



Perturbateurs endocriniens, asthme et allergies

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FERS

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Pas de COIs

Des polluants émergents!!!

Perturbateurs endocriniens

- Terme créé en 1991 par Theo Colborn pour désigner toute molécule ou agent chimique composé, xénobiotique ayant des propriétés hormone-mimétiques et décrit comme cause d'anomalies physiologiques, et notamment reproductive
- Substances chimiques d'origine naturelle ou artificielle étrangères à l'organisme. Elles peuvent interférer avec le fonctionnement du système **endocrinien** et induire des effets néfastes sur l'organisme d'un individu ou sur ses descendants (OMS, 2002).

What do Endocrine Disruptors?

- Endocrine disruptors interfere with endocrine system function
- Mimic, block, alter synthesis, metabolism or excretion of hormones
 - Setting off similar chemical reactions in the body
 - Prevent the action of normal hormones
 - Alter the concentrations of natural hormones



Common products and potential dangers

Water bottles

Some hard-plastic, reusable water bottles are made with a chemical that scientists fear can affect fetal development.

Metal cans

Bisphenol A, an ingredient in epoxy resins that line some food cans, is associated with a higher risk of cancer.

Are our products our enemy?

Chemicals
in everyday
goods disrupt
hormones

Grapes

Vinclozolin, a fungicide used in growing grapes, caused changes in lab rats that span generations.

Plastic wrap

Some plastic films used to keep foods fresh contain phthalates, chemicals that researchers find are showing up in every American's urine.

Nail polish

Dibutyl phthalate, which is added to some cosmetics, is linked to genital irregularities in infant boys.

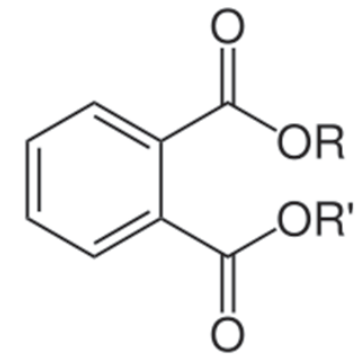
**USA
TODAY.**

Examples of Endocrine Disrupting Chemicals

- Pesticides: DDT/DDE
- Organohalogenes: PCBs, PBDEs, Dioxins
- Heavy Metals: Lead, Mercury, Cadmium
- Plastics/Plasticizers: Phthalates and BPA

Plastic

- Approximately 4% of the world's oil and gas produced is utilized as feedstock for plastics and about 3–4% is used in their manufacturing to provide energy.
- Plastics contains various types of toxic components as additive, such as di-(2-ethylhexyl)phthalate (DEHP), bisphenol A (BPA), poly halogenated compounds and heavy metals which pose a potential health risk to bthe humans.
- Not chemically bound to products and are thus released into environment or leach into other products (e.g. food
- Most of these additives are shown to be easily immobilized in the environment and this leads to harmful effects on human health like the disruption of the endocrine system but also other health problems.



Phthalic acid diesters

Plastics Are Everywhere

Plasticizers impart flexibility and durability

- Phthalates are anti-androgenic
 - 200 million pounds of DEHP was produced in 2002
- Bisphenol A is a weak estrogen
 - 2.3 billion pounds of BPA was produced in 2004

Plastics Are Everywhere

Baby shampoo study raises chemical concerns

Phthalates found in urine of infants after they were powdered or lotioned



AP Associated Press



Phthalate characteristics

- Semi-volatile compounds
 - Wide range of vapour pressures
 - Partition between gas and solid phase
 - Surfaces and particles
- Low molecular weight (LMW) phthalates (e.g. DMP, DEP, DBP) - cosmetics and PCP (polychloroprene) as scent stabiliser or for flexibility (e.g. in nail polish), also more likely to be found in air
- High molecular weight (HMW) (e.g. DEHP, DINP, DOP) - plastics, packaging, building products

Quelles expositions (comment et combien?)

Where are Phthalates found?





© 1995 American Plastics Council



You could think of them as the sixth basic food group. Oh, you certainly wouldn't eat them, but plastic packaging does help pro-

help keep air out. While others let air in to help the food we eat stay fresher longer. Plastics also let you see what you're buying,

Plastics. An Important Part Of Your Healthy Diet.

tect our food in many ways. • To help lock in freshness, plastic wrap clings tightly to surfaces. To help lock out moisture, resealable containers provide a strong seal. And plastic wrap helps extend the shelf life of perishable produce, poultry, fish and meats. • To prevent spoilage and contamination, some varieties of plastics

taking the mystery out of shopping. All of which makes them versatile, durable, light-weight and shatter-resistant. • To learn more, call the American Plastics Council at 1.800.777.9500 for a free booklet. Plastics. One part of your diet you may never break.



PLASTICS MAKE IT POSSIBLE.™
Visit us at: <http://www.plasticsresource.com>

Cleaning & Personal care products

Used primarily as plasticizers

Found in cosmetics, personal care products, pharmaceuticals, medical devices, paints, etc.



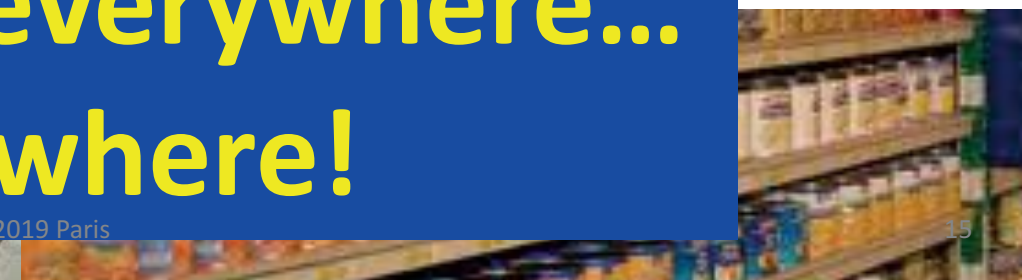
Körsbärstomat		199,00	
Plastkasse liten		9,95	
Rågbröd		2,00	
Ägg 12-pack Kronäg		16,95	
Pant		21,95	
		-4,00	
Total		304,70	
Moms%	Moms	Netto	Brutto
25,00	0,40	1,60	2,00
12,00	11,11	92,50	
6,00	11,00		

Building materials



Dietary, cook wares and packages

Sources are everywhere... everywhere!



Several different phthalates – some common ones

	Ester group	Formula	CAS	MW	Total Dietary Intake*
DMP	Dimethyl	C10H10O4	131-11-3	194.2	na
DEP	Diethyls	C12H14O4	84-66-2	222.2	10,000
DiBP	Diisobutyl	C16H22O4	84-69-5	278.4	100
DnBP	Di-n-butyl	C16H22O4	84-74-2	278.4	100
BBzP	Butylbenzyl	C19H20O4	85-68-7	312.4	850
DEHP	Di-(2-ethylhexl)	C24H38O4	117-81-7	390.6	50
DINP	Diisononyl	C26H42O4	28553-12-0	418.6	150
DIDP	Diisodecyl	C28H46O4	26761-40-0	446.7	250

*ug/kg bw/day

From Wormuth et al. 2006, Risk analysis, 26(3)

Where are Phthalates found?

