Puberté(s) Précoce(s) et Perturbateurs Endocriniens

Dr Laura Gaspari **Pr Françoise Paris** Pr Charles Sultan

Unité d'Endocrinologie et de Gynécologie Pédiatriques, Hôpital A. de Villeneuve
Département de Biologie Moléculaire DevGen, IURC
U INSERM DEFE, 1203

Journée d'Échanges Régionale
Puberté(s) précoce(s)
et perturbateurs endocriniens

Puberté(s) Précoce(s) et Perturbateurs Endocriniens

1- Rappels / la problématique des PEE

2- PEE dans notre environnement de proximité

3- PEE et Puberté

4- Conclusions

Puberté(s) Précoce(s) et Perturbateurs Endocriniens

1- Rappels / la problématique des PEE

2- PEE dans notre environnement de proximité

3- PEE et Puberté

4- Conclusions

Perturbateurs Endociniens Environnementaux: PEE

Perturbateurs endocriniens environnementaux (PEE) = polluants chimiques

- air -eau -sol -alimentation	interférence avec	synthèse métabolisme action	d'une hormone endogène (stéroïde)

Émergence de la problématique PEE

Faune sauvage

DSD
↓ Fertilité

(Guillette 1999, 2001)
(Bergman 1999)

Données Epidémiologiques/Homme

Altération de la fertilité

Hypospadias

Cryptorchidies

Micropénis

(Carlsen 1992, Auger 1995)
(Bonde 1998, Andersen 2000, Jensen 2002)

Environnement

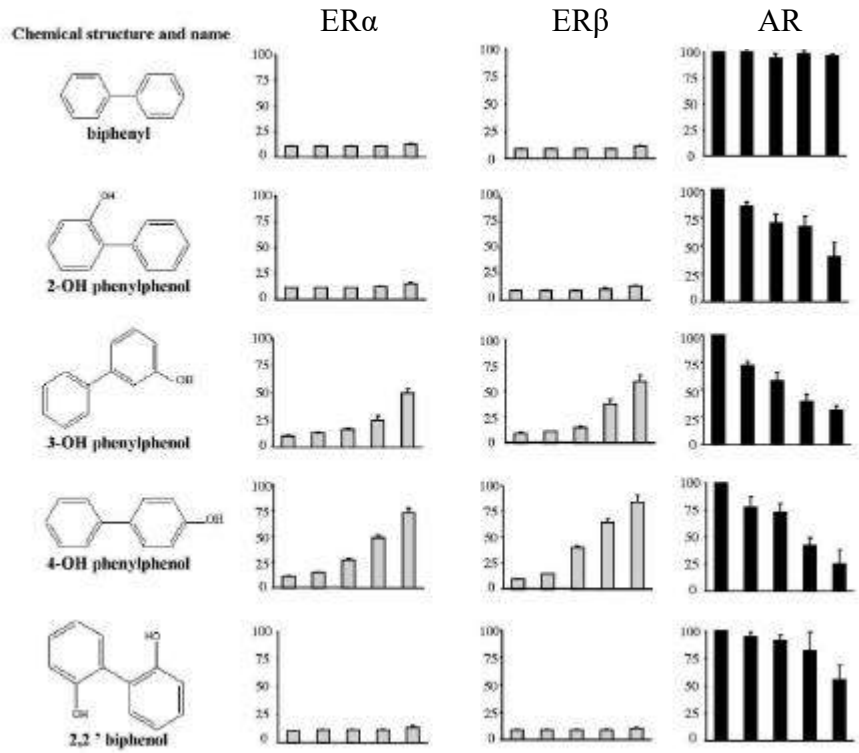
Expérimentales

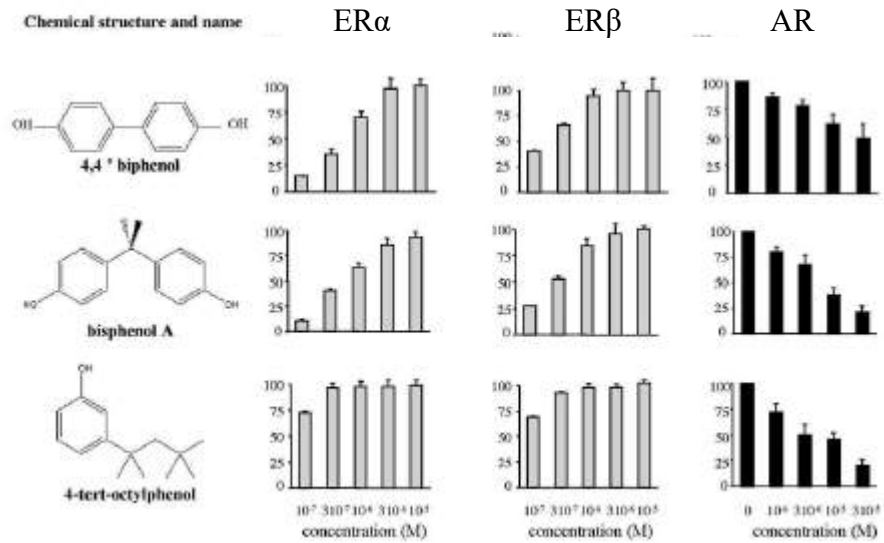
PEE

(Newbold 1996)
(Gray, 2001)

Différents types de PEE

Mécanismes d'action





Composés biphénylés → Activités estrogéniques et anti-androgéniques

Paris F, Balaguer P, Terouanne B, Servant N, Lacoste C,Cravedi JP, Nicolas JC, Sultan Ch. Mol Cell Endocrinol , 2002, 193: 43-49

EDCs	NR targets	EC50 range	Lead compound	Nature
Parabens	ERα (NR3A1)	1–10 μM	Butyl paraben	Full agonist
	ERβ (NR3A2)	1–10 μM	Butyl paraben	Full agonist
Benzophenones	ERα (NR3A1)	0.1–1 μM	Benzophenone-2	Full agonist
	ERβ (NR3A2)	0.1–1 μM	Benzophenone-2	Full agonist
	AR (NR3C4)	1–10 μM	THB	Antagonist
Bisphenols	ERα (NR3A1)	0.01–1 μM	BPA	Partial agonist
	ERβ (NR3A2)	0.01–1 μM	BPA	Partial agonist
	AR (NR3C4)	0.01–1 μM	BPA	Antagonist
	ERRγ (NR3B3)	0.001–0.1 μM	BPA	Agonist
	PXR (NR1I2)	1–10 μM	BPA	Agonist
Halogenated bisphenols	ERα (NR3A1)	0.1–10 μM	TetrachloroBPA	Partial agonist
	ERβ (NR3A2)	0.1–10 μM	TetrachloroBPA	Partial agonist
	PPARγ (NR1C3)	1–10 μM	TetrabromoBPA	Partial agonist
	TRα (NR1A1)	1–10 μM	TetrabromoBPA	Antagonist
	TRβ (NR1A2)	1–10 μM	TetrabromoBPA	Antagonist
Alkylphenols	ERα (NR3A1)	0.01–1 μM	4-tert-Octylphenol	Agonist
	ERβ (NR3A2)	0.01–1 μM	4-tert-Octylphenol	Partial agonist
	AR (NR3C4)	1–10 μM	4-tert-Octylphenol	Antagonist
	ERRγ (NR3B3)	1–10 μM	4-tert-Octylphenol	Antagonist
	PXR (NR1I2)	1–10 μM	4-tert-Octylphenol	Agonist
Phthalates	ERα (NR3A1)	1–10 μM	BBP	Agonist
	ERβ (NR3A2)	1–10 μM	BBP	Partial agonist
	PPARα (NR1C1)	1–100 μM	MEHP	Agonist
	PPARγ (NR1C3)	1–100 μM	MEHP	Agonist
Perfluorinated compounds	PPARα (NR1C1)	1–100 μM	PFOA	Agonist
	PPARγ (NR1C3)	1–100 μM	PFOA	Agonist
Pesticides	ERα (NR3A1)	0.1–10 μM	2,4′-DDE	Agonist
	ERβ (NR3A2)	0.1–10 μM	2,4′-DDE	Partial agonist
	AR (NR3C4)	0.1–1 μM	M2 vinclozolin	Partial agonist
	PXR (NR1I2)	0.1–10 μM	Pretilachlor	Agonist
Organotins	PPARγ (NR1C3)	1–10 nM	TBT	Partial agonist
	RXRα (NR2B1)	1–10 nM	TBT	Agonist

Grimaldi M, 2016, Front Endocrinol

Et d’autres mécanismes d’action:

Liaison à AhR (aryl hydrocarbone receptor)

Liaison à GPR30

Liaison aux protéines de transport de certaines hormones

Perturbent le métabolisme de certaines hormones

Maqbool F, Life Sci, 2016; Sharma RP, Envrion Int, 2017

Mécanismes épigénétiques

Curr Envir Health Rpt (2015) 2:126–136
DOI 10.1007/s40572-015-0045-0

ENVIRONMENTAL EPIGENETICS (A BACCARELLI, SECTION EDITOR)

Select Prenatal Environmental Exposures and Subsequent Alterations of Gene-Specific and Repetitive Element DNA Methylation in Fetal Tissues

Benjamin B. Green[1] · Carmen J. Marsit[1]

Environment International 114 (2018) 77–86

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Review article

Epigenetics as a mechanism linking developmental exposures to long-term toxicity

R. Barouki[a,b,*], E. Melén[c,d], Z. Herceg[e], J. Beckers[f,g,h], J. Chen[i], M. Karagas[j], A. Puga[k], Y. Xia[k], L. Chadwick[l], W. Yan[m,n], K. Audouze[o], R. Slama[p], J. Heindel[q], P. Grandjean[r,s], T. Kawamoto[t], K. Nohara[u]

Puberté(s) Précoce(s) et Perturbateurs Endocriniens

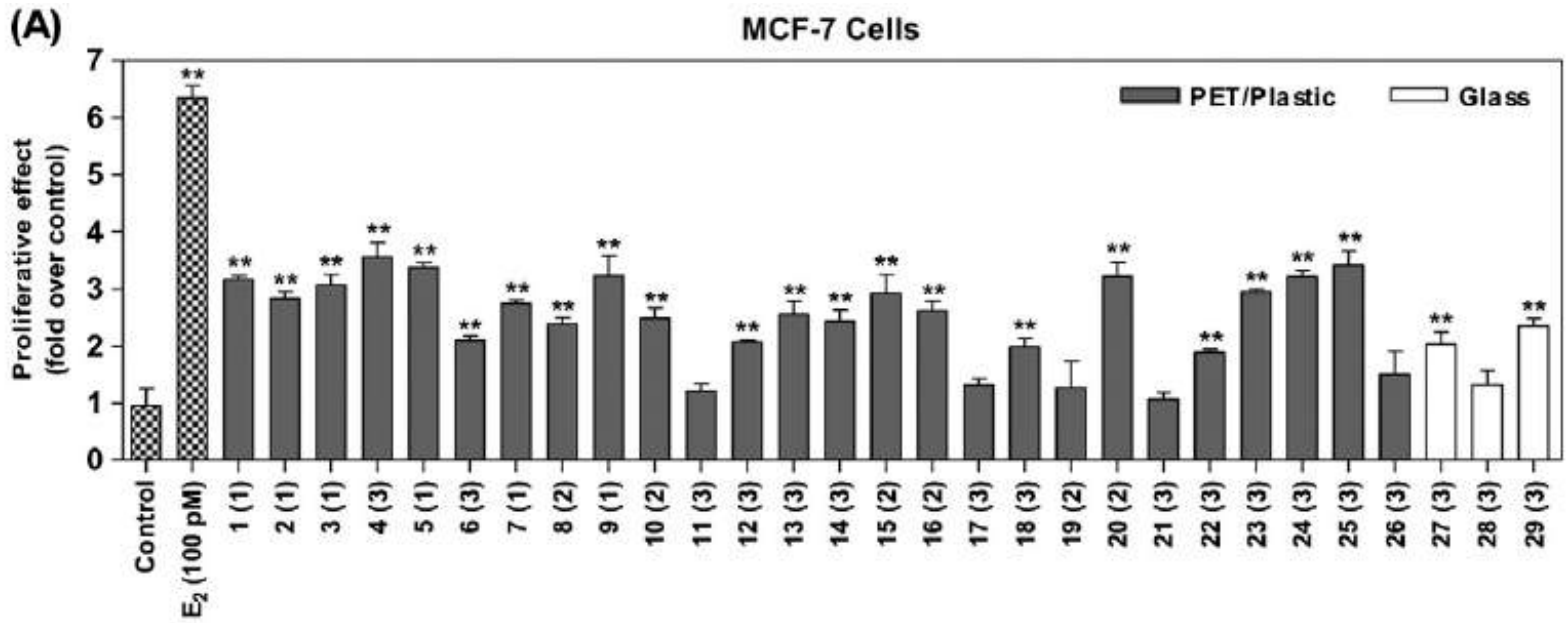
1- Rappels / la problématique des PEE

2- PEE dans notre environnement de proximité

3- PEE et Puberté

4- Conclusions

Activité Estrogénique / eau en bouteille (Espagne)



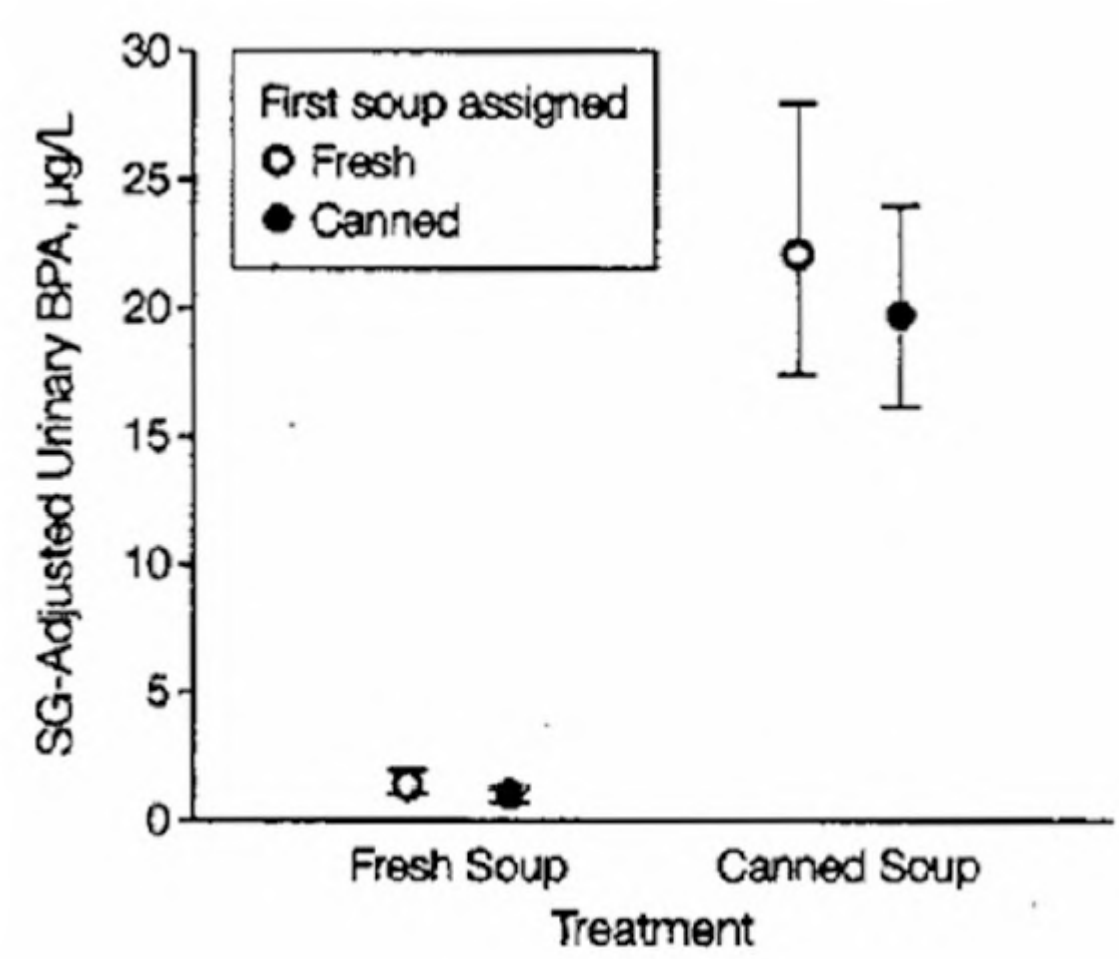
Eau en bouteille

Macarena R, Olea N, Environment International, 2015, 74: 125-135

BPA

Intérieur boites de conserve

/ dureté , caractère translucide des contenants plastiques



Carwile J, 2011, JAMA, 306(20): 2218-

BPA/ France

Cf / M^me^ Fleckenstein

Europe … 2018

ESFA (European Safety Food Authority)

