Editor-in-Chief, Toxins
Frank A. Barile, Editor-in-Chief, Toxicology in Vitro
Frans P. Nijkamp, Editor-in-Chief, European Journal of Pharmacology
Kerstin Stemmer, Assoc. Editor, Toxicology in Vitro
Albert Li, Section Editor, Chemico Biological Interactions
Kai Savolainen, Editor for Europe and rest of the World, Human and Experimental Toxicology
A. Wallace Hayes, Editor for the Americas, Human and Experimental Toxicology and Editor-in-Chief, Food and Chemical Toxicology
Nigel Gooderham, Editor-in-Chief, Toxicology Research
Alan Harvey, Editor-in-Chief, Toxicon

DIFFERENTI IPOTESI SCIENTIFICHE

Endocrine disruption: Fact or urban legend?

Gerhard J. Nohynek[a,*], Christopher J. Borgert[b], Daniel Dietrich[c], Karl K. Rozman[d]

Toxicology Letters 223 (2013) 295–305

SUBSTANCE	POTENCY / POWER	EXAMPLE
Ethinyl estradiol (oral contraceptive)	1.000.000	
Coumestrol (clover)	10.000	
Genistein (soy beans)	37	
Butylparaben (preservative)	0.5	
Benzylparaben (preservative)	0.1	

Fig. 1. Assuming that one oestrogen potency unit (see Table 1) corresponds to one horse power, the power/potency of some of the substances in Table 1 may be ranked as follows.

DIFFERENTI IPOTESI SCIENTIFICHE

Bergman *et al. Environmental Health* 2013, **12**:69
http://www.ehjournal.net/content/12/1/69

ENVIRONMENTAL HEALTH

COMMENTARY Open Access

Science and policy on endocrine disrupters must not be mixed: a reply to a "common sense" intervention by toxicology journal editors

Åke Bergman[1*], Anna-Maria Andersson[2], Georg Becher[3], Martin van den Berg[4], Bruce Blumberg[5], Poul Bjerregaard[6], Carl-Gustaf Bornehag[7], Riana Bornman[8], Ingvar Brandt[9], Jayne V Brian[10], Stephanie C Casey[5], Paul A Fowler[11], Heloise Frouin[12], Linda C Giudice[13], Taisen Iguchi[14], Ulla Hass[15], Susan Jobling[10], Anders Juul[2], Karen A Kidd[16], Andreas Kortenkamp[10], Monica Lind[9], Olwenn V Martin[10], Derek Muir[17], Roseline Ochieng[18], Nicolas Olea[19], Leif Norrgren[20], Erik Ropstad[21], Peter S Ross[12], Christina Rudén[22], Martin Scheringer[23], Niels Erik Skakkebaek[2], Olle Söder[24], Carlos Sonnenschein[25], Ana Soto[25], Shanna Swan[26], Jorma Toppari[27], Charles R Tyler[28], Laura N Vandenberg[29], Anne Marie Vinggaard[15], Karin Wiberg[20] and R Thomas Zoeller[30]

"Common sense is the collection of prejudices acquired by age eighteen"

- Albert Einstein

DIFFERENTI IPOTESI SCIENTIFICHE

Early homeostatic disturbances of human growth and maturation by endocrine disrupters

Jean-Pierre Bourguignon and Anne-Simone Parent

Curr Opin Pediatr 22:470–477
© 2010 Wolters Kluwer Health

Table 3 Relevant issues accounting for limits in identification of endocrine disrupting compound (EDC) involvement in health disorders

Issues	Implication
Low-dose mixtures	Ineffective low doses of single EDCs become effective when associated with other EDCs. Mixture effects (more likely reflecting human exposure in the real world than single EDCs) are not simply additive, but studies are complex
Latency	At the time of adult expression of disorders determined by fetal or postnatal exposure to EDCs, the demonstration of exposure is no longer possible
Agonist/antagonist of one or several hormones	A single EDC can be agonist at some subtypes of receptors to a steroid and antagonist at others. It can interact with several hormonal systems that can each play different roles depending on sex and stage of development
Nonconventional dose–response relationship	Some EDCs exhibit U-shaped or inverted-U curves of dose–response, meaning that low doses are more effective than higher doses, with resulting importance of assessment of the level of exposure
Several mechanisms of action possibly coexisting	Classical endocrine receptors as well as nonclassical endocrine or nonendocrine receptors can be involved in addition to alterations in the rates of degradation of endogenous hormones and EDCs

DIFFERENTI IPOTESI SCIENTIFICHE

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Assessment of infant exposure to food chemicals: the French Total Diet Study design

Food Additives & Contaminants: Part A, 2014

M. Hulin*, N. Bemrah, A. Nougadère, J.L. Volatier, V. Sirot and J.C. Leblanc

Table 1. Substances analysed in the infant Total Diet Study.