Product	Phthalate	Metabolite
Foods Toys Medical supplies	DEHP: di-(2-ethylhexyl) phthalate	MEHP: mono-(2-ethylhexyl) phthalate MEOHP: Mono(2-ethy-5-oxolhexyl) phthalate MEHHP: Mono(2-ethyl-5-hydroxyhexyl) phthalate MECPP: Mono(2-ethy-5-carboxypentyl) phthalate
Toys	DINP: di-isononyl phthalate DIDP: di-isodecyl phthalate DNOP: Di- <i>n</i> -octylphthalate	MINP: monoisononyl phthalate MCIOP: mono(carboxy-isoocetyl) phthalate MOINP: mono(oxoisononyl)phthalate MHINP: mono (hydroxy-isononyl)phthalate MIDP: monoisodecyl phthalate MnOP: :mono- <i>n</i> -octyl phthalate

Where are Phthalates found? (continued)

Product	Phthalate	Metabolite
PVC, vinyl floors, cosmetics	BBzP: benzyl butyl phthalate DEHP: di-(2-ethylhexyl) phthalate	MBzP: monobenzyl phthalate MEHP: mono-(2-ethylhexyl) phthalate MEOHP: Mono(2-ethy-5-oxolhexyl) phthalate MEHHP: Mono(2-ethyl-5-hydroxyhexyl) phthalate MECPP: Mono(2-ethy-5-carboxypentyl) phthalate
Cosmetics: nail polish and perfumes	DEP: diethyl phthalate DBP: dibutyl phthalate DMP: dimethyl phthalate	MEP: monoethyl phthalate MBP: monobutyl phthalate

Centers for Disease Control (CDC) 4th Report on Human Exposures

Geometric Means of Phthalates (ug/g creatinine) by age			
PHTHALATE	6-11yo	12-19yo	20yo+
mBzP	35.8	16.6	11
mEHP	3	2.07	2.14
mEOHP	26.6	14.6	12.4
mEHHP	39	21.2	18.8
mEP	96.9	168	197
mBP	38.4	20	18.3
miBP	6.94	3.4	3.3

Pathways of exposure

Sources of Exposure to Phthalates in Europeans

805

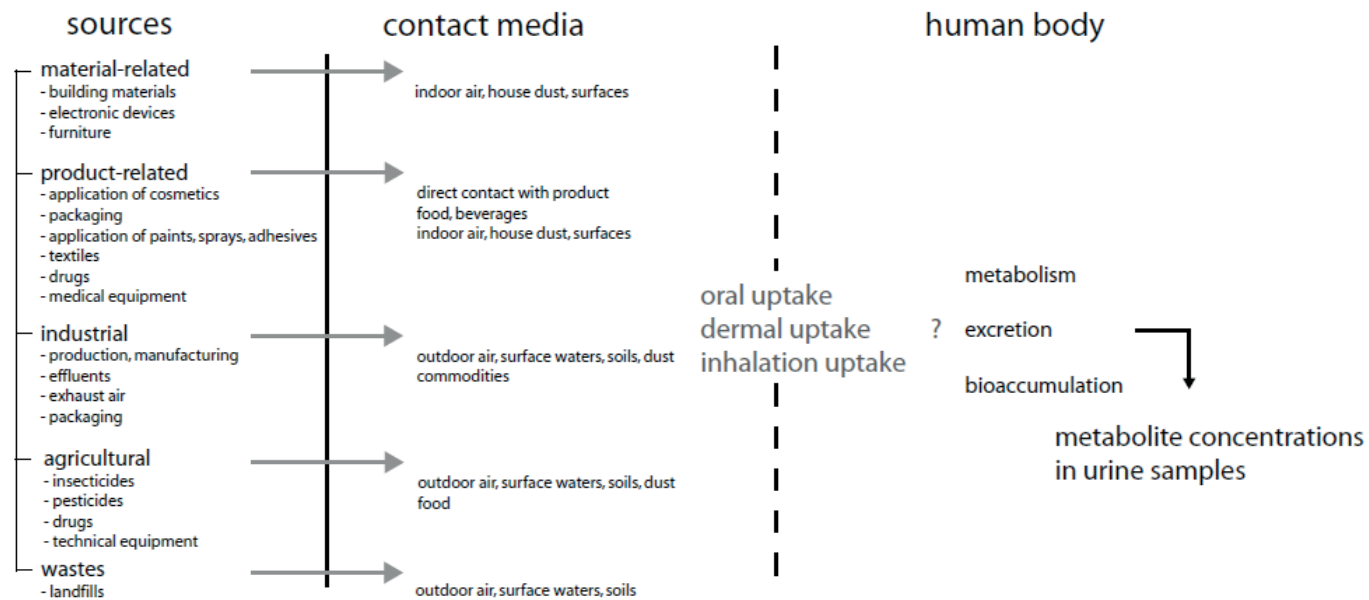


Fig. 1. Consumers are exposed to phthalates via different sources. Measurements of concentrations of phthalate metabolites in urine samples have demonstrated the ubiquitous consumer exposure to these plasticizers.

From Wormuth et al. 2006, Risk analysis, 26(3)

Exposure pathways

Indoor Environment



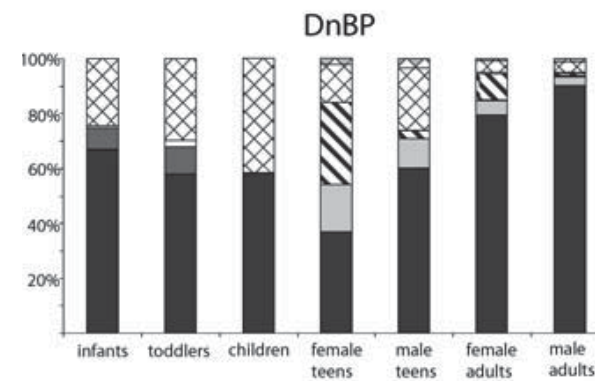
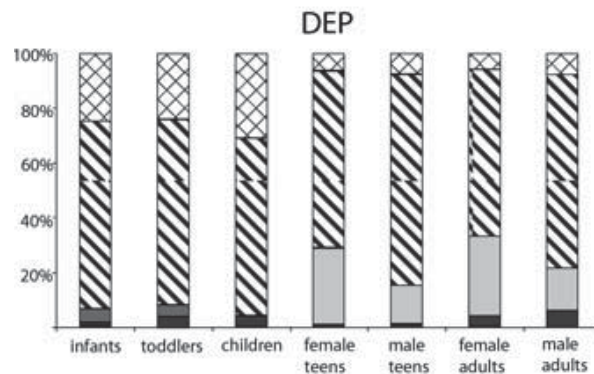
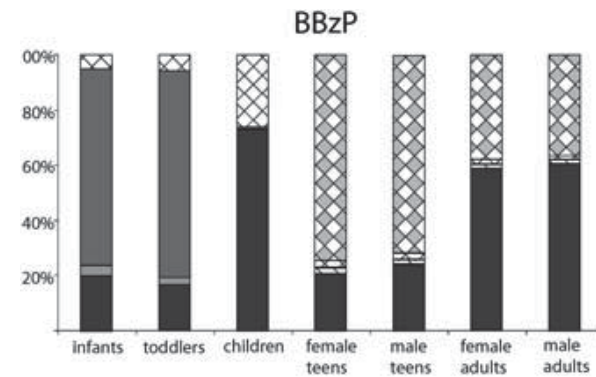
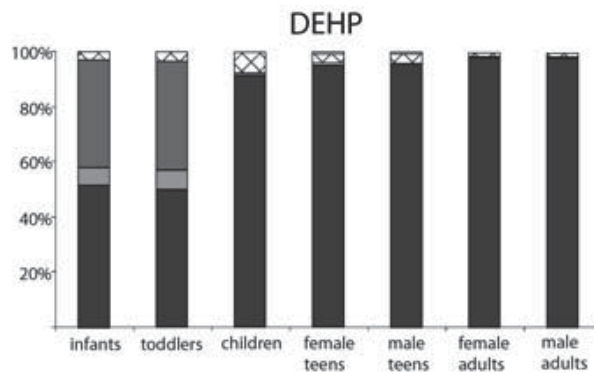
Exposure routes