Réévaluation, remise en question

Pesticides

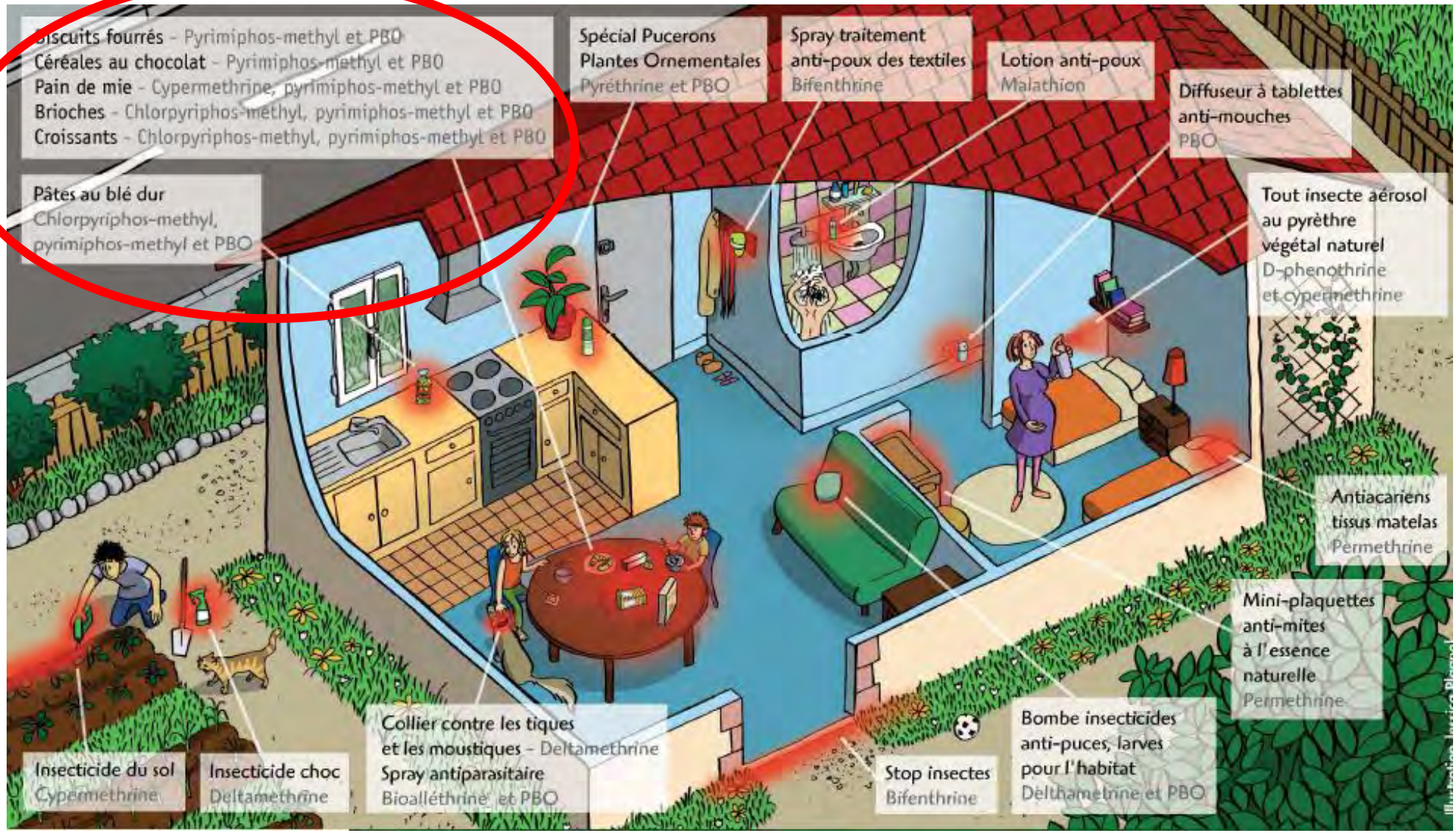
Enquête EXPPERT 1

EXposition aux Pesticides PERTurbateurs Endocriniens

Mars 2013

Recherche de pesticides / aliments couramment consommés par les enfants

Pain de mie, biscuits etc ….



75% des échantillons testés contiennent des résidus (même si < LMR)

Produit	Matières actives	PHRASE DE RISQUE	Perturbateur Endocrinien	Inhib Ach
Spaghetti Panzani	chlorpyriphos-méthyl 0,014 * mg/kg	N Xi R43 R50/53		oui
	pirimiphos-méthyl 0,084 * mg/kg	N Xn R22 R50/53		oui
	pipéronyl-butoxyde 0,063 * mg/kg		2	
BN blé complet	pirimiphos-méthyl 0,032 mg/kg	N Xn R22 R50/53		oui
	pipéronyl-butoxyde 0,018 mg/kg		2	
Petit dej Belvita	pirimiphos-méthyl 0,039 * mg/kg	N Xn R22 R50/53		oui
	pipéronyl-butoxyde 0,23 mg/kg		2	
Chocapic cereales completes	pirimiphos-méthyl 0,014 * mg/kg	N Xn R22 R50/53		oui
	pipéronyl-butoxyde 0,016 * mg/kg		2	
Spécial K 3 céréales complètes	pipéronyl-butoxyde 0,023 * mg/kg			
Doowap brioche pepites	chlorpyriphos-méthyl 0,060 * mg/kg	N Xi R43 R50/53		oui
	pirimiphos-méthyl 0,045 * mg/kg	N Xn R22 R50/53		oui
	pipéronyl-butoxyde 0,013 * mg/kg		2	
Croissants Pasquier	chlorpyriphos-méthyl 0,054 * mg/kg	N Xi R43 R50/53		oui
	pirimiphos-méthyl 0,043 * mg/kg	N Xn R22 R50/53		oui
	pipéronyl-butoxyde 0,013 * mg/kg		2	
Pain Harris	cypermethrin 0,025 mg/kg	N Xn R20/22 R37 R50/53	2	
	pirimiphos-méthyl 0,077 mg/kg	N Xn R22 R50/53		oui
	pipéronyl-butoxyde 0,12 mg/kg		2	
Pain complet Carrefour	cypermethrin 0,035 mg/kg	N Xn R20/22 R37 R50/53	2	
	pirimiphos-méthyl 0,068 mg/kg	N Xn R22 R50/53		oui
	pipéronyl-butoxyde 0,12 mg/kg		2	
Farfalle Barilla	Aucun produit détecté			
Barre de céréales Grany	Aucun produit détecté			
Barre de céréales special K	Aucun produit détecté			

La France reste le premier utilisateur de pesticides en Europe et le 3ème au monde en tonnage avec 62700 tonnes de substances actives vendues en 2011[11].

Blé = 47% des pesticides épandus sur les grandes cultures

De plus, l'an dernier le réseau Pesticide Action Network-Europe a publié une enquête[38], basée sur les données de l'EFSA (Autorité européenne de sécurité des aliments), qui montre que les consommateurs sont exposés à des pesticides perturbateurs endocriniens quotidiennement lorsqu'ils mangent de la laitue, des tomates, des concombres, des pommes et beaucoup d' autres fruits et légumes non bio. Plusieurs de ces pesticides sont pulvérisés sur les mêmes cultures et les consommateurs pourraient être exposés à des mélanges de produits chimiques dangereux. Ce mélange pose de réelles questions de santé publique. Ceci est d'autant plus inquiétant sachant que ces produits chimiques sont présents dans de nombreux autres produits de consommation courante tels que les produits biocides (produits chimiques domestiques souvent utilisé sous forme d'aérosol), les pesticides utilisés au jardin, certains produits cosmétiques ou encore certains plastiques.

www.disruptingfood.info

Aliments solides et Phtalates

Utilisés pour **Augmenter la flexibilité des matières plastiques**

Pour les phtalates diesters: fixateurs de couleur liés de façon non covalente aux polymères

Code	Sample description	DiBP	DnBP	BBzP	DEHP
S01	Minced beef 5% fat	<LoR	0.7	0.5	3.3
S02	Minced beef 15% fat	<LoR	0.7	0.3	6.8
S03	Minced veal	<LoR	1.9	0.3	104
S04	Pickled pork rib	2.6	0.7	<LoR	<LoR
S05	Cooked ham	4.1	0.7	<LoR	4.6
S06	Pork chipolata	<LoR	1.6	<LoR	3.9
S07	Sliced bacon	7.1	1.1	<LoR	6.2
S08	Strasbourg sausages	4.5	28.8	0.5	39.1
S09	White hake	10.4	3.1	0.6	44.8
S10	Breaded fish	6.3	5.1	1.6	34.7
S11	Sliced salmon	6.1	0.7	<LoR	7.3
S12	Smoked salmon	5.5	1.5	<LoR	8.8
S13	Fish stick	2.7	0.7	<LoR	3.3
S14	Cooked small prawn	<LoR	0.5	<LoR	5.6
S15	Fresh egg	6.2	0.8	<LoR	5.4
S16	Whole milk	<LoR	0.5	<LoR	21.8
S17	Concentrated milk	2.9	0.4	0.7	25.5
S18	Drinking yogurt	<LoR	0.3	<LoR	<LoR
S19	Pressed cooked paste cheese	5.1	10.6	0.6	720
S20	Grated Emmental	8.9	28.2	1.1	186
S21	Melted cheddar	9.4	12.1	0.7	155
S22	Pre-cooked rice	13.6	3.6	0.6	53.1
S23	Buckwheat pancake	3.9	1.0	<LoR	9.8
S24	White bread	9.9	1.9	0.6	12.0
S25	Croissant	20.9	41.0	1.9	536
S26	Marble cake	24.7	5.4	0.8	23.4
S27	Potato crisps	12.0	9.9	0.7	9.5
S28	Popped corn, bacon flavour	40.3	54.2	0.7	114
S29	Extruded chocolate flavoured cereals	8.7	3.0	1.2	57.9
S30	Pine nuts	250	74.2	6.8	2376

Code	Sample description	DiBP	DnBP	BBzP	DEHP
S31	Apples	7.4	6.0	1.0	69.7
S32	Artichoke puree	3.1	0.6	1.1	5.5
S33	Leek	3.5	0.5	<LoR	<LoR
S34	Cooked beetroot	3.6	1.5	<LoR	9.6
S35	Salad	5.8	0.7	0.3	3.1
S36	Macaroni chicken mixed meal for infant	5.0	1.8	10.9	49.8
S37	Rice fish mixed meal for infant	3.8	1.4	0.5	5.8
S38	Green vegetables lamb mixed meal	4.2	2.0	1.2	31.4
S39	Cheese burger	9.2	3.0	0.8	64.8
S40	Beef shepherd's pie	7.6	2.5	1.0	31.3
S41	Provencal pizza	23.2	4.2	1.6	42.0
S42	Rice pudding	3.2	1.2	0.8	52.4
S43	Salted butter	14.1	1.8	0.7	219
S44	Light margarine	5.4	0.9	1.5	40.4
S45	Pizza oil	7.9	2.4	0.6	67.1
S46	Sweets	18.6	4.1	1.5	106
S47	Apple-banana compote	<LoR	1.3	0.5	12.8
S48	Sweet tomato sauce	<LoR	1.8	0.3	6.1
S49	Red wine	<LoR	72.8	7.1	<LoR
S50	Beer	<LoR	<LoR	<LoR	<LoR
S51	Cola	<LoR	<LoR	<LoR	<LoR
S52	Coconut, whey and kiwi based drink	<LoR	0.3	<LoR	<LoR
S53	Orange juice	<LoR	0.3	<LoR	<LoR
S54	Lemon juice	19.0	2.2	0.5	<LoR

Cariou R, 2016, Food Chemistry, 196: 211-219

Polycyclic Aromatic Hydrocarbon (PAC)

Combustion incomplète

Industrie du pétrole

Food group	Adults (n = 1918)			Children (n = 1444)		
	Mean	P95	Contribution (%)	Mean	P95	Contribution (%)
Mollusks and crustaceans	0.193	1.974	13.1	0.098	2.365	4.3
Oils	0.240	0.787	16.2	0.342	1.457	15.2
Margarine	0.107	0.799	7.3	0.111	0.874	4.9
Condiments and sauces	0.015	0.153	1.0	0.027	0.199	1.2
Delicatessen	0.093	0.172	6.3	0.156	0.288	6.9
Pizzas, quiches and savory pastries	0.095	0.572	6.4	0.166	0.794	7.4
Sweet and savory biscuits and bars	0.047	0.256	3.2	0.196	0.575	8.7
Bread and rusks	0.186	0.321	12.6	0.161	0.280	7.1
Viennese bread and buns	0.035	0.203	2.4	0.117	0.417	5.2
Pastries and cakes	0.060	0.202	4.1	0.146	0.423	6.5
Fish	0.03	0.101	2.0	0.07	0.220	3.1
Sandwiches	0.029	0.253	2.0	0.043	0.299	1.9
Cooked dishes	0.065	0.294	4.4	0.140	0.311	6.2
Potato-based products	0.058	0.114	3.9	0.123	0.214	5.4
Eggs and egg products	0.021	0.096	1.4	0.025	0.133	1.1
Breakfast cereals	0.006	0.196	0.4	0.018	0.091	0.8
Butter	0.021	0.052	1.4	0.027	0.081	1.2
Meat	0.040	0.066	2.7	0.063	0.108	2.8
Poultry and game	0.029	0.089	2.0	0.041	0.128	1.8
Offal	0.001	0.031	0.1	0.001	0.047	0.0
Cream desserts	0.020	0.106	1.4	0.070	0.290	3.1
Cheese	0.023	0.036	1.5	0.032	0.056	1.4
Vegetables	0.016	0.057	1.1	0.018	0.078	0.8
Hot drinks	0.002	0.035	0.1	0.006	0.044	0.3
Coffee	0.028	0.111	1.9	0.001	0.044	0.0
Ultra-fresh dairy products	0.011	0.021	0.7	0.023	0.038	1.0
Milk	0.008	0.046	0.6	0.039	0.132	1.7
Softdrinks	0.000	0.030	0.0	0.000	0.093	0.0

Veyrand B, 2013, Environ Intern, 54: 11-17

Veyrand B, 2013, Environ Intern, 54: 11-17

safety issue. Comparison of the present data with the last exposure estimation performed in 2003 in France indicates a three times decrease in the exposure level. Similar trends have been reported in other countries and related mainly to environmental causes (general reduction of industrial and traffic emissions (Wang et al., 2009) resulting in a decrease in atmospheric PAH levels (Meijer et al., 2008)). Aside from these environmental conditions that may lead to

Meijer S, 2008, Environ, Sci Technol, 42: 3213-3218

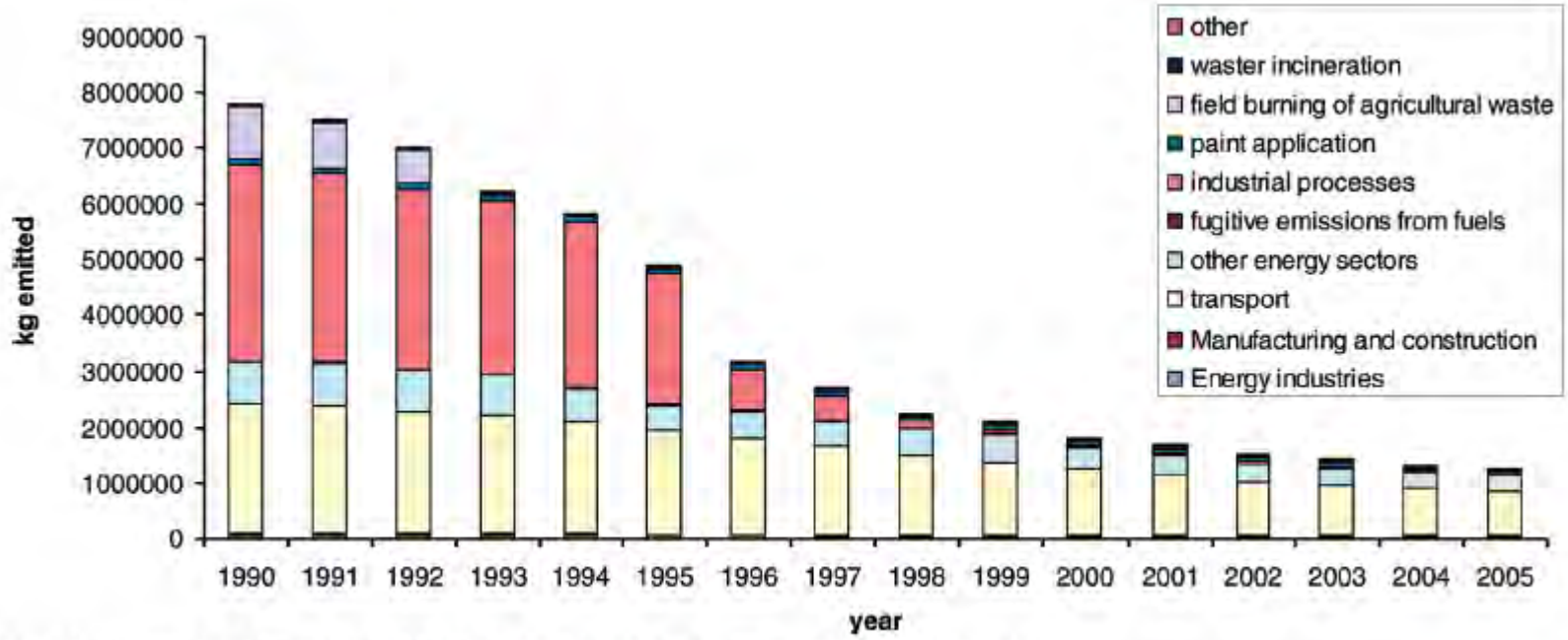


FIGURE 3. U.K. atmospheric emissions of the EPA16 PAHs between 1990 and 2005 (kg).