Groups	Origin: Natural or environmental contamination of natural origin	Origin: Environmental contamination of anthropogenic origin	Origin: Used in food contact materials	Origin: Used for technological or agricultural reasons or formed during food process	Substances or congeners
Mycotoxins	×				Aflatoxins: AFB1, AFB2, AFG1, AFG2, AFM1 Ochratoxins: OTA Patulin Trichothecens: DON, DON3, DON15, Niv, T2, HT2, DAS, PatX, Ver, MAS, T2-triol Zearalenon: ZEA Fumonisins: FB1, FB2 Alternaria toxins: AOH, AME, TA
Phytoestrogens	×				Isoflavons: genistein, daidzein, glycitein, biochanin A, formononetin, equol Coumestrans: coumestrol Lignans and enterolignans: matairesinol, secoisolariciresinol, enterodiol
Natural steroids	×				Estrogens: a-estradiol, b-estradiol, estrone Androgens: dihydrotestosteron, epitestosteron, 4-androstènedione, testosteron, 5b-dihydrotestosteron, androsterone, 5a-dihydrotestosteron, 17b-testosteron, 17a-testosteron, epiandrosteron, 5b-androstane-3one-17b-ol, etiocholanolone, DHEA Progestagenes: progesteron
Minerals	×				Calcium, sodium, magnesium, potassium, iron, zinc
Inorganic contaminants	×	×	×		Essential trace elements: chromium, cobalt, copper, lithium, manganese, molybdenum, nickel, selenium, vanadium Toxic trace elements: aluminium, antimony, arsenic, cadmium, lead, mercury, tin, barium, strontium, gallium, silver, tellurium, germanium
Dioxins and furans	×	×			PCDD: TCDD_2378, PCDD_12378, HCDD_123478, HCDD_123678, HCDD_123789, HCDD_1234678, OCDD PCDF: TCDF_2378, PCDF_12378, PCDF_23478, HCDF_123478, HCDF_123678, HCDF_234678, HCDF_123789, HCDF_1234678, HCDF_1234789, OCDF
PCBs		×			PCB-DL: PCB_77, PCB_81, PCB_126, PCB_169, PCB_105, PCB_114, PCB_118, PCB_123, PCB_156, PCB_157, PCB_167, PCB_189 PCB-NDL: PCB_28, PCB_52, PCB_101, PCB_138, PCB_153, PCB_180
Brominated flame retardants		×			PBDE:BDE 28, BDE 47, BDE 99, BDE 100, BDE 153, BDE 154, BDE 183, BDE 209 PBB: BB52, BB101, BB153 HBCD: α, β, γ TBBPA
Perfluorinated compounds		×	×	×	PFOS, PFBS, PFHxS, PFHpS, PFDS PFOA, PFBA, PFPA, PFHxA, PFHpA, PFNA, PFDA, PFUnA, PFDoA, PFTrDA, PFTeDA
Phtalates		×	×		DnBP, DEHP, DINP, DIDP, DEP, DiBP, BBP, DCHP, DOP, di-butyl sebacate, di-(2-ethylhexyl)adipate

(continued)

Assessment of infant exposure to food chemicals: the French Total Diet Study design