- Inhalation through air
- Ingestion of dust, food, breast milk?
- Dermal absorption from personal care products, cosmetics, surfaces, particles

Some phthalate concentrations in dust

Phthalate	Country	Median Range (mg/kg)
DEHP	Germany	480-970
DEHP	Denmark (Homes)	210-858
DEHP	Denmark (Daycare/schools)	500-3214
DEHP	Bulgaria	1050
DEHP	Sweden	770
BBzP	Germany	13-30
BBzP	Denmark (Homes)	4
BBzP	Denmark (Daycare/schools)	16
BBzP	Bulgaria	340
BBzP	Sweden	135

Estimated exposure pathways (Wormuth)



inhalation pathways
indoor/outdoor air
spray paints



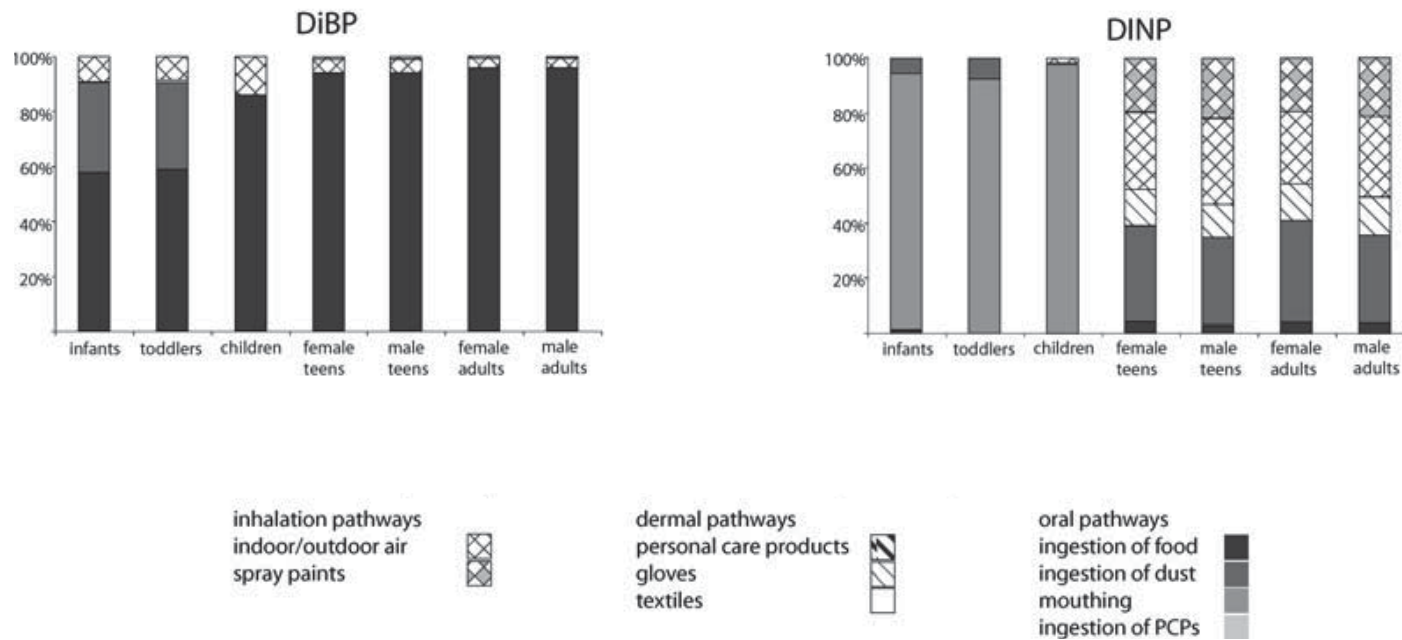
dermal pathways
personal care products
gloves
textiles



oral pathways
ingestion of food
ingestion of dust
mouthing
ingestion of PCPs



Estimated exposure pathways (Wormuth)



Other results

- De Brouwere (INTERA) found that for non-food pathways, most infant exposure comes from ingestion of soil/dust or dermal absorption from soil/dust, mouthing of toys, and, to a smaller extent, dermal absorption from surface films
- Beko et al. estimated intakes from urine concentrations and intakes from dust and air exposure
 - 431 Danish children
 - 23 exceeded DiBP TDI
 - 22 exceeded DnBP
- 25-30% of study populations in Koch and Beko exceeded cumulative TDI (DEHP, DnBP, DiBP)

Spatial and Temporal patterns

- Levels in homes depends on products used
- Germany - levels of MBP and DEHP metabolites decreased over 1988-2003
- US - MBP decreased but not DEHP
- Since 2007 phthalates are restricted in child toys
- DEHP, DBP, BBP being replaced by DIDP, DINP

Quels effets toxicologiques et épidémiologiques?

Phthalate toxicity (1)

- Co-exposures

- Koch, Fromme use h

$$HI = \sum \left(\frac{DI_{DEHP}}{TDI_{DEHP}} + \frac{DI_{DnBP}}{TDI_{DnBP}} + \frac{DI_{DiBP}}{TDI_{DiBP}} \right)$$

- US EPA suggests a cumulative risk assessment framework for male reproductive outcome
 - Other anti-androgens include vinclozolin, procymidone, linuron, prochloraz, 5-alpha reductase inhibitors, azole fungicides, PBDEs, TCDD, some PCBs