Puberté(s) Précoce(s) et Perturbateurs Endocriniens

1- Rappels / la problématique des PEE

2- PEE dans notre environnement de proximité

3- PEE et Puberté

4- Conclusions

Impact sur la santé / enfant / adulte

1. Différenciation sexuelle masculine fetale
2. Croissance staturo-pondérale fetale, post-natale
3. Neurodéveloppement
4. Timing / tempo de la puberté (fille)
5. Fréquence du cancer du testicule / jeune
6 .Baisse de la spermatogénèse
7. Fréquence du cancer de la prostate
8. Altération fertilité / femme
9. Fréquence du cancer du sein
10. Perturbation / thyr.
11. Syndrome métabolique

Kiess W, Best Pract Res Clin Endocrinol Metab, 2021, 35 (5):101516-

Fudvoye J, Best Pract Res Clin Endocrinol Metab, 2019, 33: 101300

Lopez-Rodriguez, Best Pract Res Clin Endocrinol Metab, 2021, 35 (5):101579-

Retentissement sur la santé de l'enfant

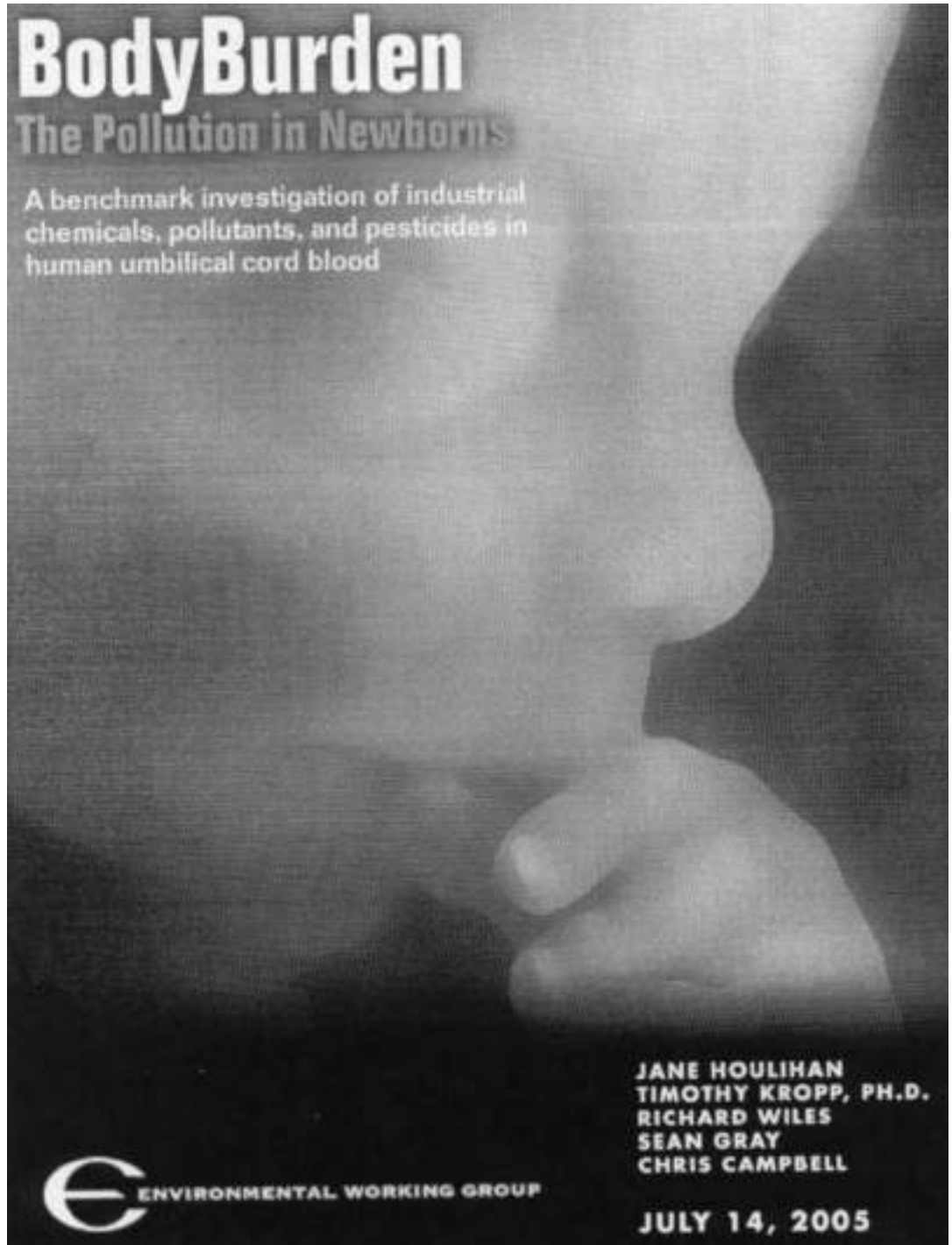
Exposition durant l'enfance

Mais aussi **Fenêtres d'exposition / de vulnérabilité**

Exposition in utéro

In the newborn cord blood

> 400 E.E.D. !



Example studies of concentration of selected PCBs in pregnant women, by location and study years.

Location	Study years	N	Sample	Median concentration (ng/g lipid) PCB-153	∑PCBs	Congeners included in ∑PCBs	First author, year (reference)
North America							
US	1959–1965	593	MS	1.7 mmol/L	7.9 mmol/L	28, 52, 74, 105, 118, 138, 153, 170, 180, 194, 203	McGlynn, 2009 (90)
US (California)	1960–1963	289	MS	0.79 μg/L			Cohn, 2011 (91)
US (California)	1964–1967	399	MS	133	616	101, 105, 110, 118, 137, 138, 153, 156, 170, 180, 187	James, 2002 (92)
US (Massachusetts)	1993–1998	573	CS		0.19 ng/g	118, 138, 153, 180	Sagiv, 2010 (23)
US (Illinois, Chicago)	1993–1998	252	MS	86			McGraw, 2009 (93)
Canada (Nunavik)	1995–2001	159	MP	105.3 (GM)	313.2 (GM)	28, 52, 99, 101, 105, 118, 128, 138, 153, 156, 170, 180, 183, 187	Muckle, 2001 (94)
		98	CP	86.9 (GM)	279.9 (GM)		
Canada (Southwest Quebec)	N/A	39 (1st Tri)	MP	0.07 μg/L	0.33 μg/L	28, 52, 99, 101, 105, 118, 128, 138, 153, 156, 170, 180, 183, 187	Takser, 2005 (95)
		145 (2nd Tri)	MP	0.08 μg/L	0.35 μg/L		
		101 (at delivery)	MP	0.09 μg/L	0.39 μg/L		
		92 (CP)	CP	0.02 μg/L	0.16 μg/L		
US (New York)	1996–1997	79	MS	0.26 ng/g			Bloom, 2007 (96)
US (California, Salinas)	1999–2001	24	MP	4.4			Bradman, 2007 (97)
US (nationwide)	2003–2004	75	MS	8.8		118, 138 and 158, 153, 180	Woodruff, 2011 (89)
US (Ohio)	2003–2006	175	MS	11.0			Braun, 2014 (98)
Canada	2005–2007	173	MS	4.7–41 (GM)			Curren, 2014 (99)
Canada (Quebec)	2007–2008	349	MP	8.0	18.9		Serme-Gbedo, 2016 (100)
US (California)	2010–2011	77	MS	3.0			Morello-Frosch, 2016 (in preparation)
		63	CS	4.4			
Europe							
The Netherlands and Germany (GRD cohort)	1990–1995	523	CP/CS	150.0 ng/L			Casas, 2015 (101)
Faroe Islands (FAROES2 cohort)	1994–1995	173	MS	394.4 ng/L			Casas, 2015 (101)
Sweden	1994–1995	57	MS	430.0			Fängström, 2005 (102)
Spain (INMA cohort)	1997–2008	868	MS	93.8 ng/L			Casas, 2015 (101)
		1,254	CS	135.2 ng/L			
The Netherlands	1998–2000	97	CS	89.8	290.0	105, 118, 138, 146, 153, 156, 170, 180, 183, 187	Berghuis, 2013 (103)
Germany (Duisburg)	2000–2002	227	MWB	115.2 ng/L			Casas, 2015 (101)
The Netherlands	2001–2002	62	MS	63.0			Roze, 2009 (31)
Belgium (Flanders, FLEHSI cohort)	2002–2004	1,061	CP	60.0 ng/L			Casas, 2015 (101)
Eastern Slovakia	2002–2004	966	MS	143.0	415.0	28, 52, 101, 105, 114, 118, 123, 138, 149, 153, 156, 157, 163, 167, 170, 171, 180, 189	Jusko, 2012 (104)
Greenland	2002–2004	546	MS	126.4 ng/L			Casas, 2015 (101)
Poland	2002–2005	84	CS	43.4 ng/g fat (AM)			Hernik, 2013 (105)
France (Brittany)	2002–2006	396	CS	110.0 ng/L			Casas, 2015 (101)

Wang. Environmental exposures and pregnancy. Fertil Steril 2016.

Wang A, Fertil Steril, 2016, 106 (4):905-

Molecular and Cellular Endocrinology 429 (2016) 41–49

Contents lists available at ScienceDirect

Molecular and Cellular Endocrinology

journal homepage: www.elsevier.com/locate/mce

The xenoestrogens, bisphenol A and *para*-nonylphenol, decrease the expression of the ABCG2 transporter protein in human term placental explant cultures

E. Sieppi [a, b], K. Vähäkangas [c], A. Rautio [b], F. Ietta [d], L. Paulesu [d], P. Myllynen [b, e, *]

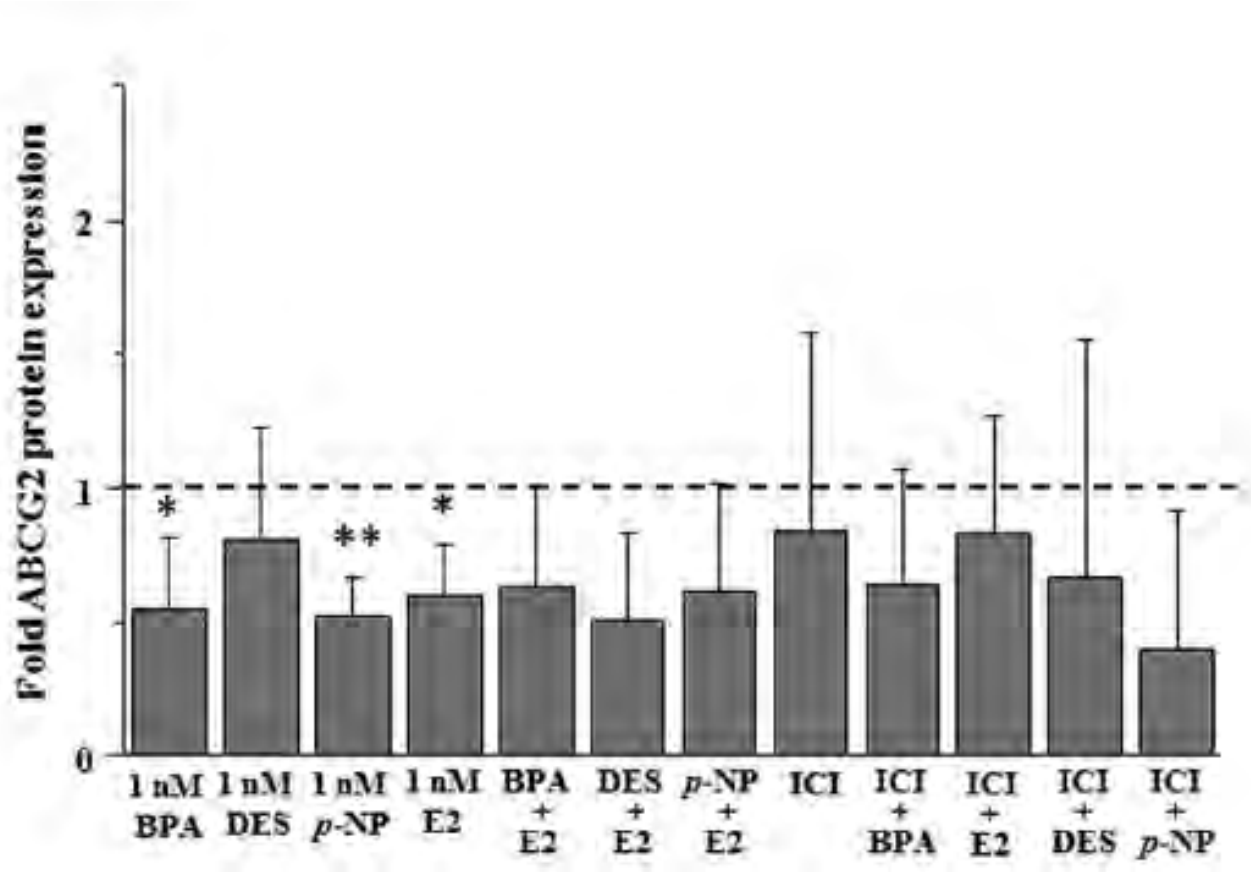
[a] Research Unit of Biomedicine, Pharmacology and Toxicology, University of Oulu, P.O. Box 5000, 90014, University of Oulu, Oulu, Finland
[b] Centre for Arctic Medicine, Thule Institute, University of Oulu, P.O. Box 7300, 90014, University of Oulu, Oulu, Finland
[c] Faculty of Health Sciences, School of Pharmacy/Toxicology, University of Eastern Finland, P.O. Box 1627, 70211, Kuopio, Finland
[d] Department of Life Sciences, University of Siena, Via Aldo Moro 2, 53100, Siena, Italy
[e] Nordlab Oulu, P.O. Box 500, 90029, OYS, Oulu, Finland

Villosités choriales en cultures

PEE dans le milieu de culture

Expression du transporteur ABCG2

protège le fœtus contre des agents chimiques extérieurs présents dans la circulation foetale



BPA et p-NP diminuent l'expression placentaire de ABCG2

ER interviendrait dans cette diminution

Sieppi E, 2016, MCE, 429: 41-

Puberté: aboutissement de différentes étapes de maturation qui débutent in utéro et se poursuivent en période postnatale

Minipuberté

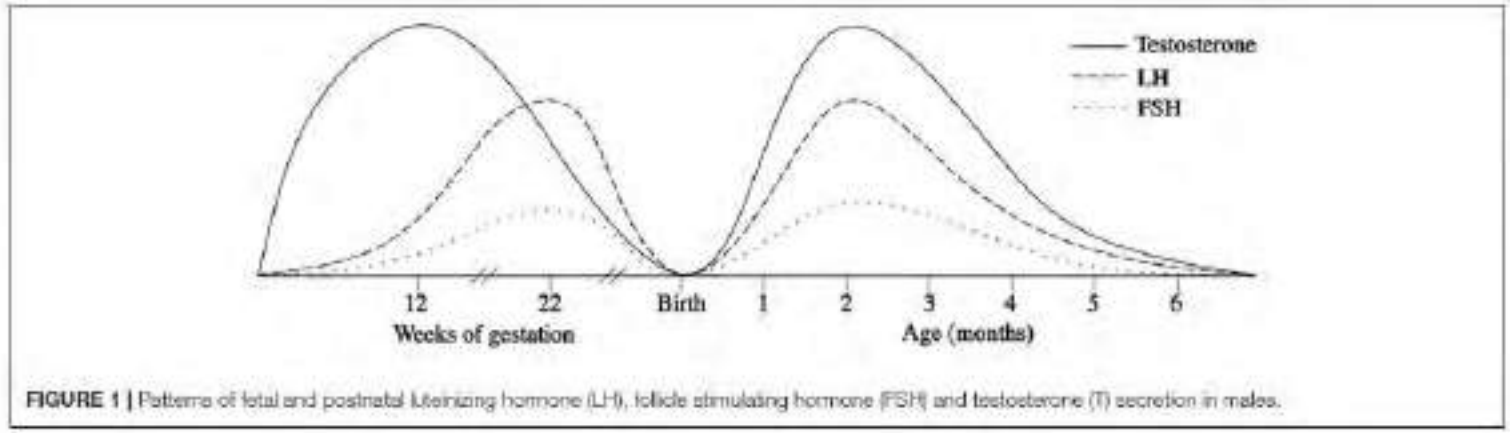


FIGURE 1 | Patterns of fetal and postnatal luteinizing hormone (LH), follicle stimulating hormone (FSH) and testosterone (T) secretion in males.

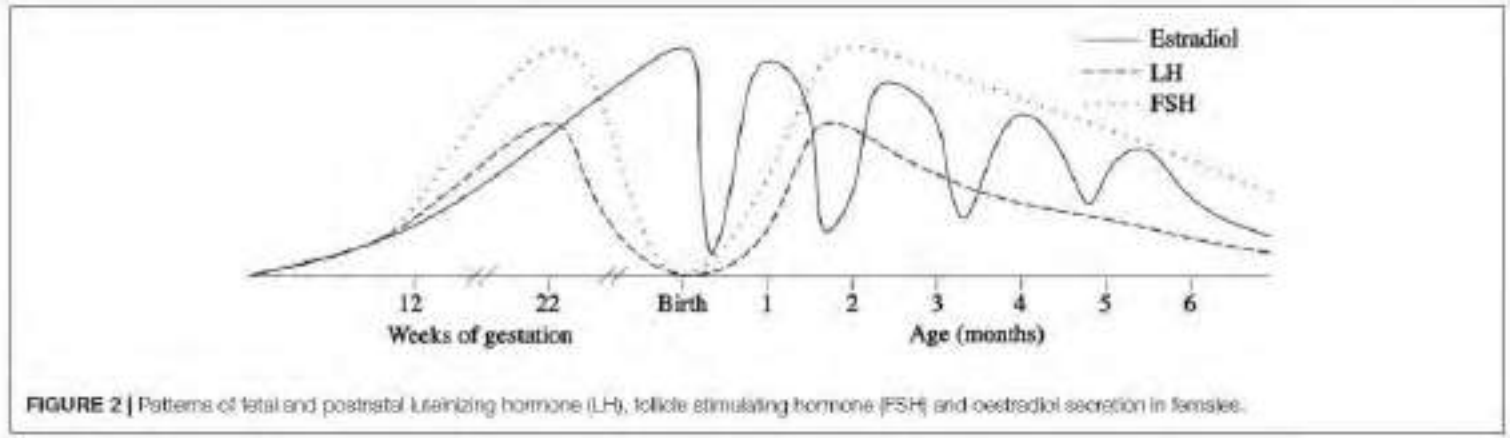


FIGURE 2 | Patterns of fetal and postnatal luteinizing hormone (LH), follicle stimulating hormone (FSH) and oestradiol secretion in females.