Food Additives & Contaminants: Part A, 2014

M. Hulin*, N. Bemrah, A. Nougadère, J.L. Volatier, V. Sirot and J.C. Leblanc

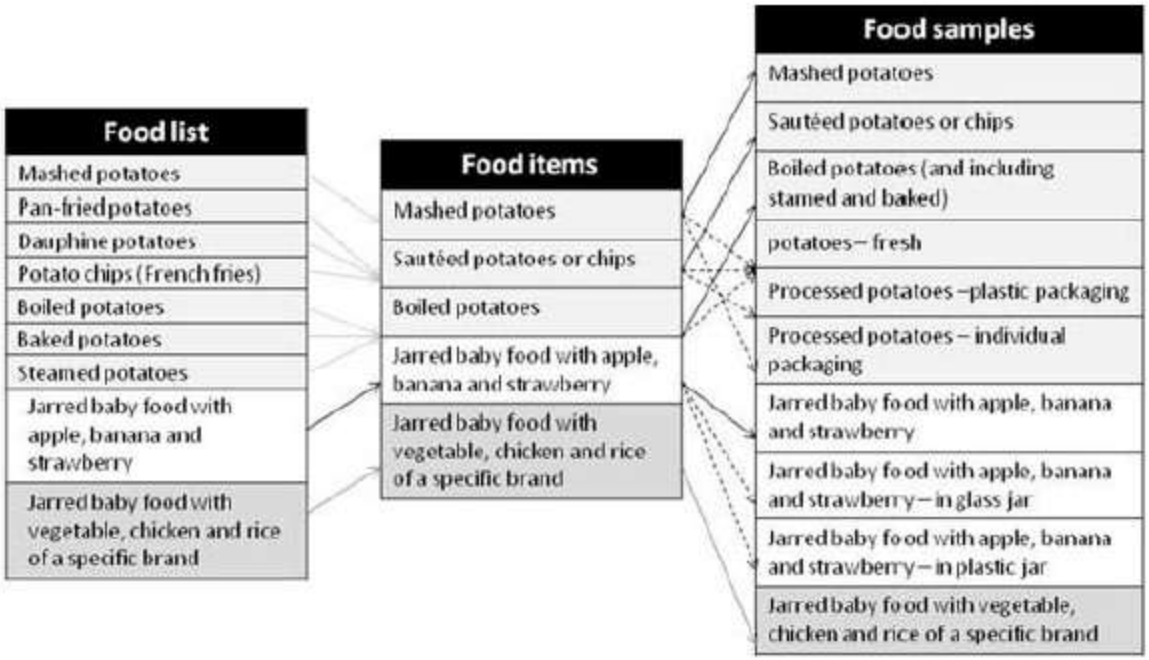

Figure 1. Example of the establishment of a sampling plan from food list to food samples.

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5) **PREVENZIONE**

PREVENZIONE

LIMITA O EVITA	PRIVILEGIA O SOSTITUISCI
1. Evita il ristagno di aria e polvere negli ambienti chiusi dove i bambini piccoli gattonano o giocano in terra	Garantisci il ricambio di aria negli ambienti chiusi ed effettua una adeguata e periodica pulizia; assicura una corretta manutenzione degli aspirapolveri (pulizia filtri e camera di raccolta, sostituzione sacchi ove presenti)
2. Se hai pavimenti in PVC contenenti DEHP su cui giocano bambini, utilizza un tappeto in fibra non trattata	
3. Limita l'uso di capi di abbigliamento per l'infanzia con trattamenti opzionali idrorepellenti o antimacchia	Privilegia capi di abbigliamento di origine e composizione ben identificabili
4. Evita materassi per lettini con rivestimento o telo impermeabile non conforme alle norme vigenti e comunque evita rivestimenti per materassi in PVC morbido contenente DEHP	
5. Utilizza fodere in fibre non trattate se hai fasciatoi e/o passeggini rivestiti in PVC morbido contenente DEHP; in generale, evita che i bambini entrino in contatto con la bocca con oggetti in PVC	
6. Per scaldare latte, bevande e pappe utilizza contenitori integri e solo secondo le indicazioni del produttore	
7. Lascia che i liquidi caldi si raffreddino prima di travasarli in contenitori di plastica non destinati all'uso ad elevate temperature	
8. Lava accuratamente biberon e altri contenitori dopo la sterilizzazione; non utilizzare biberon in policarbonato (non più consentiti)	
9. Abitua il bambino a consumare alimenti freschi e di stagione; risciacqua frutta e verdura in scatola prima del consumo	
10. Evita il consumo di alimenti con parti carbonizzate o bruciate	Per la cottura dei cibi destinati ai bambini, privilegia metodi che preservino il contenuto di vitamine idrosolubili (ad es. cottura a vapore)

PREVENZIONE

Science of the Total Environment 517 (2015) 125–131

Developing an intervention strategy to reduce phthalate exposure in Taiwanese girls

Chung-Yu Chen [a], Yen-Yin Chou [b], Shio-Jean Lin [b], Ching-Chang Lee [a,c,*]

Table 1
Intervention strategies used in this study.

Recommended intervention items	Detail of items
Nutrition supplements and medication	Information about using nutrition supplements and medications was collected, but they were not restricted if they were prescribed or recommended by a physician. Otherwise, the participants were asked to stop taking them for one week.
Cosmetics and personal care products	Using essential oils, perfumes, skin lotions, and nail polish was restricted. The volume and frequency of shower gel and shampoo used were recorded.
Plastic containers	Eating and drinking from plastic bowls and bottles were restricted.
Microwaved food	Microwaving food in paper or plastic boxes or wrapped in plastic was restricted.
Food with plastic bag or plastic wrap cover	Food with a plastic bag or plastic wrap cover was restricted.
Building materials and handwashing	The duration and frequency of puzzle floor-mat contact, playing on the ground, and eating food without washing hands were recorded.
Time–activity pattern	For any item above, the real onset time and events on usage were recorded.

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