Risk Factors through the Lifespan

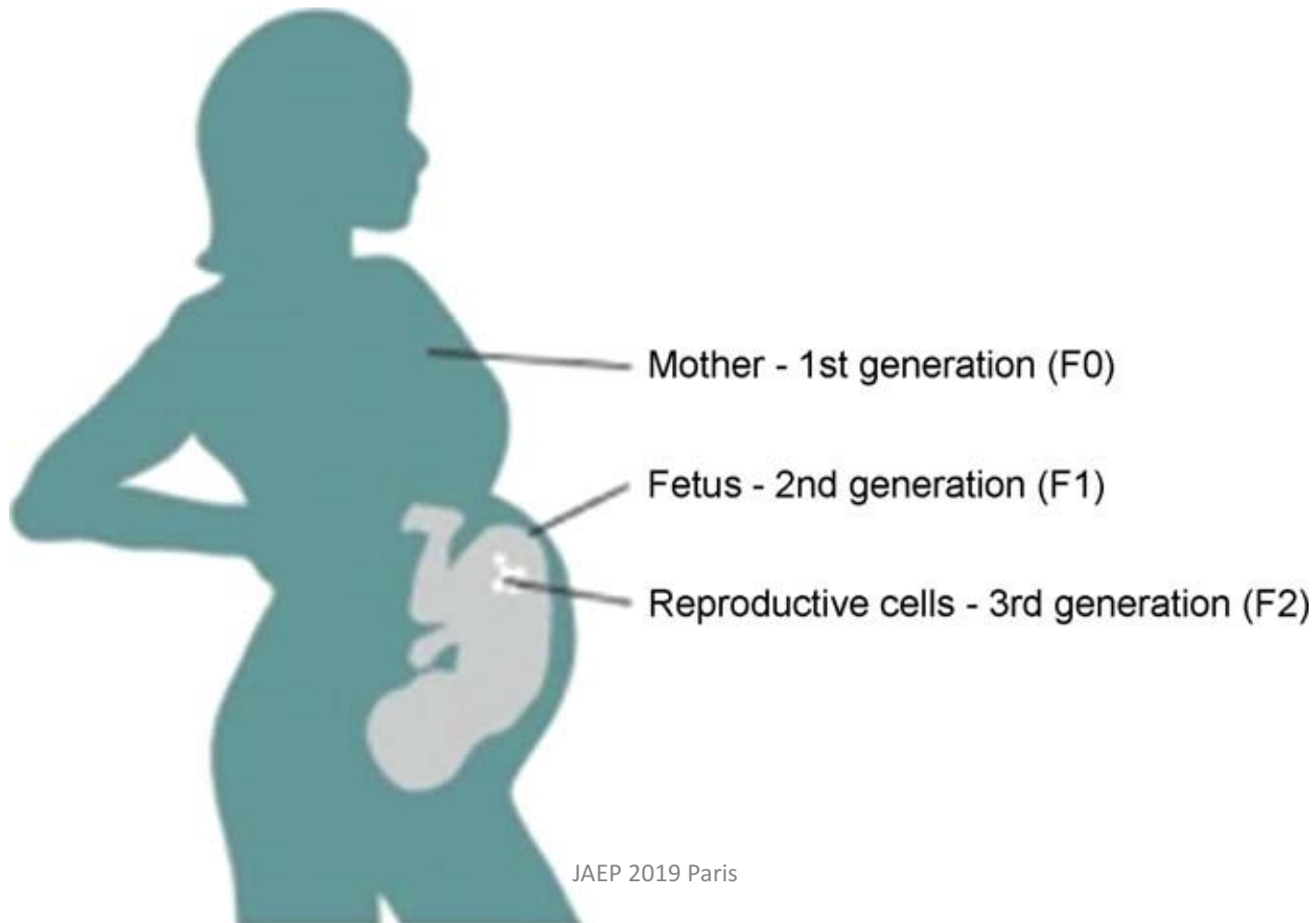
Pregnancy	Birth	Infancy	Childhood	Adolescence	Adulthood
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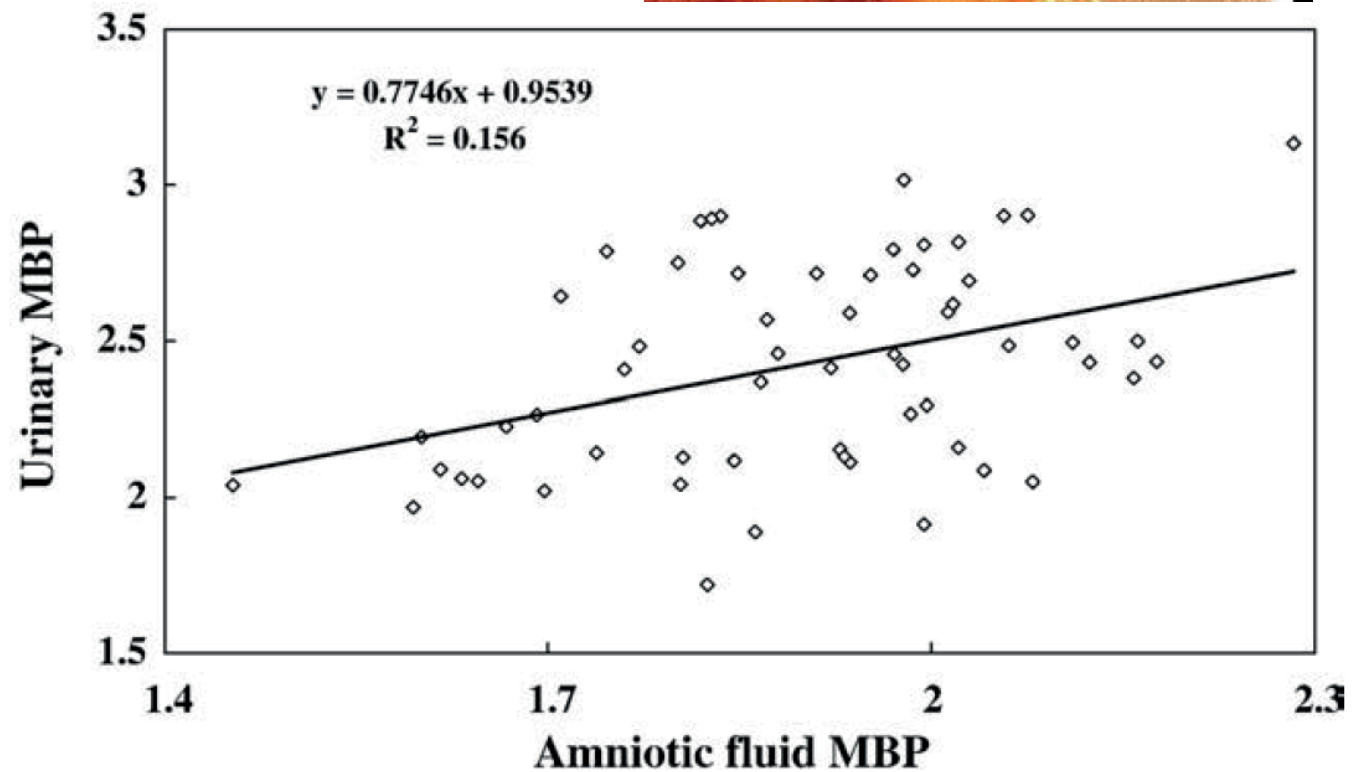
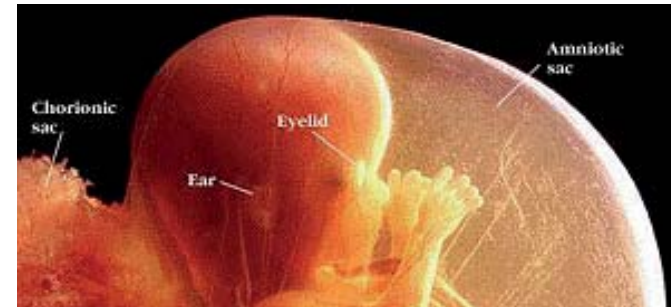




**Fetal life is
important due
to
development**

And remember that **three** generations are exposed.....