Lanciotti L, Front Endocrinol , 2018 Jul 23;9:410-

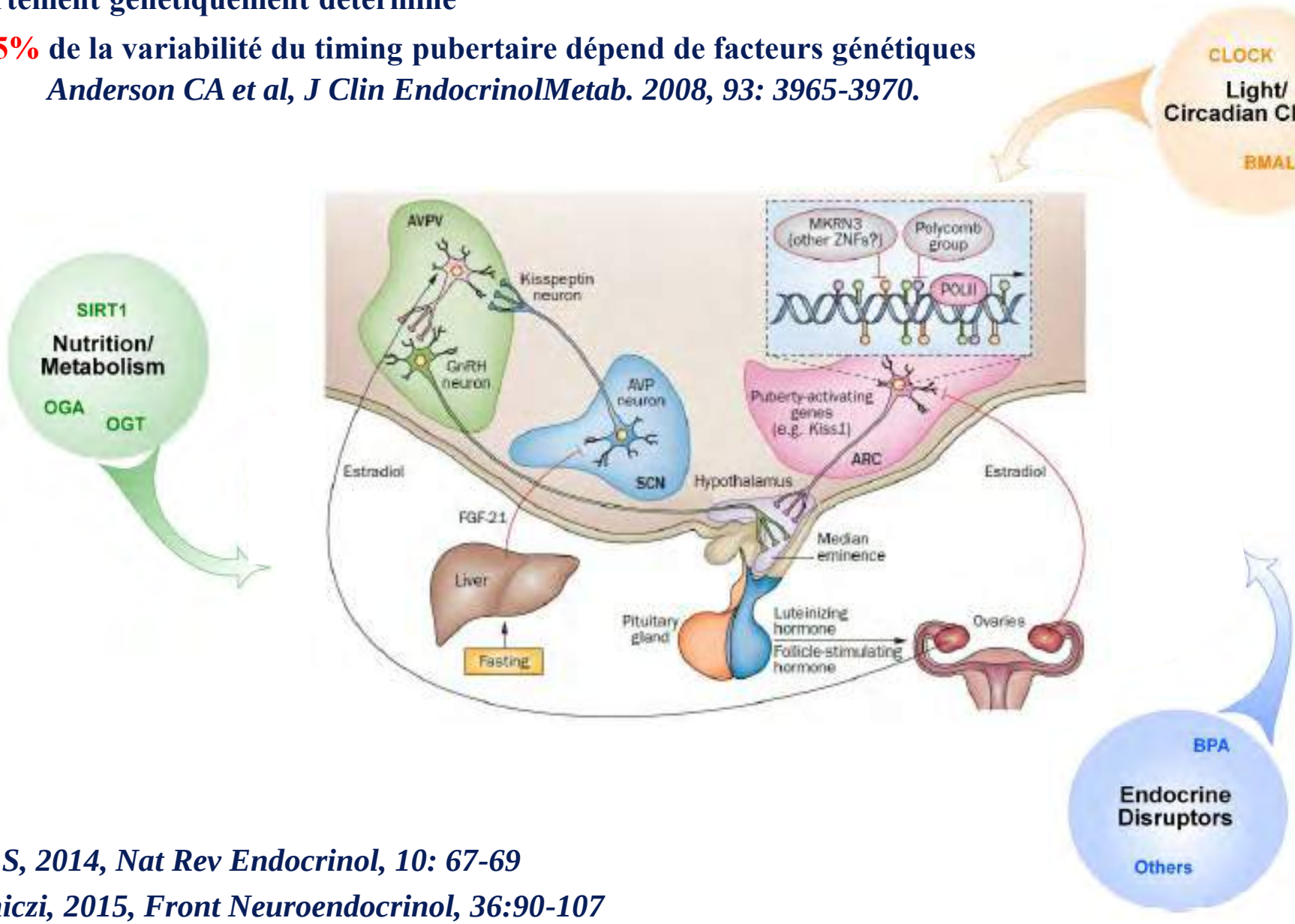
Age de début de puberté: **8 to 13 ans / filles**

9 to 14 ans / garçons

Âge fortement génétiquement déterminé

50-75% de la variabilité du timing pubertaire dépend de facteurs génétiques

Anderson CA et al, J Clin EndocrinolMetab. 2008, 93: 3965-3970.



Ojeda S, 2014, Nat Rev Endocrinol, 10: 67-69

Lominiczi, 2015, Front Neuroendocrinol, 36:90-107

Épigénétique et puberté

* Méthylation

Gène Kiss 1 est freiné dans l'enfance par un complexe protéique, polycomb group (PcG)[1]

PcG: EED et CBX7

La méthylation des gènes Eed et Cbx7 à la puberté[2]:

Diminue l'expression de ces deux gènes

Diminue le synthèse des protéines EED et CBX7

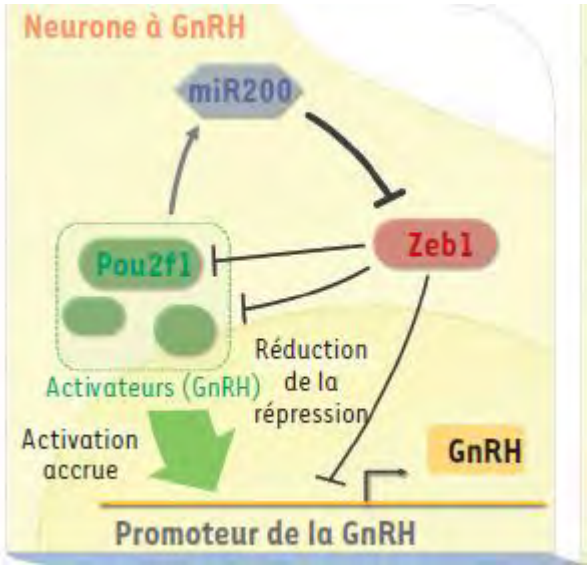
Lève le frein exercé par PcG sur le promoteur du gène Kiss 1

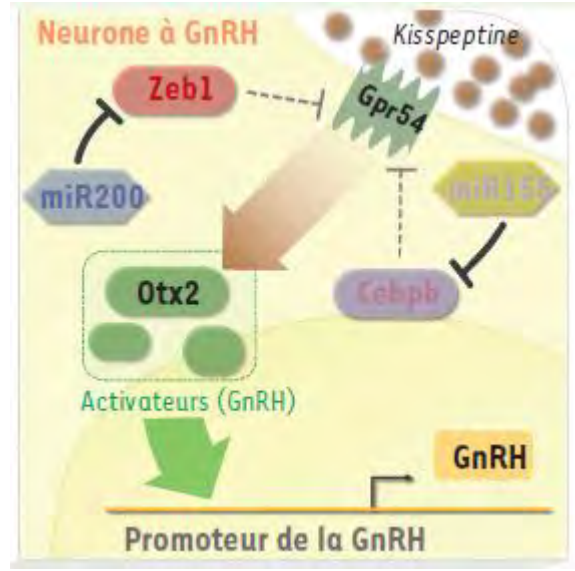
1- Lominiczi A, 2013, Nat Neurosc, 16: 281-289; 2- Lominiczi A, 2015, Front Neuro, 36:90-107

* miRNA

Souris génétiquement modifiées: pas de miRNA au niveau des N à GnRH[1]

→ hypog. hypogonadotrope sévère, perte d'expression de GnRH





Des facteurs freinateurs du gène du GnRH (Cebp, Zeb) seraient freinés au moment de la puberté par des miRNA respectivement miR-155 et miR-200/429

1- Messina A, 2016, Nat Neurosci, 19:835-44

PLOS BIOLOGY

November 7, 2019

RESEARCH ARTICLE

Hypothalamic miR-30 regulates puberty onset via repression of the puberty-suppressing factor, Mkrn3

Violeta Heras[1], Susana Sangiao-Alvarellos[2], Maria Manfredi-Lozano[1], María J. Sanchez-Tapia[1], Francisco Ruiz-Pino[1], Juan Roa[1], Maribel Lara-Chica[1], Rosario Morrugares-Carmona[1], Nathalie Jouy[3], Ana P. Abreu[4], Vincent Prevot[3], Denise Belsham[5], Maria J. Vazquez[1,6], Marco A. Calzado[1], Leonor Pinilla[1,6], Francisco Gaytan[1,6], Ana C. Latronico[7], Ursula B. Kaiser[4], Juan M. Castellano[1,6‡*], Manuel Tena-Sempere[1,6,8‡*]

Des mécanismes épigénétiques **méthylation**

expression de miRNA

Viendraient freiner des facteurs inhibiteurs de Kiss/GnRH à la puberté

Definition of PP

Breast development < 8 years old / girls

Testicular volume > 4ml < 9 years old / boys

More common in girls than in boys **prevalence (Danemark)** **0.2% girls**

< 0.05% boys

Teilmann G., Pediatrics, 2005, 116: 1323-1328

Diagnosis of PP

Increased growth velocity

Advance in bone age

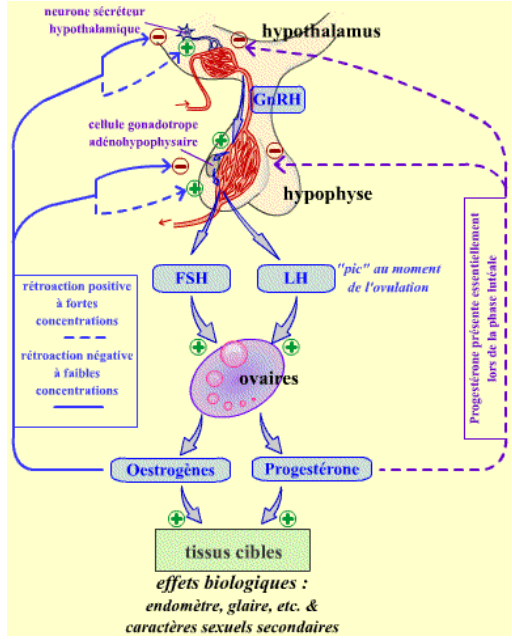
1- Confirm that there is PP (positive diagnosis)

2- Characterize the kind of PP → to etiology

Central

Most common (90%)

Idiopathic +++ 90%



Peripheral

Pubertés précoces et PEE

Epidémiologiques

- Age de début de puberté
- Prém. thélarches
- PPC

Etudes Expérimentales

Environnement

Notre Expérience

Epidémiologiques

- **Age de début de puberté**
- **Prém. thélarches**
- **PPC**

Etudes Expérimentales

Environnement

Notre Expérience

Tendance séculaire à un rajeunissement de l'âge d'entrée en puberté

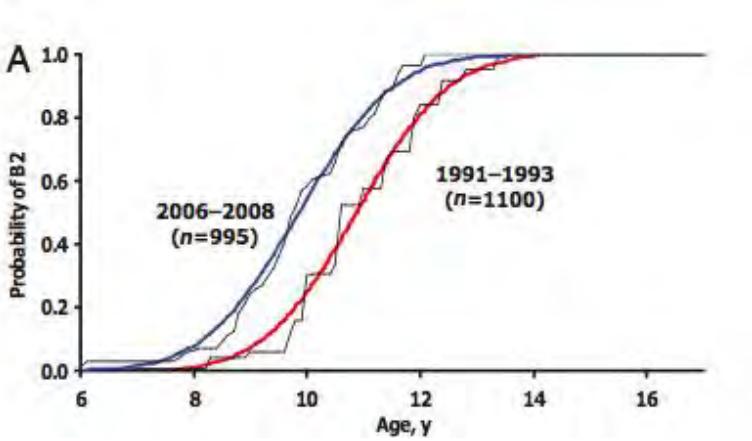
- Aux USA prévalence d'un développement pubertaire S2 à l'âge de 8 ans

  15% à 48% (selon l'origine ethnique)

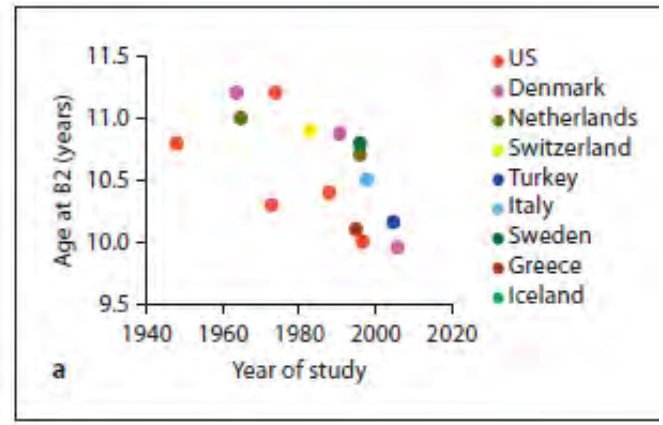
Herman-Giddens, Archives of Pediatrics and Adolescent Medicine, 1997, 155:1022-1028

- En Europe

Se poursuit



Aksglaede L, Pediatrics, 2009, 123: e932-939



Sorensen K., Horm Res Paediatr , 2012, 77: 137-145

JAMA Pediatrics | Original Investigation

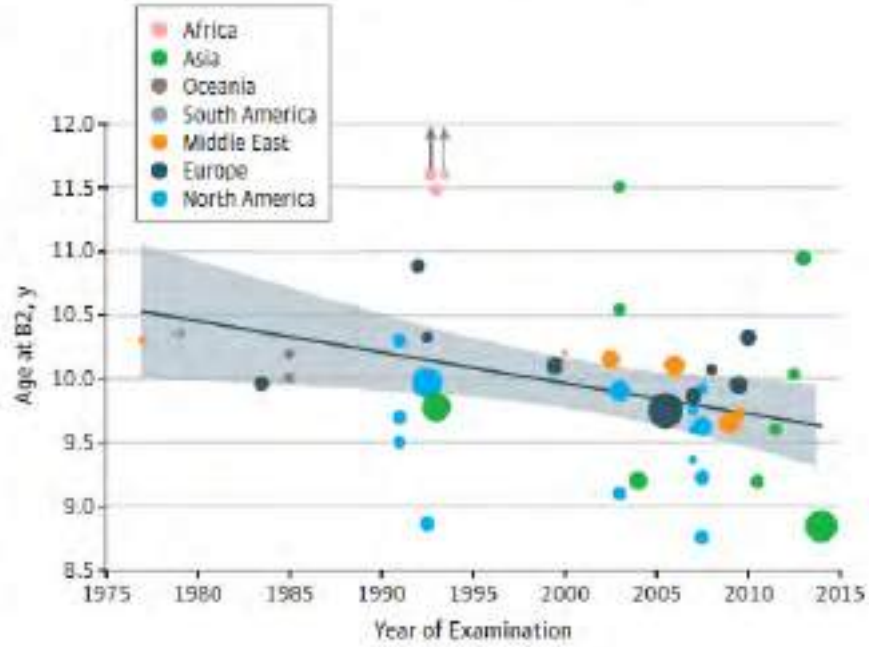
Worldwide Secular Trends in Age at Pubertal Onset Assessed by Breast Development Among Girls

A Systematic Review and Meta-analysis

Camilla Eckert-Lind, MB; Alexander S. Busch, MD, PhD; Jørgen H. Petersen, PhD; Frank M. Biro, MD; Gary Butler, MD; Elvira V. Bräuner, PhD; Anders Juul, MD, DMSc, PhD

JAMA Pediatr. 2020;174(4):e195881. doi:10.1001/jamapediatrics.2019.5881
Published online February 10, 2020.

Figure 2. Secular Changes in Age at Onset of Tanner Breast Stage 2 (B2) From 1977 to 2013 Around the World According to Year of Study



PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

COMMENTARY

The Enigmatic Pursuit of Puberty in Girls

Herman-Giddens., November 2013

Furthermore, because early puberty and menarche are associated with many detrimental health and psycho-social issues, we must not accept this premature development as the "new normal."

BMI-Puberté-USA:

1239 fillettes 6 à 8 ans

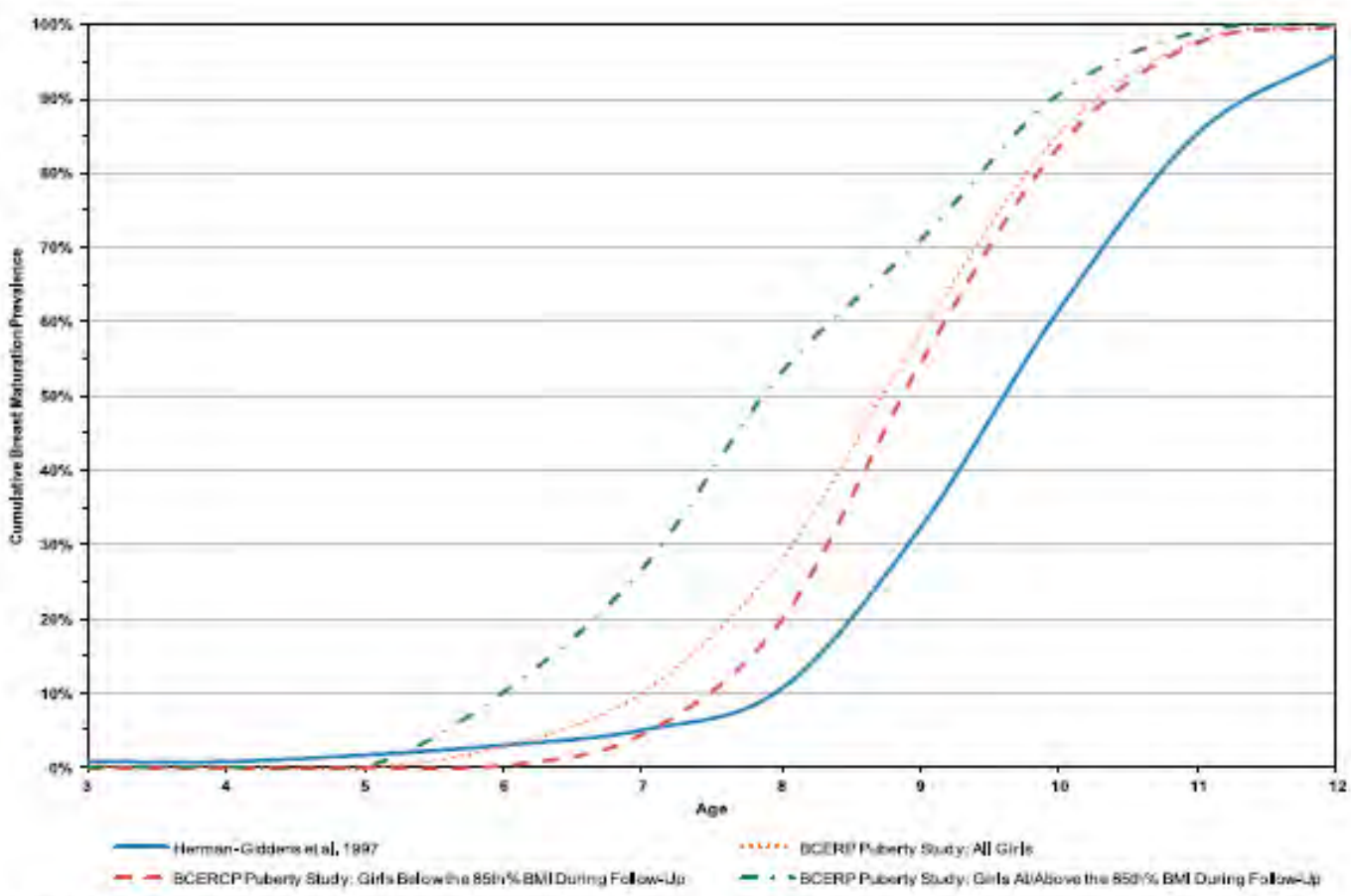


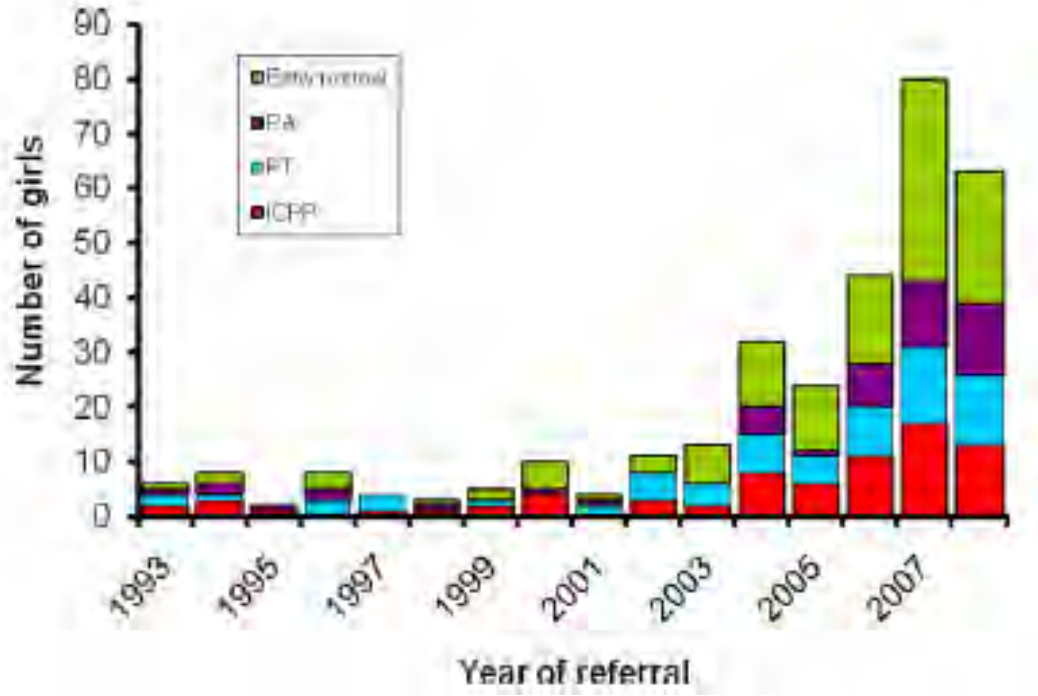
FIGURE 1
Comparing the cumulative prevalence of Breast Stage 2+ for non-Hispanic white participants between the BCERP Puberty Study and PROS.[9]

↓ de l'âge de la thélarche, BMI intervenant pour environ 14,2% de cette variance

Biro F., Pediatrics , 2013, 132 (6):1019-1027

Augmentation d'incidence des précocités pubertaires vraies

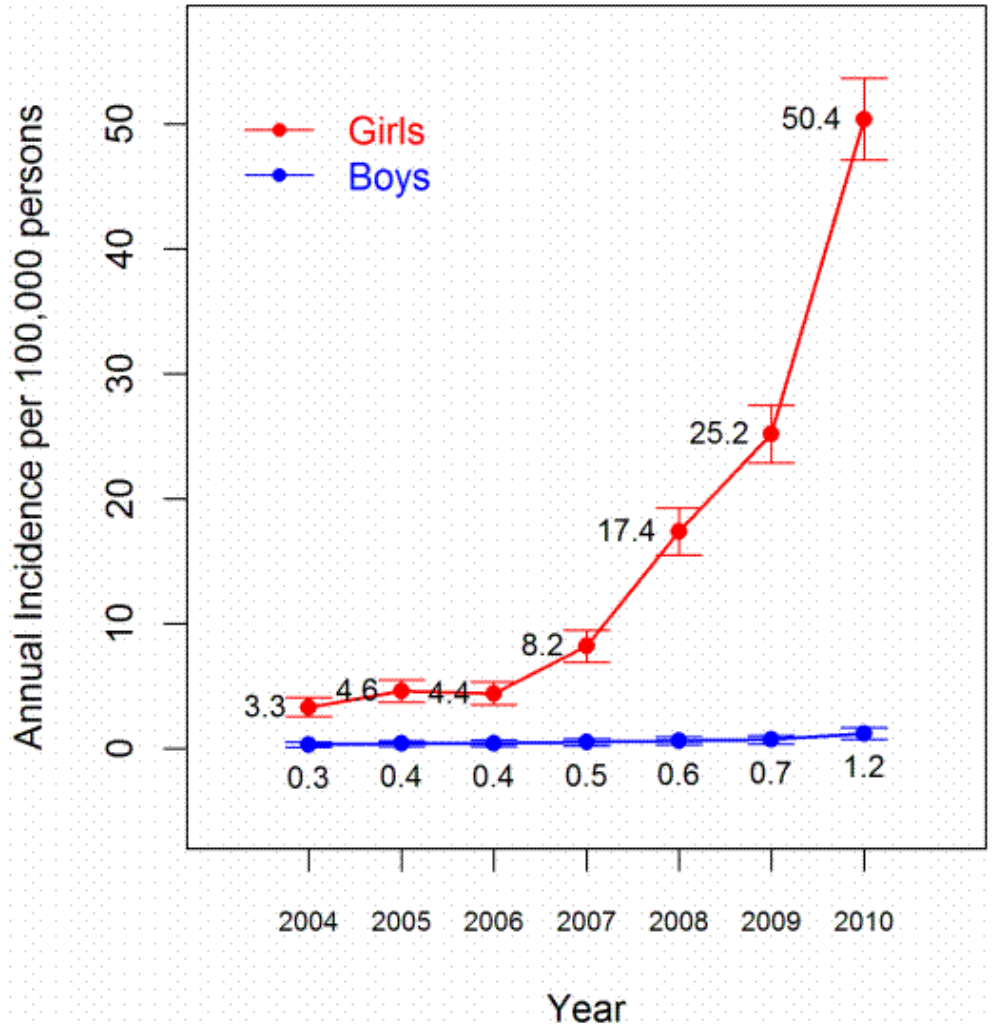
- Registres Danois



Mogensen S., J Clin Endocrinol Metab, 2011, 96: 1393-1401

A Significant Increase in the Incidence of Central Precocious Puberty among Korean Girls from 2004 to 2010

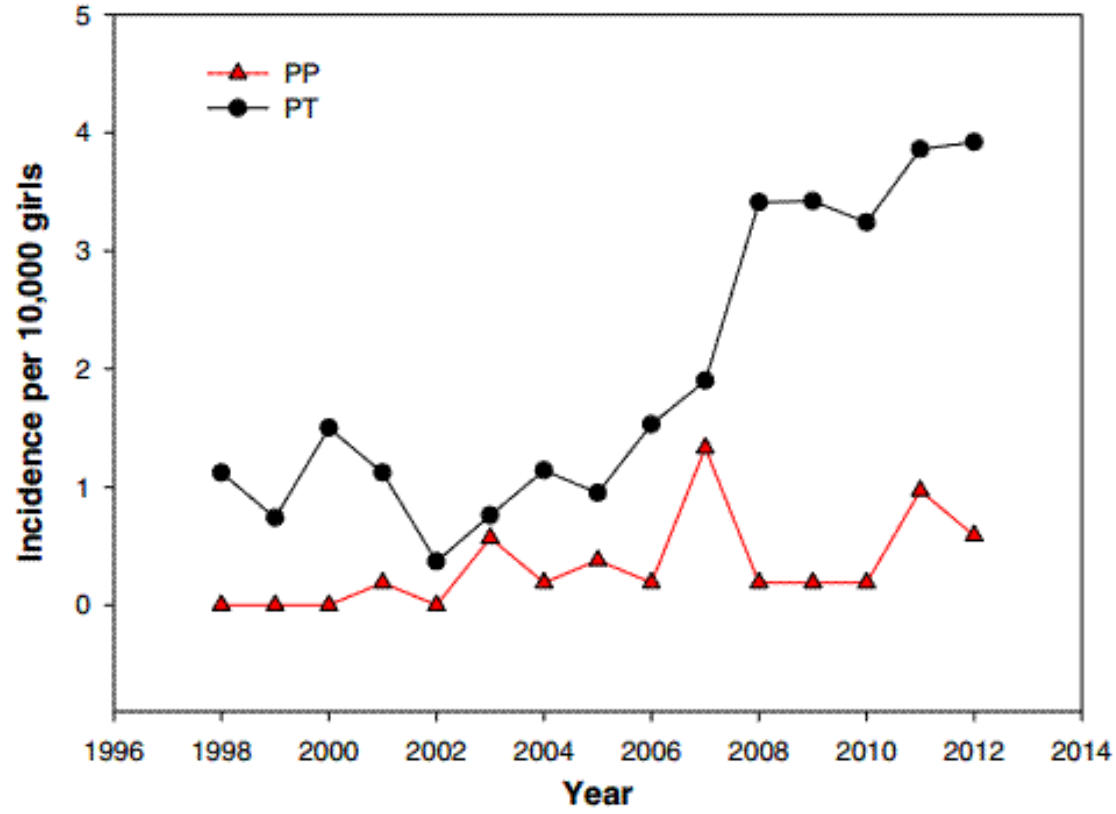
Shin Hye Kim[1], Kyoung Huh[2], Sungho Won[2], Kuk-Wha Lee[4], Mi-Jung Park[1]*



PLOS ONE | DOI:10.1371/journal.pone.0141844 November 5, 2015

Increasing incidence of premature thelarche in the Central Region of Denmark - Challenges in differentiating girls less than 7 years of age with premature thelarche from girls with precocious puberty in real-life practice

Mia Elbek Sørnod[1*], Esben Thyssen Vestergaard[2,3†], Kurt Kristensen[1] and Niels Holtum Birkebæk[1]



Incidence of precocious puberty and premature thelarche expressed as an incidence rate and defined as:

$$\frac{\textit{No. of girls who got a diagnosis of PP or PT in a certain year}}{\textit{Total no. of girls } 1/2\text{–}7 \textit{ years living in the region}}$$

JAMA Network Open

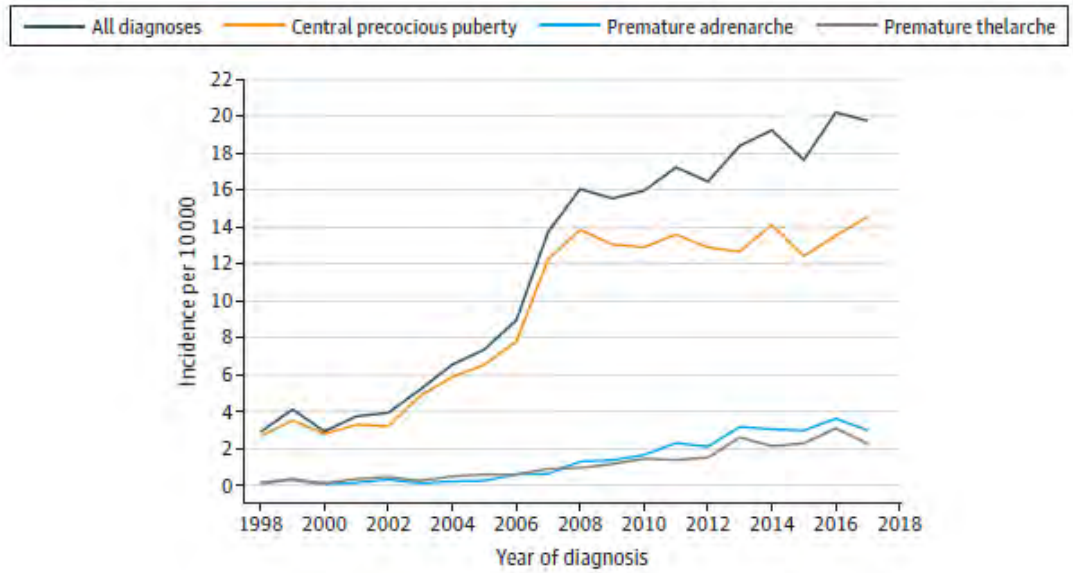
October 12, 2020

Original Investigation | Pediatrics

Trends in the Incidence of Central Precocious Puberty and Normal Variant Puberty Among Children in Denmark, 1998 to 2017

Elvira V. Bräuner, PhD; Alexander S. Busch, PhD, MD; Camilla Eckert-Lind, MB; Trine Koch, MSc; Martha Hickey, MBChB, MD; Anders Juul, MD, PhD, DMSc

Figure 1. Trends in the Annual Incidence Among Girls With Danish Origin by Year of Incident Diagnosis, 1998 to 2017



Répartition géographique

Marked geographic patterns in the incidence of idiopathic central precocious puberty: a nationwide study in France

European Journal of Endocrinology (2018) **178**, 33–41

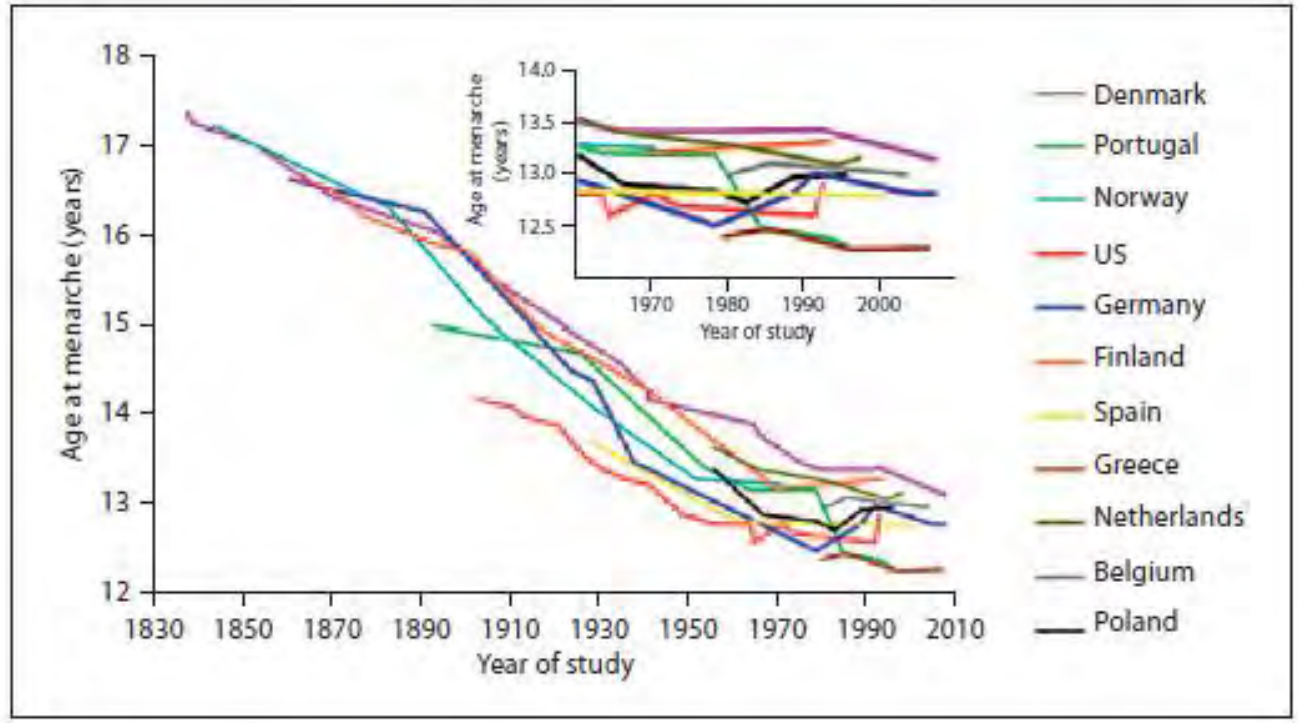
Joëlle Le Moal[1,*], Annabel Rigou[1,*], Alain Le Tertre[1], Perrine De Crouy-Channel[1], Juliane Léger[3] and Jean-Claude Carel[3]

Conclusions: The results suggest that the risk factors are similar for boys and girls and justify further investigations of the role of the environment.

Fitted incidence rates for ICPP in French *départements* in girls under the age of nine years (2A) and boys under the age of 10 years (2B) at first delivery of GnRH agonist, based on drug reimbursement data for 2011–2013. A full colour version of this figure is available at https://doi.org/10.1530/EJE-17-0379.

