Fonction thyroïdienne et perturbateurs endocriniens

Michel Pugeat

Fédération d'Endocrinologie du Pôle Est Hospices Civils de Lyon
et INSERM U1060 Institut CaRMeN

L'Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail

Définition:

- Les perturbateurs endocriniens sont définis de manière générale comme des substances chimiques d'origine naturelle ou artificielle qui peuvent interférer avec le fonctionnement des glandes endocrines.
- Cette action peut passer par différentes voies :

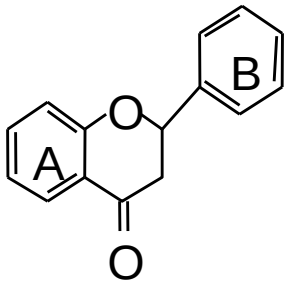
- mimer l'action d'une hormone naturelle et entrainer ainsi la réponse due à cette hormone
- empêcher une hormone de se fixer à son récepteur et ainsi de transmettre le signal hormonal
- perturber la production ou la régulation des hormones ou de leurs récepteurs.

Classification des perturbateurs endocriniens

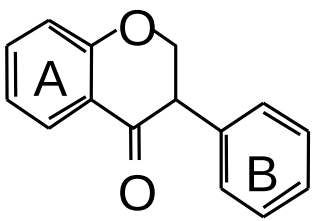
- Origine naturelle

Les phyto-œstrogènes

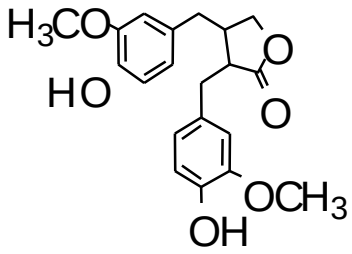
Flavonoides	Isoflavonoides	Lignanes	Coumestrans



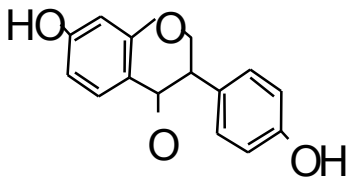
Légumineuses



Soja et dérivés, haricots, lentilles...



Carottes, ail, fenouil, céréales, graine de lin...



Brocolis

Modèles d'études *in vitro* des effets perturbateurs thyroïdiens des phytoestrogènes

Compound	Iodide uptake	TPO activity	TR agonist	TR antagonist	T_4 binding to TTR
4-MBC	↓	—	ND	ND	ND
4-NP	↓	↓	↑	↓	ND
Adiol	↓	—	ND	ND	ND
BPA	—	↓	ND	ND	ND
BP2	—	↓	↑	—	ND
BP3	—	—	↑	—	ND
Daidzein	ND	ND	ND	ND	↓
Dibutylphthalate	—	—	ND	ND	ND
E_2	↓	—	ND	ND	ND
F21388	ND	↓	ND	ND	ND
Genistein	↓	↓	↑	—	↓
Glycitein	ND	ND	ND	ND	↓
Linuron	—	—	↑	—	ND
OMC	↓	—	↑	—	ND
Procymidon	—	—	ND	ND	ND
Resveratrol	—	↓	↑	—	ND
Silymarin	—	↓	↑	—	ND
Xanthohumol	↑	—	ND	ND	ND

Modèles d'études *in vivo* des effets perturbateurs thyroïdiens des phytoestrogènes

Compound	Histology	tT_4	tT_3	TSH	ME		5´DI	
					Liver	Kidney	Liver	Kidney
E_2	—	—	—	—	↑	—	↓	↑
Adiol	—	—	—	—	↑	↑	—	↑
4-Nonylphenol	⇑	↑	↑	—	—	—	—	—
OMC	—	↓	—	—	—	↑	↓	↓
4-MBC	—	↓	↑	↑	—	—	—	↓
Genistein	ND	↑	—	—	↓	—	—	↑
8-PN	ND	—	↑	—	↓	—	—	—
Resveratrol	ND	—	↑	—	↓	—	—	↑
Soy	—	↓	—	—	↓	—	—	↑
Soy + E_2	—	—	—	—	↑	↑	↓	↑
Soy + 4-nonylphenol	—	↓	—	—	—	—	—	↑
Soy + OMC	—	↓	—	—	↑	—	↓	↓
Soy + 4-MBC	—	↓	↓	—	—	—	—	↓