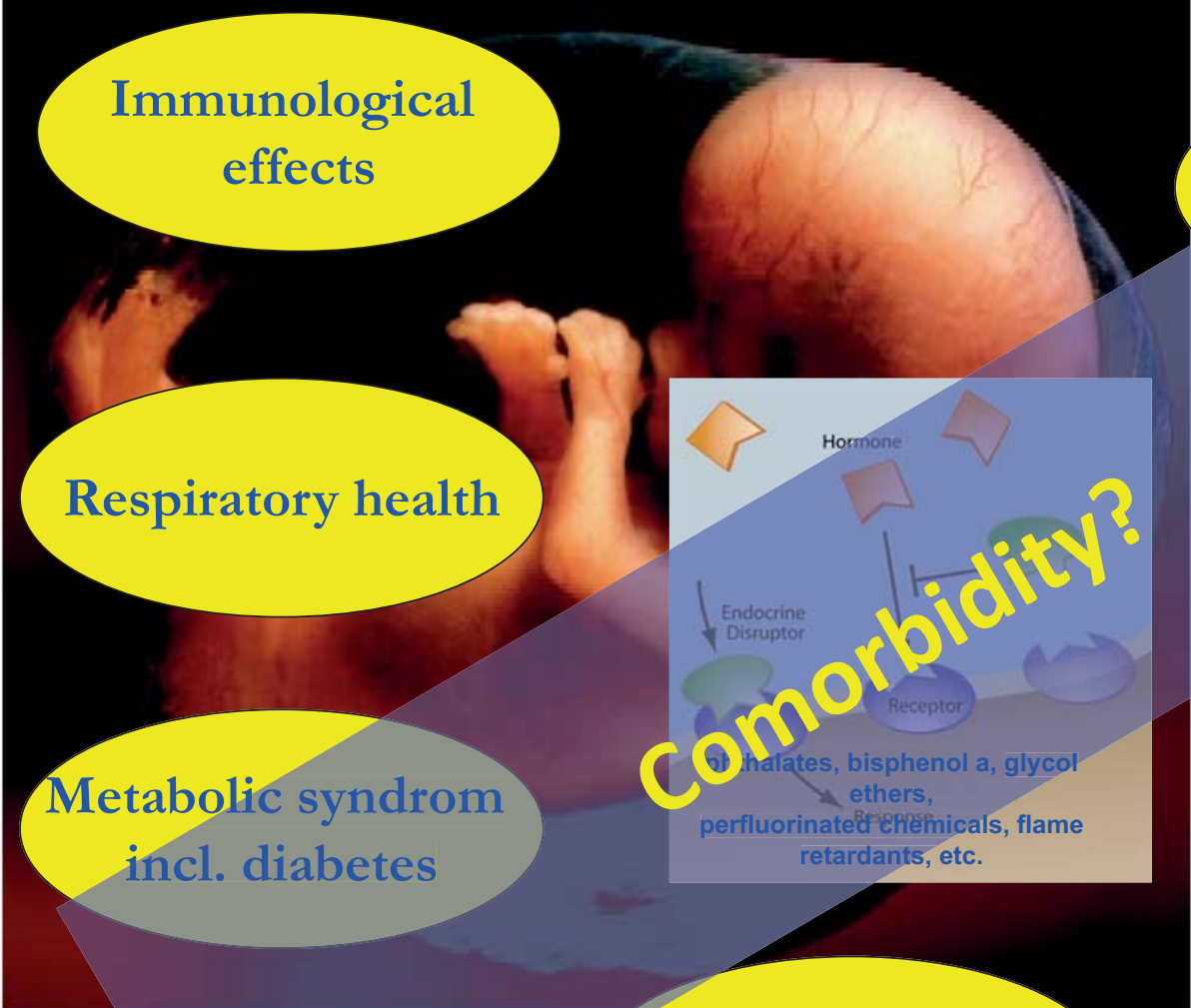




Health effects of phthalates

In animal studies there is evidence of:

- Adverse birth outcomes
- Reproductive toxicity
- Male reproductive tract particularly sensitive



Immunological effects

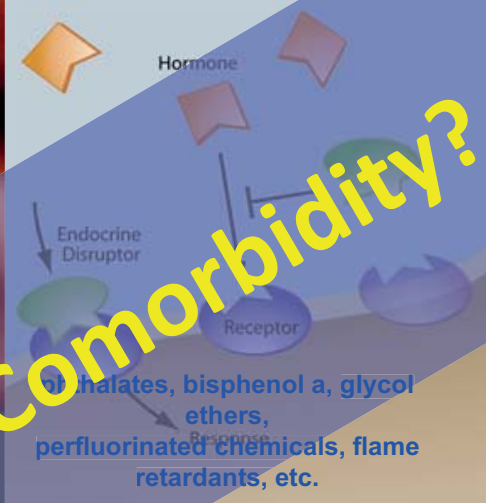
Respiratory health

Metabolic syndrome incl. diabetes

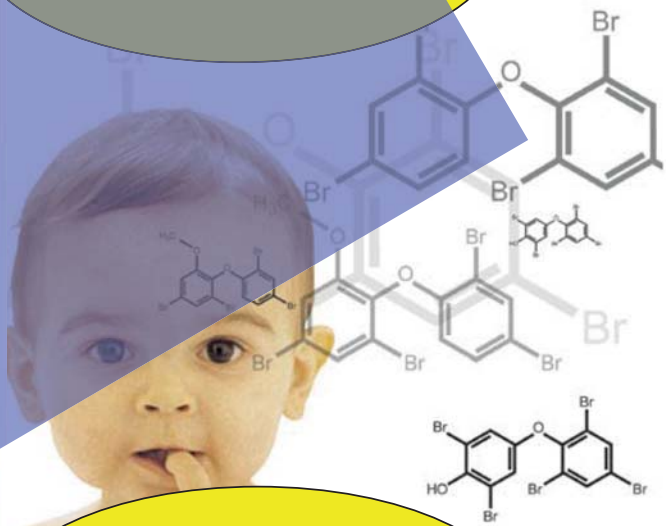
Developmental neurotoxicology

Reproductive health

Hormonal cancer



Comorbidity?

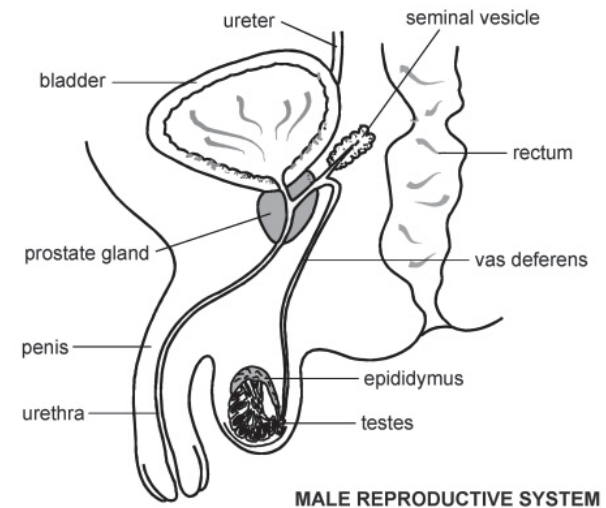


Beginning a lifetime of vulnerability. A recent study found that in utero exposures to endocrine-disrupting chemicals...