Age de la ménarche:

tend à se stabiliser



Sorensen K., Horm Res Paediatr , 2012, 77: 137-145

Précocités pubertaires et exposition particulière

Effets périphériques sur CSS et/ou croissance et maturation de l'activité estrogénique des PEE

*** Epidémie de prématures thélarches Puerto Rico**

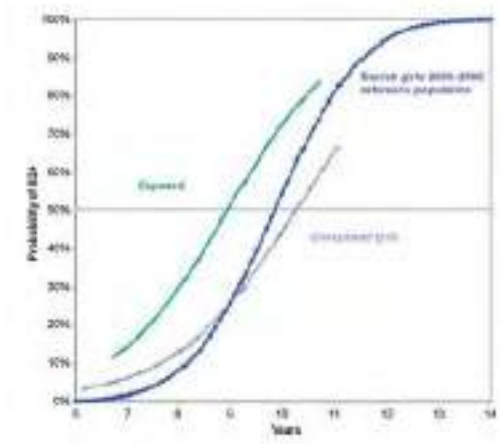
↑ conc. Sérique de phtalates / témoins

Colon, Env Health Perspective, 2000, 108: 895-900

*** Filles de mères exposées pdt la grossesse/ travail aux pesticides**

thélarche
interrogatoire

Wohlfahrt- Veje, IJA, 2012: 1-9



. Michigan

151 filles > 20 ans et leurs mères (Michigan)

Évaluation âge DPR filles

Prélèvements répétés mères / PCB, DDE

→ extrapolation taux PCB, DDE pdt la grossesse

↑ exposition in utéro au DDE : ↓ âge DPR

Vasiliu, Human Reprod, 2004, 19: 1506-1512

Adoption, PPC et PEE

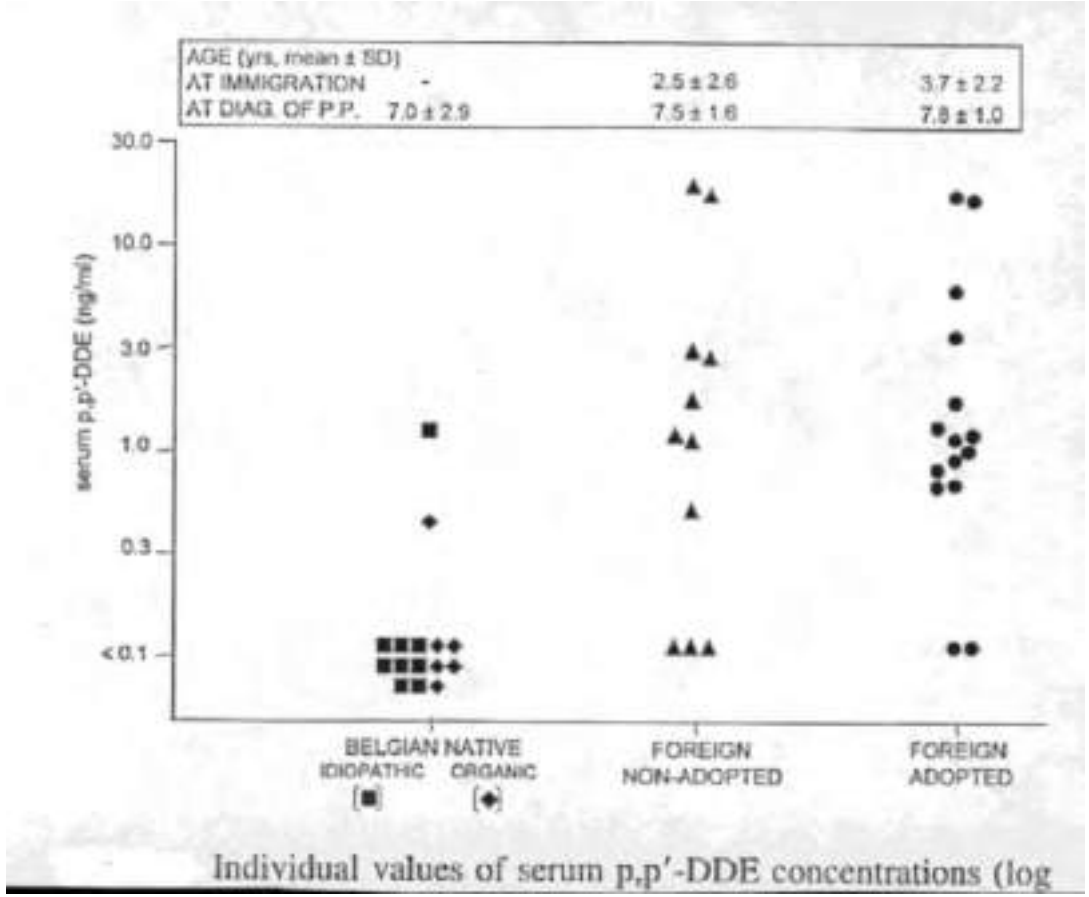
145 Belges PPC

40 étrangers

28 adoptés

12 non adoptés

Risque de pub précoce x 80 chez des enfants issus de adoption internationale



Krstevska-Konstantinova, Human Reprod, 2001, 16: 1001-1026

J Environ Sci Health A Tox Hazard Subst Environ Eng. 2013;48(8):912-7. doi: 10.1080/10934529.2013.762734.

Association between precocious puberty and some endocrine disruptors in human plasma.

Yum T[1], Lee S, Kim Y.

Abstract

Endocrine disruptors that mimic natural hormones and inhibit the action of hormones have recently attracted attention as one of the main cause of precocious puberty. In this study, the levels of 7 EDCs and 3 isoflavones that exhibit estrogen-like actions were measured in the plasma of precocious puberty patients and compared to control subjects to determine if there is an association between the onset of precocious puberty and the levels of EDCs in the plasma. EDCs examined in this study were bisphenol-A (BPA), di(2-ethylhexyl) phthalate (DEHP), dibutyl phthalate (DBP), mono(2-ethylhexyl) phthalate (MEHP), monobutyl phthalate (MBP), n-nonyl phenol (n-NP), and t-octylphenol (t-OP), and whereas the isoflavones were equol, genistein, and diadzein. The level of MBP in the plasma of patients was 1.3 times higher than that of the controls. The levels of t-OP and n-NP in the plasma of patients were respectively 1.15 and 1.2 times higher than those of the control group. Finally, the levels of the diadzein, equol and genistein were 1.37, 1.3 and 2.67 times higher than those of the control group, and genistein showed a statistically meaningful result (P = 0.0008). The results suggest that these six substances (MBP, t-OP, n-NP, daidzein, equol, and genistein) have an effect on precocious puberty.

Environmental Research 159 (2017) 143–151

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Phthalate and bisphenol A exposure during in utero windows of susceptibility in relation to reproductive hormones and pubertal development in girls

Deborah J. Watkins[a,*], Brisa N. Sánchez[b], Martha Maria Téllez-Rojo[c], Joyce M. Lee[a,d], Adriana Mercado-García[c], Clara Blank-Goldenberg[e], Karen E. Peterson[f,g], John D. Meeker[a]

117 femmes enceintes (1997-2004)
dont 97 pvt urine 1T, 2T, 3t

120 filles incluses en 2011, âgé de 8-13ans

BPA 2T // dévt mammaire plus précoce

Phtalate 3T // plus précoce

→ Fenêtre de vulnérabilité

Epidémiologiques

- Age de début de puberté
- Prém. thélarches
- PPC

Etudes Expérimentales

Environnement

Notre Expérience

Arguments / Mécanismes d'action (cf)

*Effets « estrogen like »

© Med Sci Monit, 2009; 15(6): RA137-145
PMID: 19478717

WWW.MEDSCIMONIT.COM
Review Article

Estrogen-like endocrine disrupting chemicals affecting puberty in humans – a review

Jonathan R. Roy[1], Sanjoy Chakraborty[2], Tandra R. Chakraborty[1]

Effects of EEDC on reproduction of prenatal and pubertal girls.

EEDC	Exposure	Type of Action	Findings	Reference
DDE	Pubertal girls	Estrogen mimicker/blocker	Earlier menarche	Vasiliu et. al. 2004, [20]
Dioxin	Pubertal girls	Estrogen blocker	Abnormal breast dev	Den Hond et. al., 2002 [42]
Bisphenol A	Prenatal girls	Estrogen blocker	Precocious puberty	Howdeshell et. al., 1999 [62]
PCB	Pubertal girls	Estrogen mimicker/blocker	No significant effect	Vasiliu et. al., 2004 [20]
PBB	Prenatal girls	Estrogen mimicker	Earlier menarche and earlier pubic hair stage	Blanck et. al., 2000 [61]
Phthalate esters	Pubertal girls	Estrogen mimicker	Causes de-feminization	Colon et. al., 2000 [63]

*Effets épigénétiques

Arguments / études animales: effet PEE / GnRH

*** PEE et ouverture vaginale (ov) plus précoce souris exposées**

Methoxychlore anté et néonatal

Gray LE, Fundam Appl Toxicol, 1989, 121):92-

BPA, DES néonatal

Honma S, Reprod Toxicol, 2002, 16(2): 117-

Génistéine, Zéaralénone néonatal

Nikaido Y, Reprod Toxicol, 2004, 18 (6): 803-

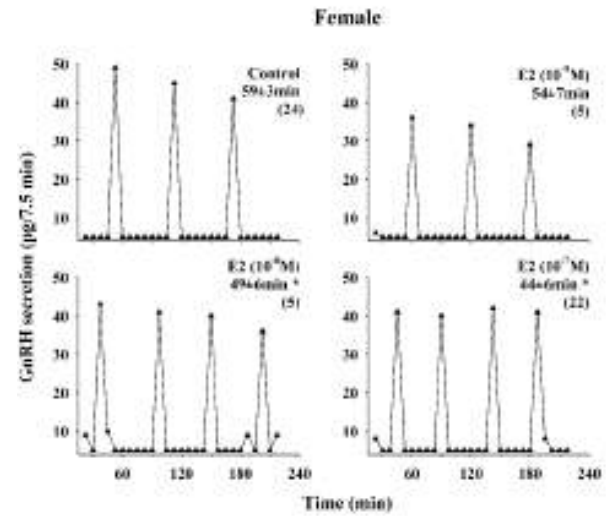
*** op'DDT → ouverture vaginale plus précoce ainsi que:**

stimule la synthèse de GnRH

Rasier, Bourguignon, MCE, 2006, 254: 187-201

↑ pulsatilité des N à GnRH (comme E2)

Matagne, Endocrinology, 2004, 145(6): 2775-83



*** Explants de neurones hypothalamiques à GnRH + DDT et/ou E2**

Augmentation de la sécrétion de GnRH en réponse au Glutamate

Impliquant ER, AhR, et AMPA

Rasier, Biol Reprod, 2007, 77: 734-

Rasier, Toxicol Sci, 2008, 102:33-

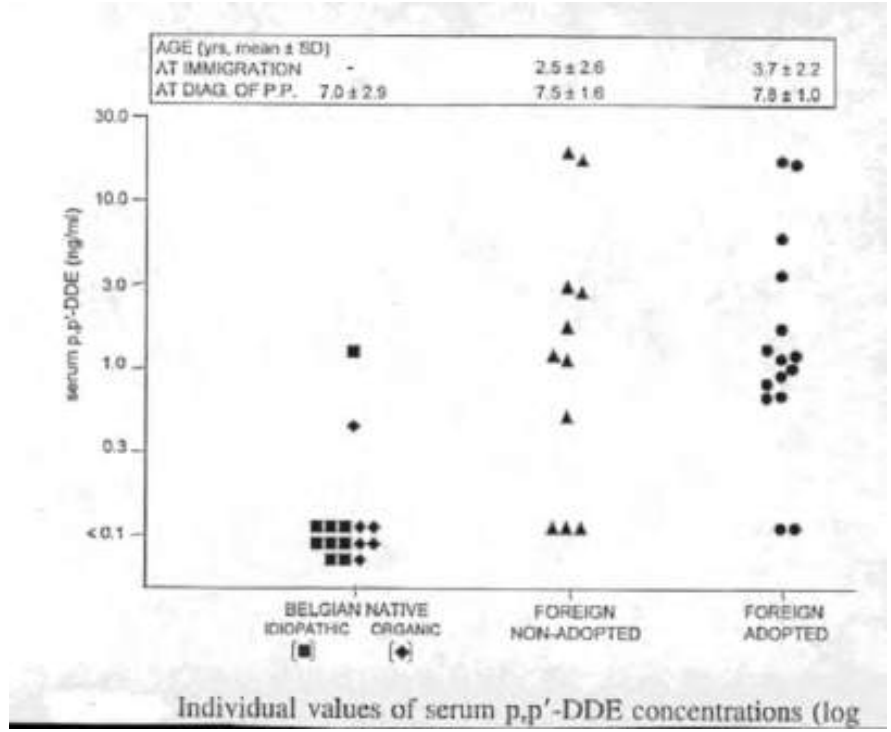
↑ pulsatilité des N à GnRH (comme E2)

Matagne, Endocrinology, 2004, 145(6): 2775-83

Maturation hypothalamique par exposition

DDT malgré un frein hypophysaire, révélé lors

de la soustraction à l'exposition



Individual values of serum p,p'-DDE concentrations (log

Krstevska-Konstantinova, Human Reprod, 2001, 16: 1001-1026

*** Exposition néonatale à molécules estrogéniques (E2, BPA, PCB Génistéine)**

module le système Kiss-peptine GPR54

variantes d'un noyau hypothalamique à l'autre

Tena Sempere, IJA, 2010: 360-368

Reproductive Toxicology 44 (2014) 73–84

Contents lists available at ScienceDirect

Reproductive Toxicology

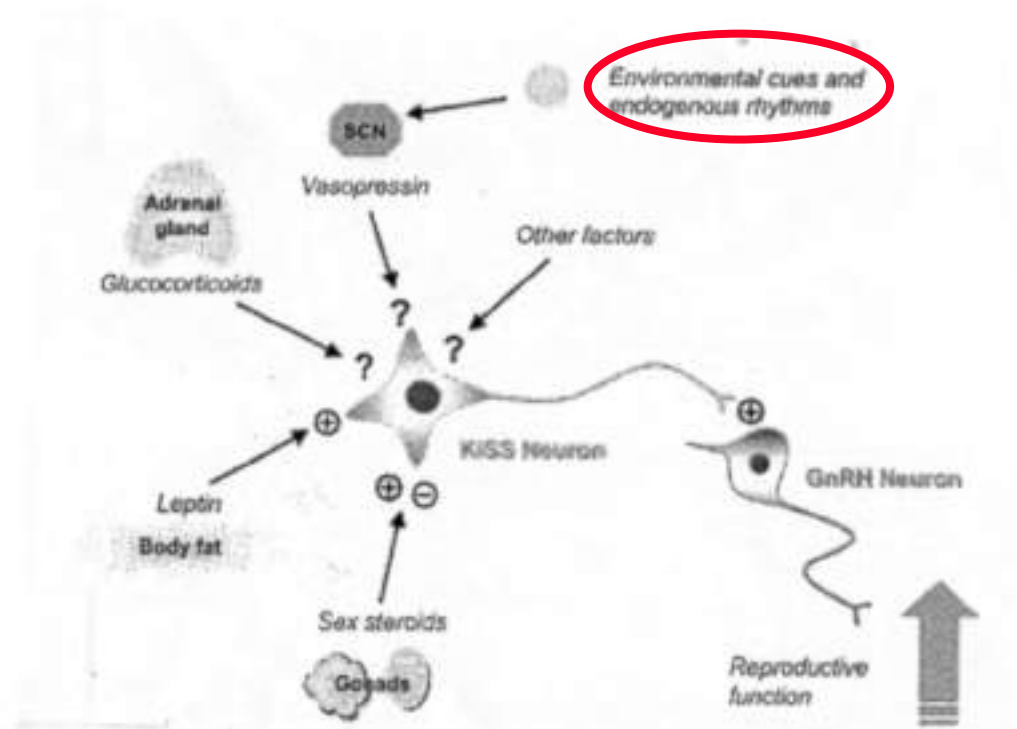
journal homepage: www.elsevier.com/locate/reprotox

Endocrine disrupting chemicals affect the Gonadotropin releasing hormone neuronal network

Johanna K. Mueller[a], Sabine Heger[a,b,*]

[a] Institute of Clinical Biochemistry, Hannover Medical School, Hannover, Germany
[b] Children's Hospital "Auf der Bult", Hannover, Germany

PEE : action centrale (et périphérique : ER alpha)



Kisspeptin neurons may act as central processors for relaying signals from the periphery to GnRH neurons. Metabolic and environmental factors regulate reproductive function, which ensures that reproduction proceeds only when metabolic and environmental conditions are favorable.

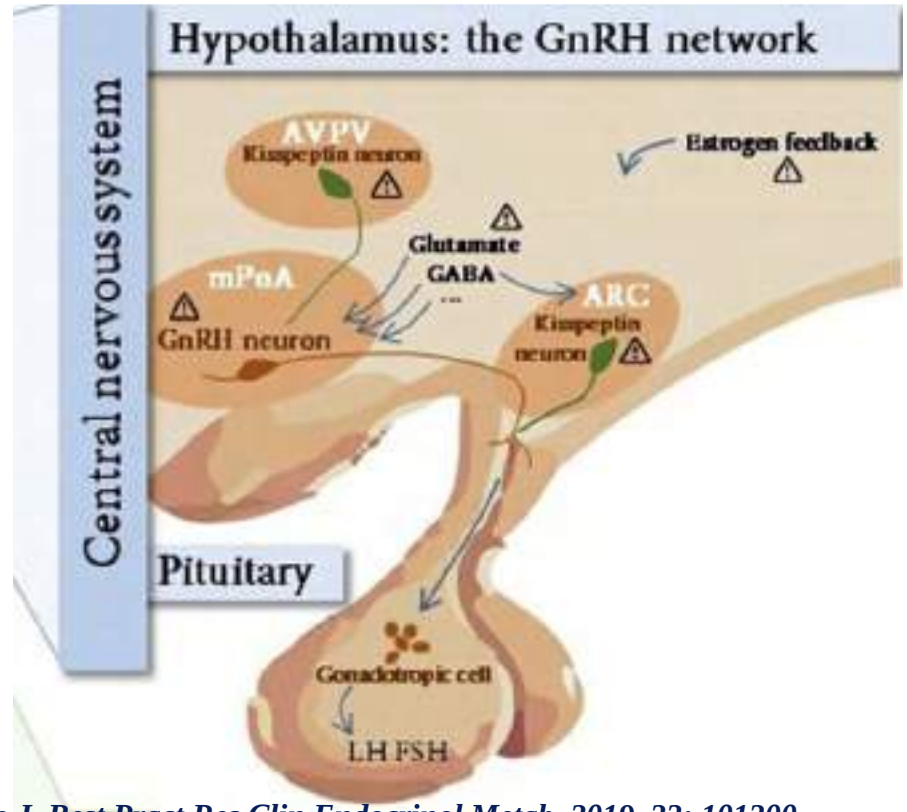
* Sexual steroïds differencial action on hypothalamus nucleus

Hrabovszky, 2013, Front Endocrinol, 20(4):130

The hypothalamic ARC (medial hypothalamus) is an important site of negative feedback of E to the reproductive axis

The rostral periventicular region of hypothalamus (AVPV) would be involved in positive feedback of E to the reproductive axis

Both negative and positive estrogen feed-back are mediated by ERα / mice
N Kiss



Fudvoye J, Best Pract Res Clin Endocrinol Metab, 2019, 33: 101300

Environmentally Relevant Perinatal Exposures to Bisphenol A Disrupt Postnatal Kiss1/NKB Neuronal Maturation and Puberty Onset in Female Mice

Francisco Ruiz-Pino,[1,2,3] Desiree Miceli,[4,5*] Delphine Franssen,[1,2,3] Maria Jesus Vazquez,[1,2,3] Alice Farinetti,[4,5] Juan Manuel Castellano,[1,2,3] GianCarlo Panzica,[4,5*] and Manuel Tena-Sempere[1,2,3*]*

[1]Instituto Maimónides de Investigación Biomédica de Cordoba (IMIBIC), Department of Cell Biology, Physiology and Immunology, University of Cordoba, Avda, Cordoba, Spain
[2]Hospital Universitario Reina Sofia, Cordoba, Spain
[3]CIBER Fisiopatología de la Obesidad y Nutrición, Instituto de Salud Carlos III, Cordoba, Spain
[4]Department of Neuroscience "Rita Levi Montalcini," University of Torino, Torino, Italy
[5]Neuroscience Institute Cavalieri-Ottolenghi (NICO), Orbassano, Italy

Environmental Health Perspectives

127(10) October 2019

L'exposition post natale au BPA / souris perturbe l'organisation de N Kiss / AVPV et ARC

RESULTS: Perinatal exposure to BPA, in a range of doses largely below the no observed adverse effect level (NOAEL; 5 mg/kg BW/d, according to the FDA), was associated with pubertal differences in the female progeny compared with those exposed to vehicle alone, with an earlier age of vaginal opening but consistently lower levels of circulating luteinizing hormone. Mice treated with BPA exhibited a persistent, but divergent, impairment of Kiss1 neuronal maturation, with more kisspeptin cells in the rostral (RP3V) hypothalamus but consistently fewer kisspeptin neurons in the arcuate nucleus (ARC). Detailed quantitative analysis of the ARC population, essential for pubertal development, revealed that mice treated with BPA had persistently lower Kiss1 expression during (pre)pubertal maturation, which was associated with lower Tac2 (encoding NKB) levels, even at low doses (5 μg/kg BW/d), in the range of the tolerable daily intake (TDI), recently updated by the European Food Safety Authority.