Phthalates Syndrome

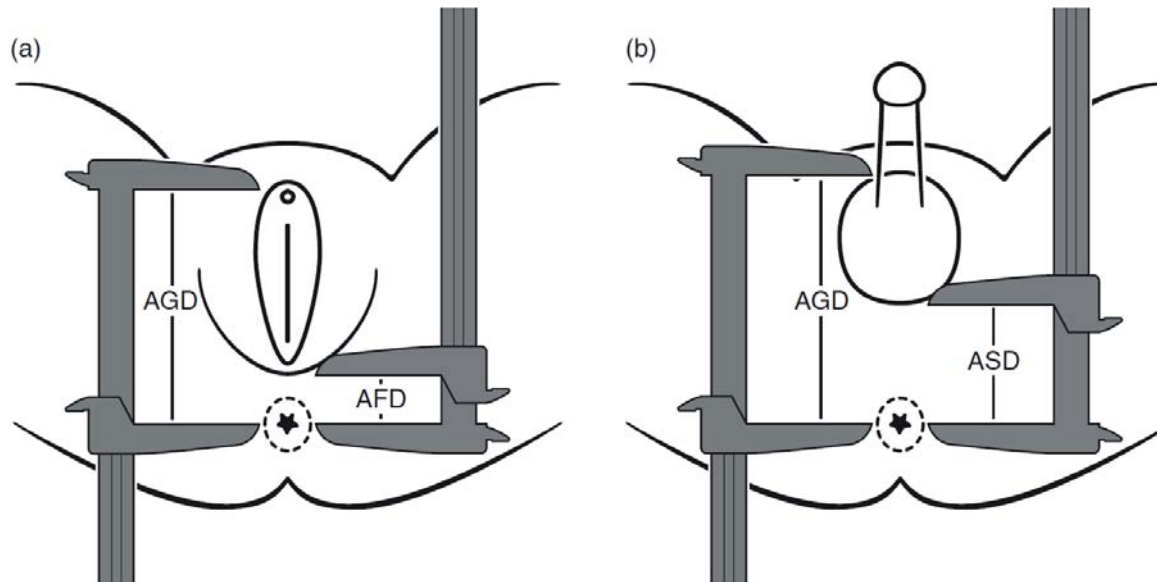
Anti-Androgen Effects

- Hypospadias
- Undescended Testes
- Fetal Germ Cell Effects
- Infertility
- Decreased Anogenital Distance



Foster PMD, Int J Androl, 2006.

Anogenital Distance n=169



Sathyanarayana et al. Int J of Androl, 2009.

Decreased anogenital distance is a measure of anti-androgen exposure n=85

Table 5. Mean (median) phthalate monoester metabolite levels by AGI category.

Monoester metabolite	AGI category [mean (median; ng/mL)]		
	Long ^a (n = 17)	Intermediate ^b (n = 43)	Short ^c (n = 25)
MBP	13.1 (11.5)	22.2 (13.1)	38.7 (24.5)
MBzP	10.6 (6.6)	15.1 (7.7)	25.8 (16.1)
MEP	124 (47.1)	592 (112)	1,076 (225)
MiBP	2.3 (1.5)	3.3 (2.1)	7.7 (4.8)

^aLong, AGI ≥ 75th percentile of expected AGI. ^bIntermediate, 25th percentile ≤ AGI < 75th percentile of expected AGI.

^cShort, AGI < 25th percentile of expected AGI.

Anogenital Distance is normally twice as long in males as in females

Swann et al. Environ Health Perspect, 2005.

Prenatal Exposure to BPA and child wheeze from birth to 3 yrs

- Cohort of 398 mother-infant pairs and assessed serial maternal BPA and parent-reported child wheeze every 6 months for 3 years.
- Mean prenatal BPA at 16 weeks gestation was associated with increased odds of wheeze in early life 6 months to 3 years

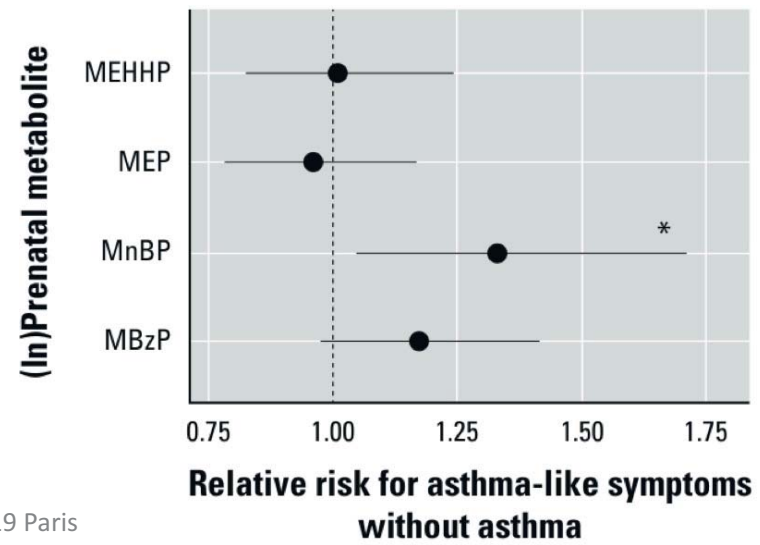
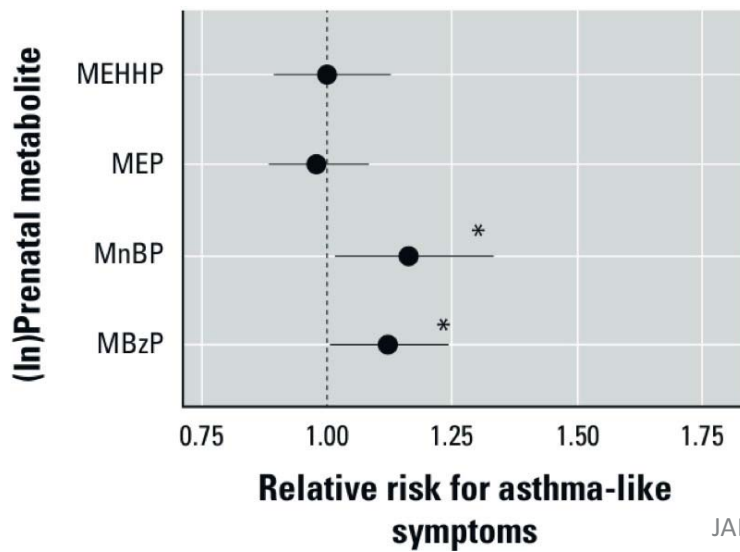
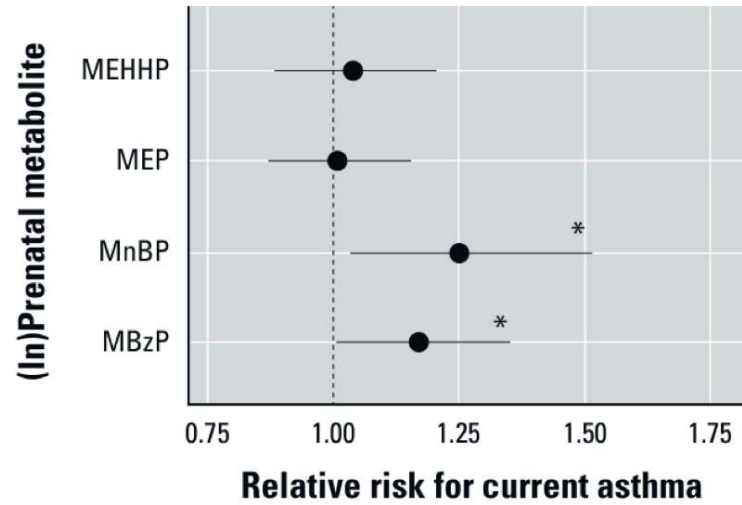
Effect of prenatal exposure to phthalates on child's asthma

- Prenatal exposure to two phthalates - chemicals commonly used in plastics and cosmetics, such as skin moisturizers - may significantly increase the risk of childhood asthma.



Source : Whyatt Rmet al,
Environ Health Perspect. 2014
Oct;122(10):1141-6

Asthma in Inner-City Children at
5-11 years of age and
prenatal exposure to
Phthalates, Wyatt, EHP, 2014





In Utero Exposure to Select Phenols and Phthalates and Respiratory Health in Five-Year-Old Boys: A Prospective Study

Céline Vernet,¹ Isabelle Pin,^{1,2} Lise Giorgis-Allemand,¹ Claire Philippat,¹ Meriem Benmerad,¹ Joane Quentin,^{1,2} Antonia M. Calafat,³ Xiaoyun Ye,³ Isabella Annesi-Maesano,⁴ Valérie Siroux,^{1*} Rémy Slama,^{1*} and the EDEN Mother-Child Cohort Study Group[†]

¹Inserm, CNRS, University Grenoble Alpes, Institute for Advanced Biosciences (IAB), U1209, Team of Environmental Epidemiology Applied to Reproduction and Respiratory Health, Grenoble, France

²Centre Hospitalier Universitaire (CHU), Service de pédiatrie, Grenoble, France

³Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

⁴Epidemiology of Allergic and Respiratory Diseases (EPAR) Department, IPLESP, INSERM & UPMC Paris 6, Sorbonne Université, Paris, France

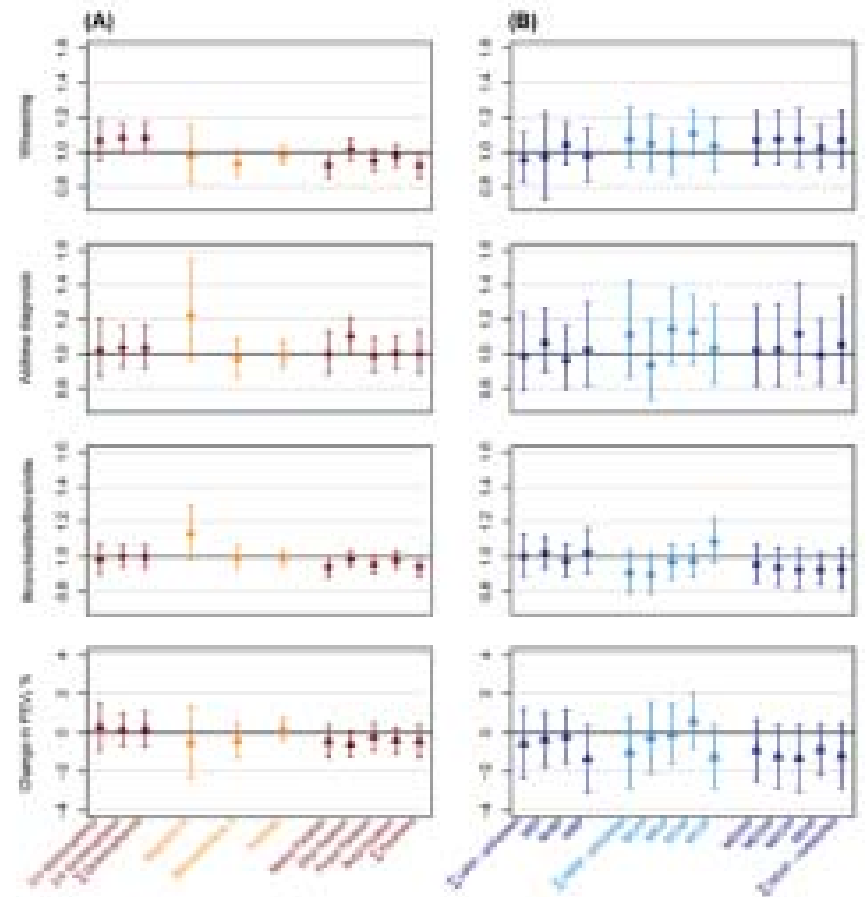


Figure 1. Adjusted associations of (A) phenols and (B) phthalates metabolites to childhood standardized concentrations with respiratory outcomes (FEV₁, n = 377) and FEV₁/FVC in boys (data, n = 226, 2,529/9 subjects). Effect estimates for 1-unit increase in background standardized concentrations, adjusted for season, residence size, parental history of asthmatoallergy, maternal ethnicity, maternal parental education level, gestation at birth, smoking during pregnancy, parental passive smoking, other siblings, child care, and additionally adjusted for boy's height and age in spirometry analysis. Multiple regression was used in family setting unless in parentheses (1:10 regression, zero partition). Phenolic and phthalate metabolites concentrations were standardized for urine sampling conditions (see Methods section). Diamond and triangle markers represent OR and beta values, respect only, with error bars for 95% CI.

Prenatal Exposure to Phthalates and the Development of Eczema Phenotypes in Male Children: Results from the EDEN Mother–Child Cohort Study

Munawar Hussain Soomro,^{1,2} Nour Baiz,¹ Claire Philippat,³ Celine Vernet,³ Valerie Siroux,³ Cara Nichole Maesano,¹ Shreosi Sanyal,¹ Remy Slama,³ Carl-Gustaf Bornehag,^{4,5} and Isabella Annesi-Maesano¹