CONCLUSIONS: Our data attest to the consistent, but divergent, effects of gestational exposures to low concentrations of BPA, via the oral route, on phenotypic and neuroendocrine markers of puberty in female mice, with an unambiguous impact on the developmental maturation not only of Kiss1, but also of the NKB system, both essential regulators of puberty onset. https://doi.org/10.1289/EHP5570

Mol Cell Endocrinol. 2015 October 15; 414: 42–52. doi:10.1016/j.mce.2015.07.013.

Sexually Dimorphic Effects of Gestational Endocrine-Disrupting Chemicals on MicroRNA Expression in the Developing Rat Hypothalamus

Viktoria Y. Topper[1], **Deena M. Walker**[2], and **Andrea C. Gore**[1,2,3,*]

[1]Institute for Cellular and Molecular Biology, The University of Texas at Austin, Austin, Texas 78712

This study examined developmental changes and sexual dimorphisms in hypothalamic microRNAs, and whether gestational exposures to environmental endocrine-disrupting chemicals (EDCs) altered their expression patterns. Pregnant rat dams were treated on gestational days 16 and 18 with vehicle, estradiol benzoate, or a mixture of polychlorinated biphenyls. Male and female offspring were euthanized on postnatal days (P) 15, 30, 45, or 90, and microRNA and mRNA targets were quantified in the medial preoptic nucleus (MPN) and ventromedial nucleus (VMN) of the hypothalamus. MicroRNAs showed robust developmental changes in both regions, and were sexually dimorphic in the MPN, but not VMN. Importantly, microRNAs in females were up-regulated by EDCs at P30, and down-regulated in males at P90. Few changes in mRNAs were found. Thus, hypothalamic microRNAs are sensitive to prenatal EDC treatment in a sex-, developmental age-, and brain region-specific manner.

Epidémiologiques

- Age de début de puberté
- Prém. thélarches
- PPC

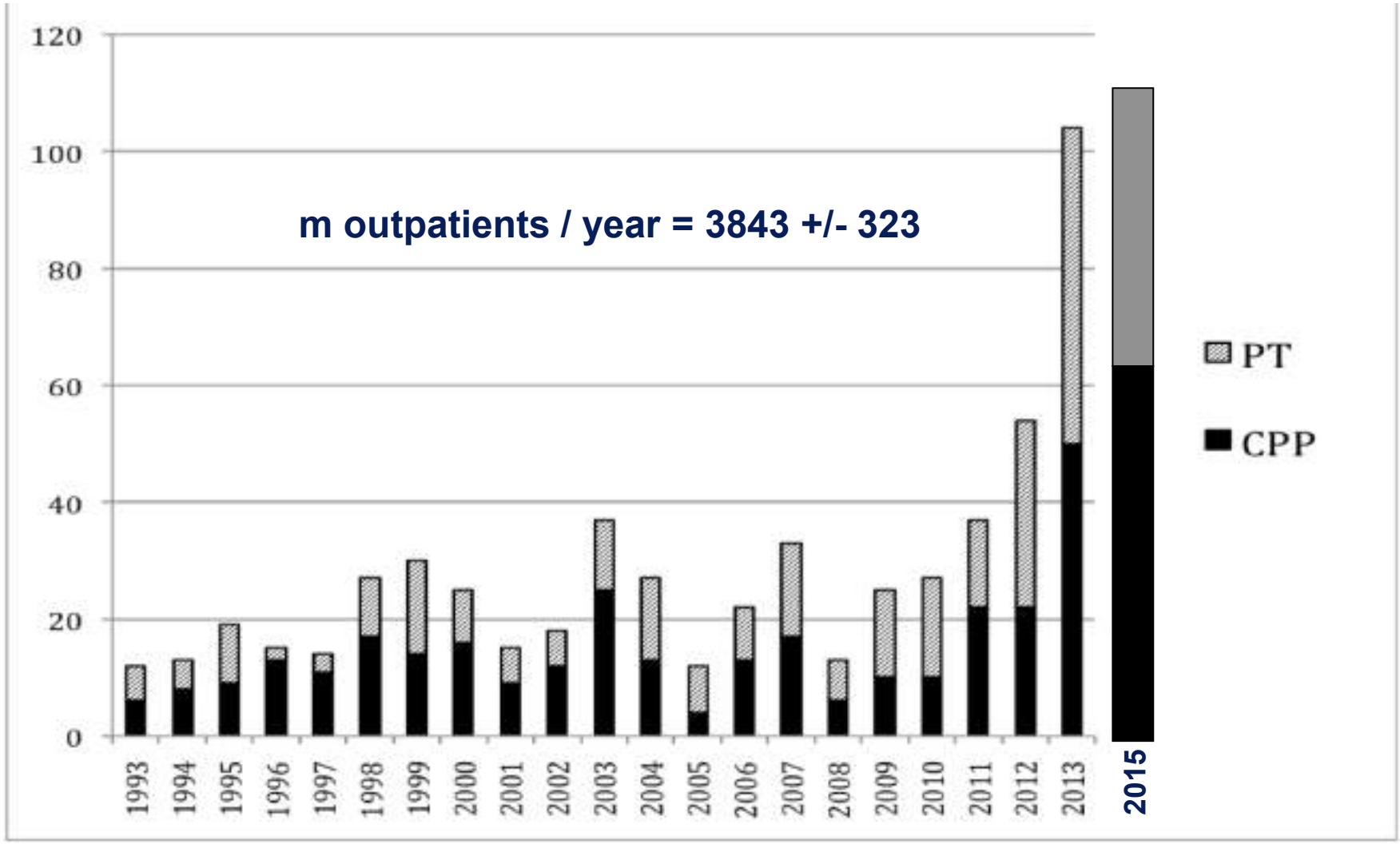
Etudes Expérimentales

Environnement

Notre Expérience

Dramatic rise in incidence of precocious puberty in girls over the past 20 years in the South of France

L. Gaspari, E. Morcrette, F. Dala Valle, C. Jandel, F. Paris and C. Sultan



PEE

- **Précocité pubertaire F : l'explosion**

Année 2015 : n = 110

1) **PPC n = 67 (95% idiopathique)**
2) **PT n = 43 (100% idiopathique)**

Rôle de l'environnement ?

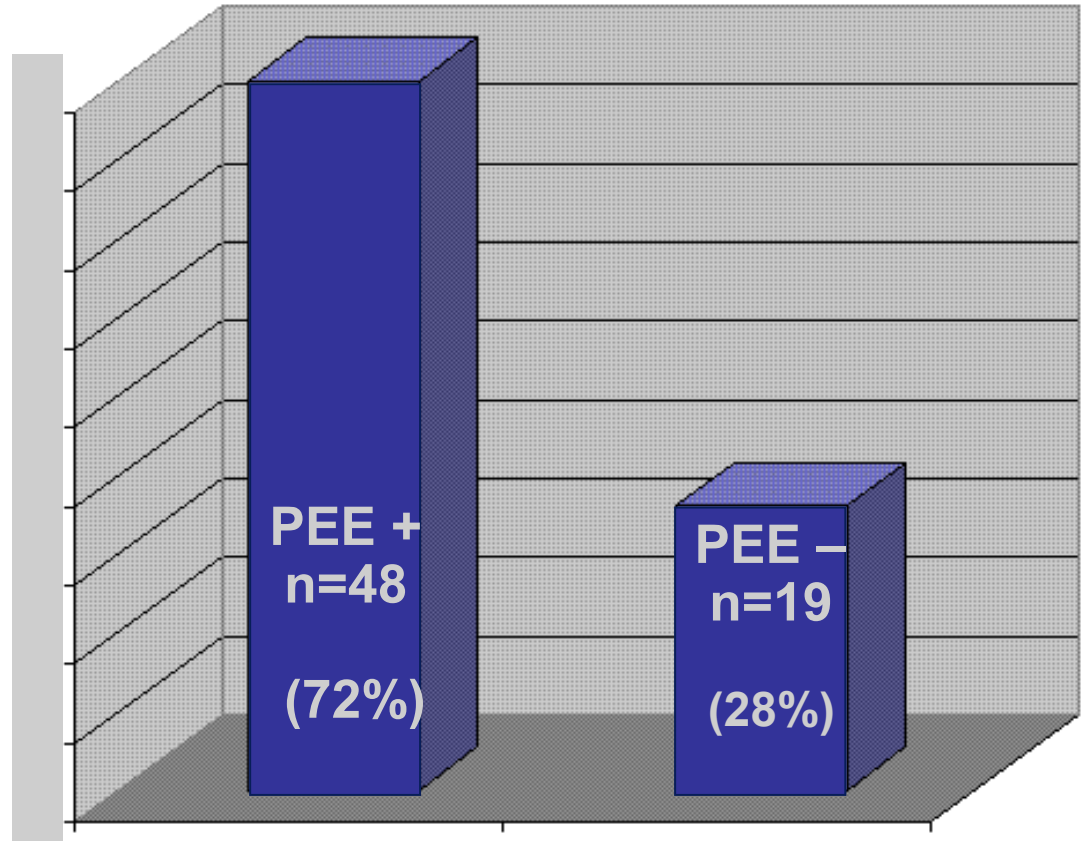
- **Habitationnel**
- **Profession des parents**

Puberté Précoce Centrale

N = 67

PEE + : n = 48

- **Vignobles 29/48**
- **Arbres fruitiers 6/48**
- **Etangs 3/48**
- **Entretien 3/48**
- **Peinture/esth 3/48**
- **Golf 1/48**
- **Industrie chimique 1/48**

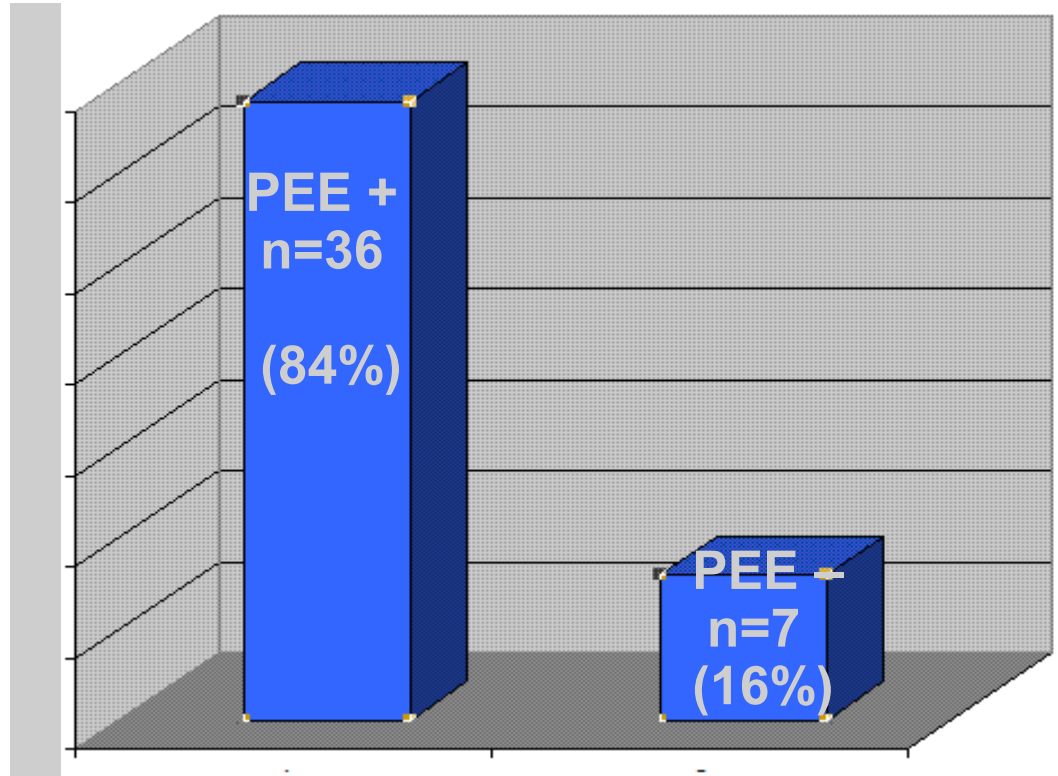


Puberté Précoce Périphérique

N = 43

PEE + : n = 36

- **Vignobles 22/36**
- **Arbres fruitiers 5/36**
- **Etangs 2/36**
- **Maraichers 2/36**
- **Entretien 1/36**
- **Propriété agr. 2/36**
- **Céréales 1/36**
- **Magasin botanique 1/36**
- **Piscine 1/36**
- **Golf 1/36**



Peripheral precocious puberty in a 4-month-old girl: role of pesticides?

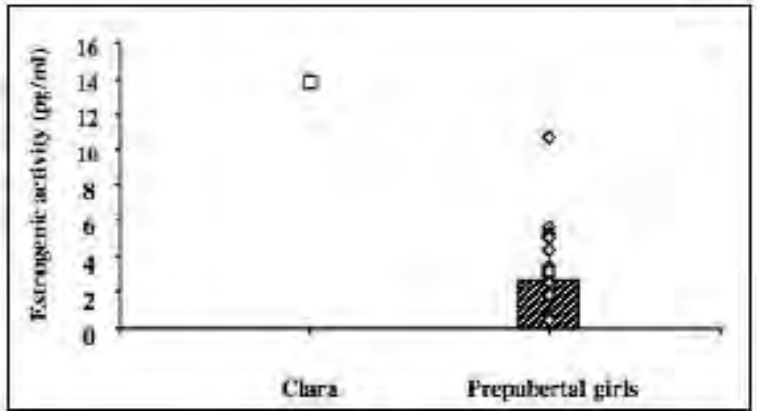
Gynecol Endocrinol, 2011, Sept. 27 (9): 721-4

Clara, 4 mois, un épisode de métrorragies

Habitation dans une zone de stockage de pesticides

S3, P1, A1 Utérus pubère (échographie) Test au LHRH plat

Figure 1: Endocrine investigations showed dramatically high estrogen bioactivity in Clara (13.5 ± 1.0 pg/mL) vs. controls (3.5 ± 2.2 pg/mL), according to Paris *et al*[16].

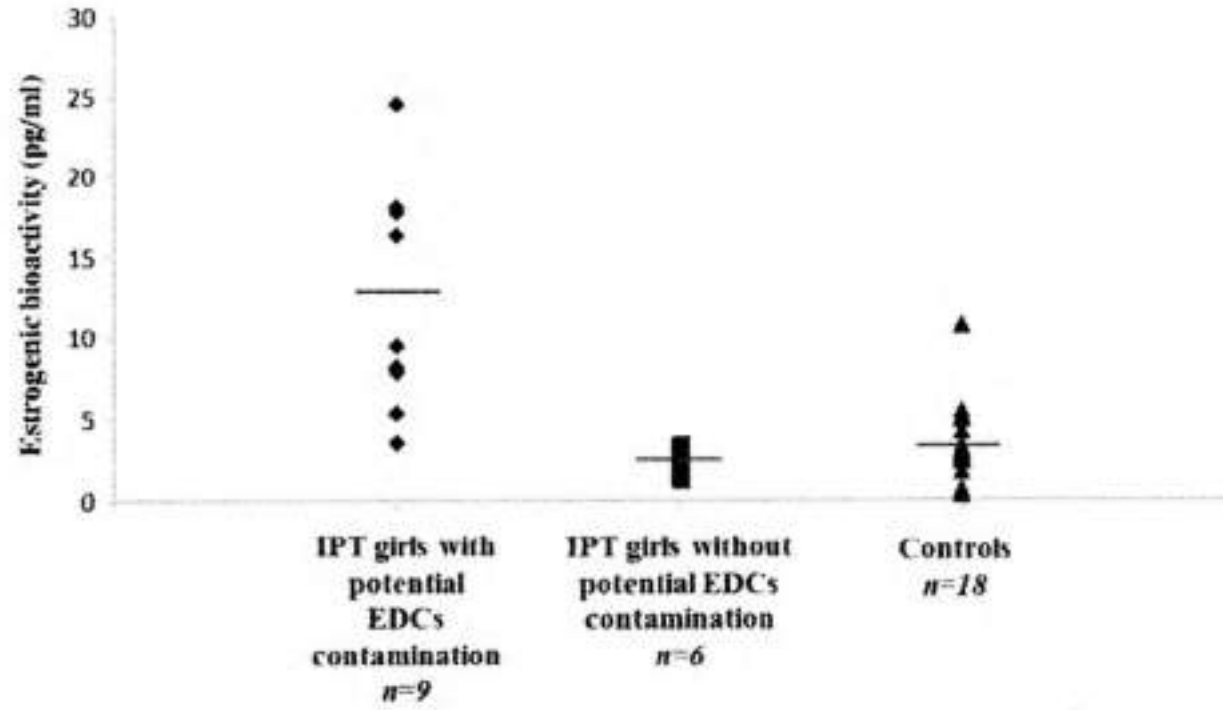


INFANT	FATHER	MOTHER	SOIL
Lindane	-	Lindane	Lindane
p,p'-DDD	-	p,p'-DDD	p,p'-DDD
p,p-DDT	-	p,p-DDT	p,p-DDT
Endosulfan	Endosulfan	Endosulfan	Endosulfan

Increased serum estrogenic bioactivity in girls with premature thelarche: a marker of environmental pollutant exposure?

Françoise Paris[1,2]*, Laura Gaspari[1,2]*, Nadège Servant[2], Pascal Philibert[2], and Charles Sultan[1,2]

Gynecol Endocrinol, 2013, 27 (8): 788-92



Activité estrogénique sérique
Évolutions …

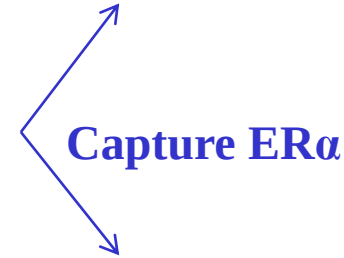
Travailler sur du sérum de fillettes présentant une puberté précoce

- Evaluant leur activité estrogénique (AE)

Et Typer cette AE

Paris F, Balaguer P, Sultan Ch. J Clin EndocrinolMetab, 2002, 87 (2): 791-797

Estrogènes de forte affinité (Estrogènes naturels, E2++)



Estrogènes faible affinités, PEE?

Evaluation and characterization of estrogenic activity (EA) / girls with PP

1- At the basal level: EA

Measures	estrogens of High affinity (natural estrogens, E2++)
	estrogens Low affinity (ex ED)

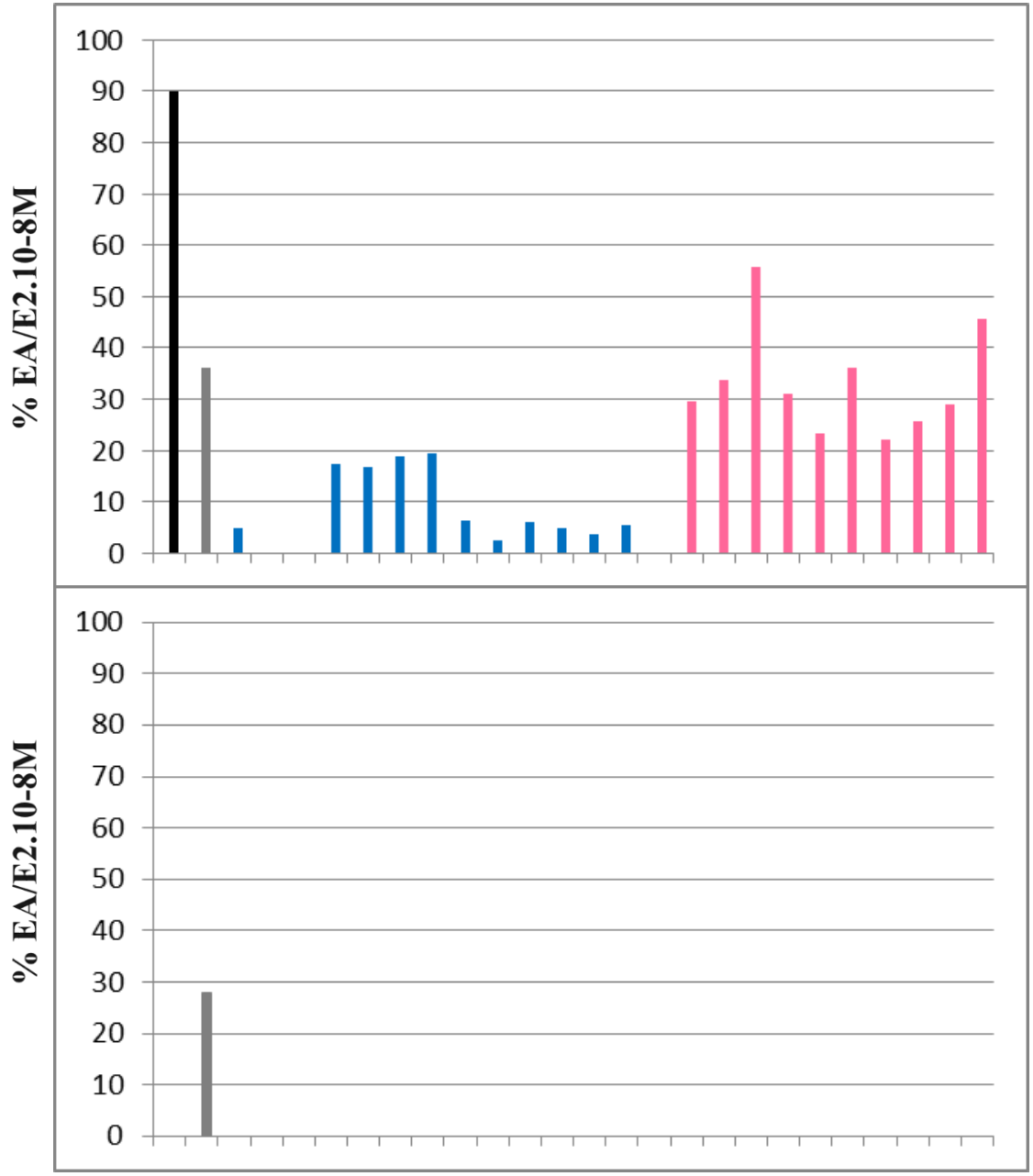
2- At a second time = residual EA= REA

After incubation of the girl's serum with Estrogen Receptor α (ERα) in limited amount over night / captures estrogens of high affinity

Measures estrogens of Low affinity (ex ED)

EA

REA



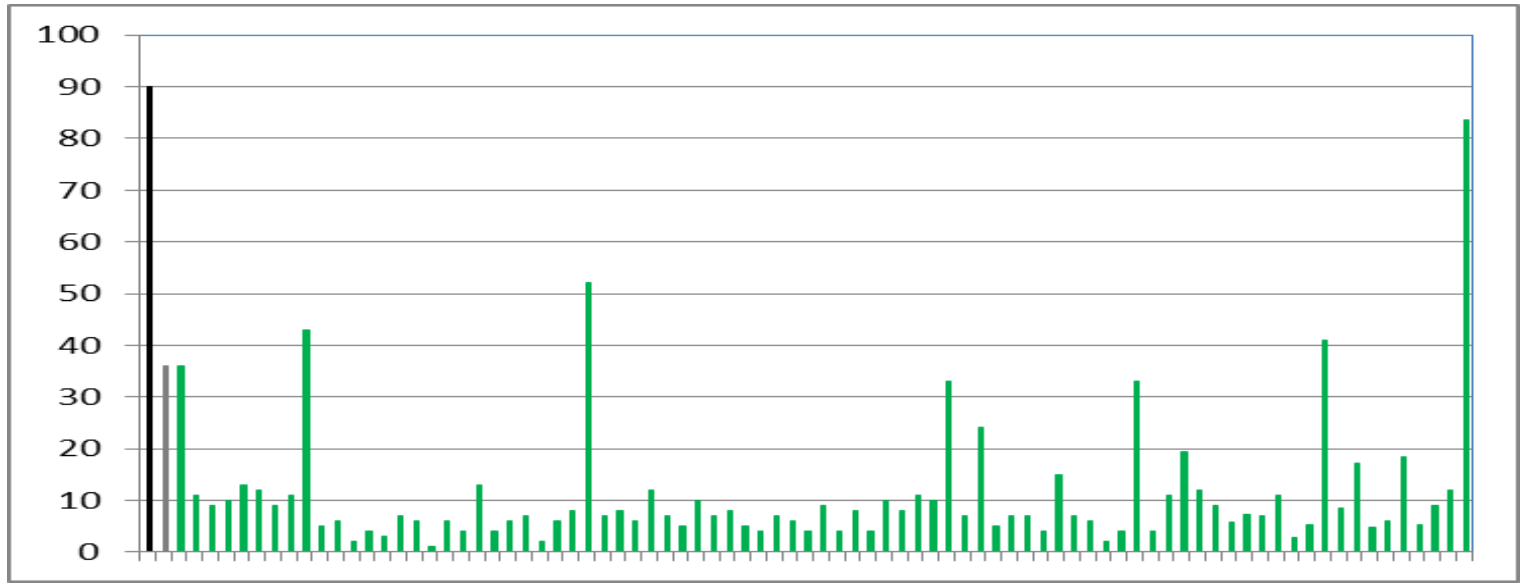
17β Estradiol

Octylphenol

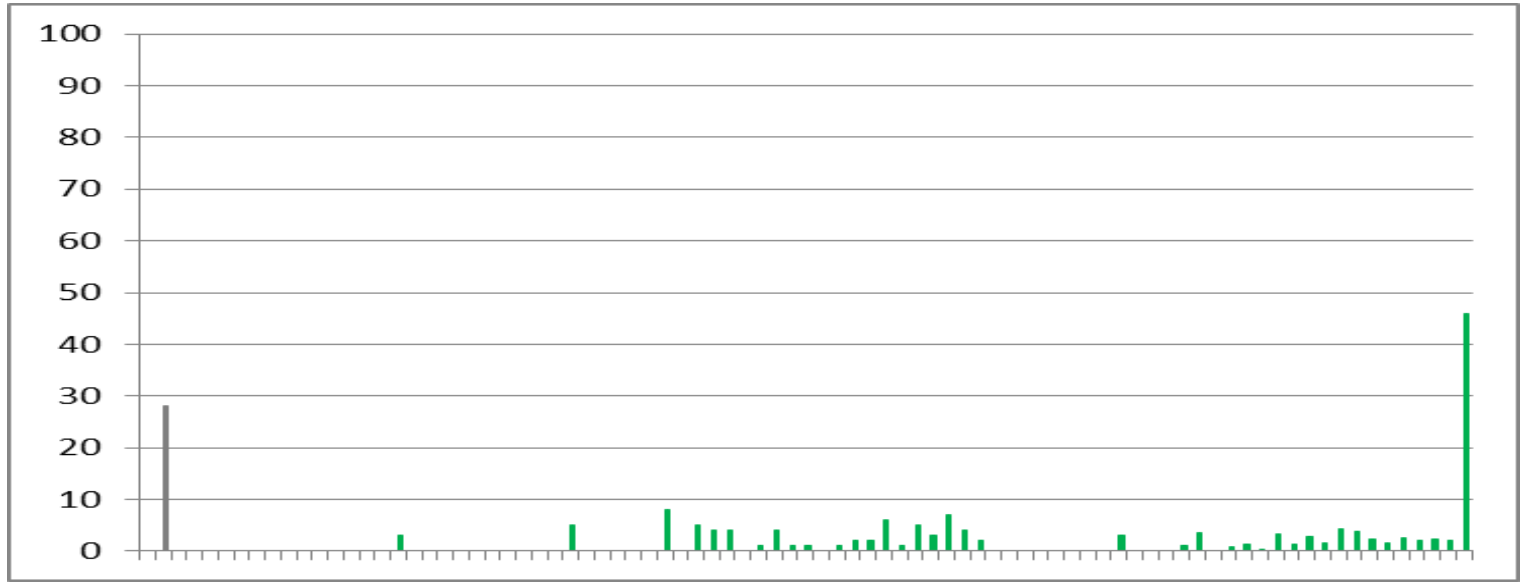
Prepubertal girls

Pubertal girls

EA



REA



17β Estradiol

Octylphenol

Precocious puberty

Puberté(s) Précoce(s) et Perturbateurs Endocriniens

1- Rappels / la problématique des PEE

2- PEE dans notre environnement de proximité

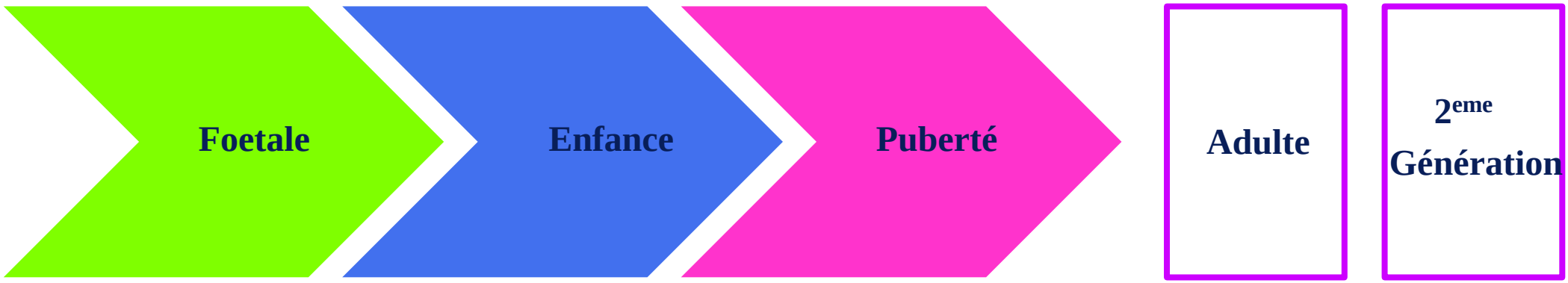
3- PEE et Puberté

4- Conclusions

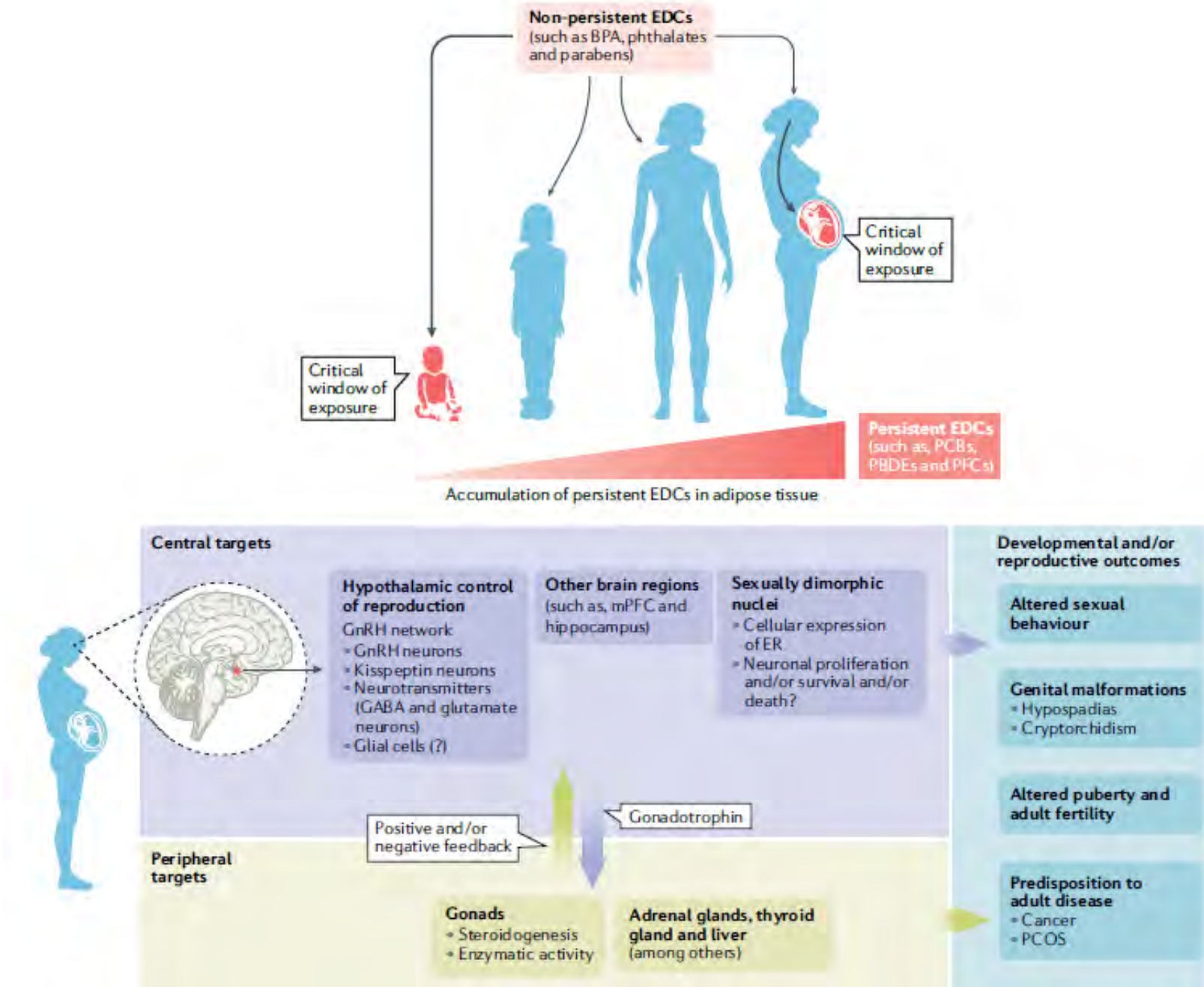
Perturbateurs Endocriniens

Ce n’est pas la dose mais la période d’exposition qui fait le « poison »

Notion d’effets cocktails



DOHaD



Lopez-Rodriguez D, Nat Rev, 2021, Feb (17)

Perturbateurs Endocriniens

Impact sur la santé

Mais, ne pas sombrer dans un positionnement extrême

Tous les PEE d'une même famille ne sont pas toxiques

Interdire certains PEE → molécules de substitution

Principe de précaution / périodes de susceptibilités

Poursuite des études mécanistiques

Développer des méthodes de dépistage d'une exposition aux PEE / un patient