Phthalate metabolite	Unadjusted			Adjusted ^a		
	HR ^b	95% CI	p-Value	HR	95% CI	p-Value
MEP	1.04	0.93, 1.15	0.47	1.04	0.94, 1.16	0.42
MBP	1.00	0.89, 1.12	0.96	1.03	0.92, 1.15	0.60
MiBP	1.16	1.01, 1.33*	0.03	1.16	1.01, 1.34*	0.03
MECPP	0.97	0.84, 1.12	0.73	0.98	0.84, 1.13	0.77
MEHHP	0.99	0.86, 1.13	0.90	0.99	0.88, 1.14	0.93
MEOHP	1.01	0.88, 1.15	0.91	1.01	0.88, 1.16	0.86
MEHP	0.96	0.86, 1.07	0.50	0.96	0.85, 1.08	0.47
MBzP	0.99	0.88, 1.12	0.99	1.02	0.90, 1.15	0.69
MCOP	1.04	0.91, 1.19	0.48	1.09	0.95, 1.25 [†]	0.05
MCP	1.02	0.88, 1.17	0.81	1.05	0.91, 1.22	0.50
MCNP	1.02	0.90, 1.14	0.74	1.03	0.92, 1.17	0.56
ΣDEHP	0.99	0.96, 1.03	0.77	0.98	0.94, 1.03	0.57

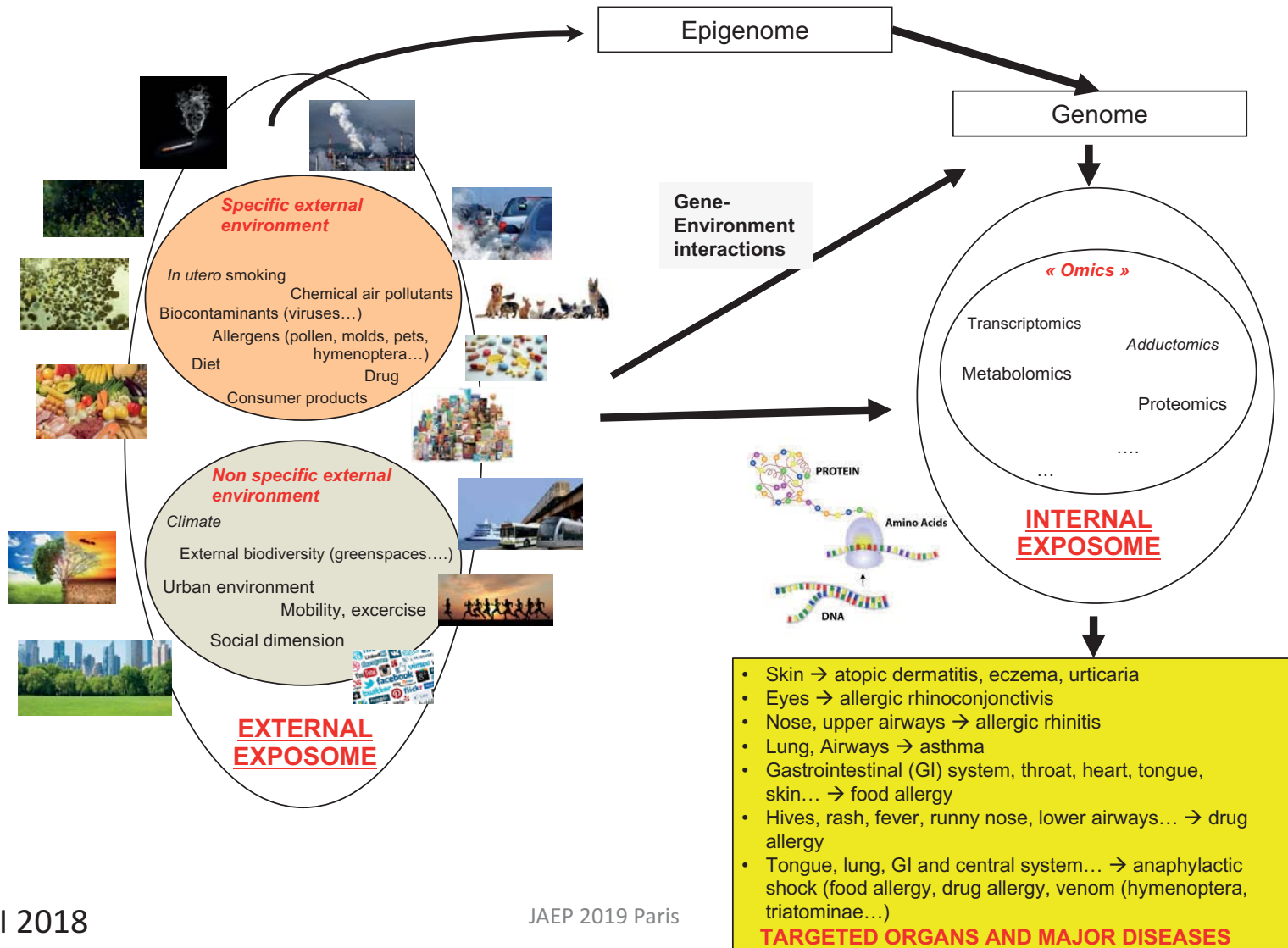
RESULTS: At 5 y of age, the prevalence of ever eczema was 30.4%. Metabolites of di-isobutyl phthalate (DiBP) and di-isononyl phthalate (DiNP) were positively associated with early-onset (0–24 mo of age) eczema (15.7%) and late-onset (24–60 mo of age) eczema (14.7%). Applying the Cox's model showed a significant association of occurrence of eczema in the first 5 y of life with DiBP and DiNP metabolites. Among IgE-sensitized boys, metabolites of di-*n*-butyl phthalate (DBP) and DiBP were significantly associated with ever eczema {hazard ratio (HR) = 1.67 [95% confidence interval (CI): 1.10, 2.54], $p=0.01$ and HR = 1.87 (95% CI: 1.01, 3.48), $p=0.04$, respectively}.

^bHR according to the proportional Cox's model.

Lien entre exposition des bébés à un cocktail de polluants chimiques et diminution de la fonction respiratoire

- Certaines substances (composés perfluorés (les PFC, qu'on retrouve notamment dans les poêles antiadhésives, certains emballages alimentaires et les revêtements anti-tâches), l'éthyl-parabène (un conservateur utilisé dans de nombreux cosmétiques) et plusieurs molécules issues de la dégradation des phtalates) *associées à une fonction respiratoire diminuée chez l'enfant*

Exposome involvement in allergy



What Can You Do to Reduce Phthalates Exposures?

Precautionary Approach:

- Eat fresh foods
- Avoid use in microwave
- Avoid use in dishwasher
- Wet mop and dust frequently
- Seek phthalates free labels
- Keep it simple, less is more
- www.cosmeticsdatabase.org



Handling plastic waste

As plastics are not readily degraded and are very stable in the ambient environment, their disposal in the environment has currently created a considerable pollution problem.

Presently, the management of waste plastics is a major environmental issue. Several strategies have been adopted for the handling of plastic waste which includes:

- Recycling
- depositing in landfill
- incineration, microbial
- Degradation
- conversion into useful materials.

Ce qu'il faut retenir :

- ➔ 1^{er} point: Les enfants sont excessivement exposés aux PE dès la vie *in utero*
- ➔ 2^{ème} point: De plus en plus de données montrent que l'exposition aux PE est responsable d'excès de symptômes et maladies allergiques et respiratoires
- ➔ 3^{ème} point: Des actions de prévention peuvent être menées pour réduire les dangers et les risques liés aux PE



www.epar.fr



Merci

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IPLESP - Institut Pierre Louis d'Epidémiologie et Santé Publique
JAEP 2019 Paris