Phyto-estrogènes et fonction thyroïdienne

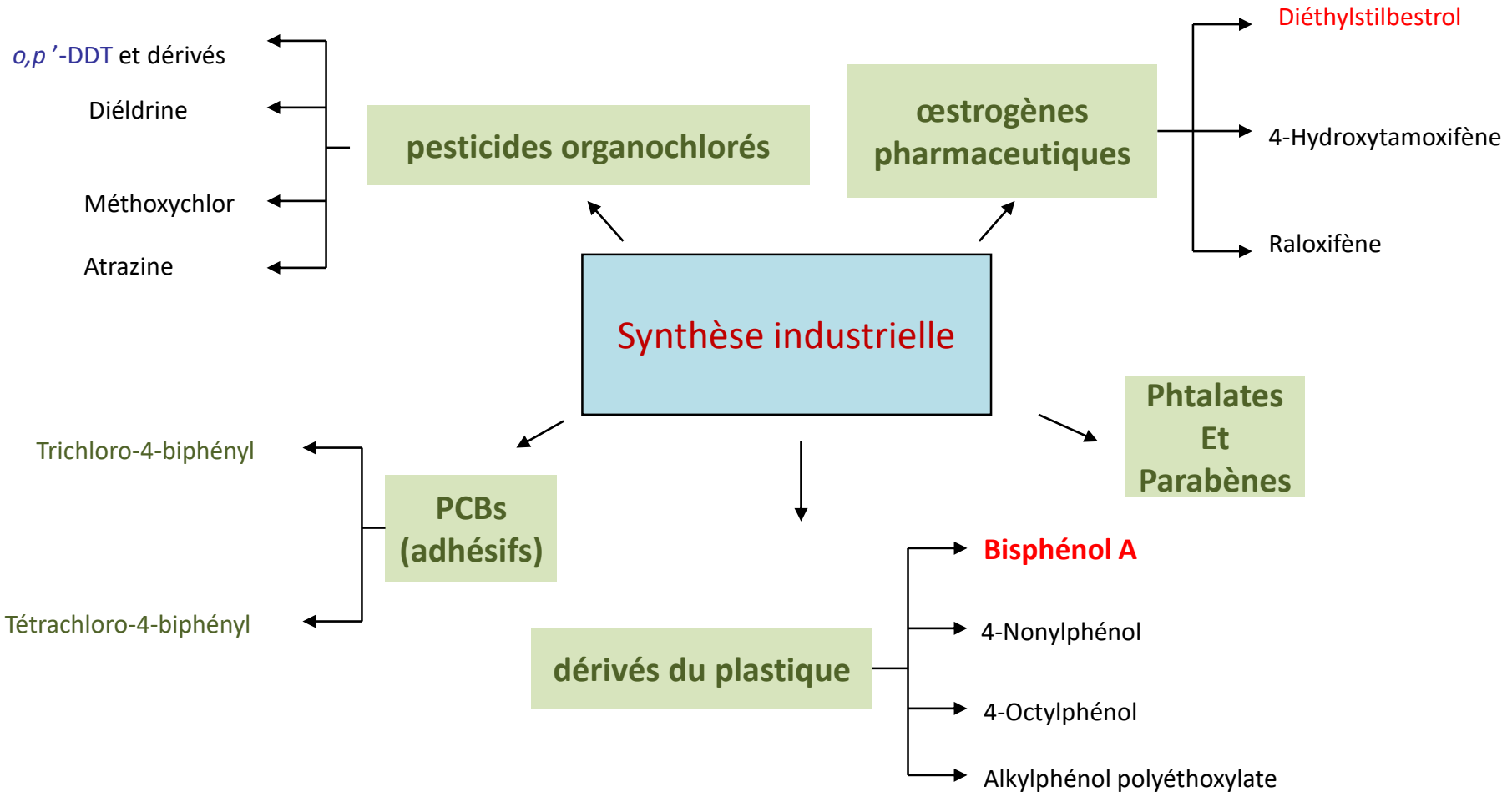
- *du fait de l'analogie de structure des isoflavones avec les hormones thyroïdiennes,* leur consommation peut modifier les taux circulants d'hormones thyroïdiennes par un effet sur la synthèse (inhibition de la peroxydase thyroïdienne) ou sur la conversion de T4 en T3 (déiodases)

Phyto-estrogènes et fonction thyroïdienne

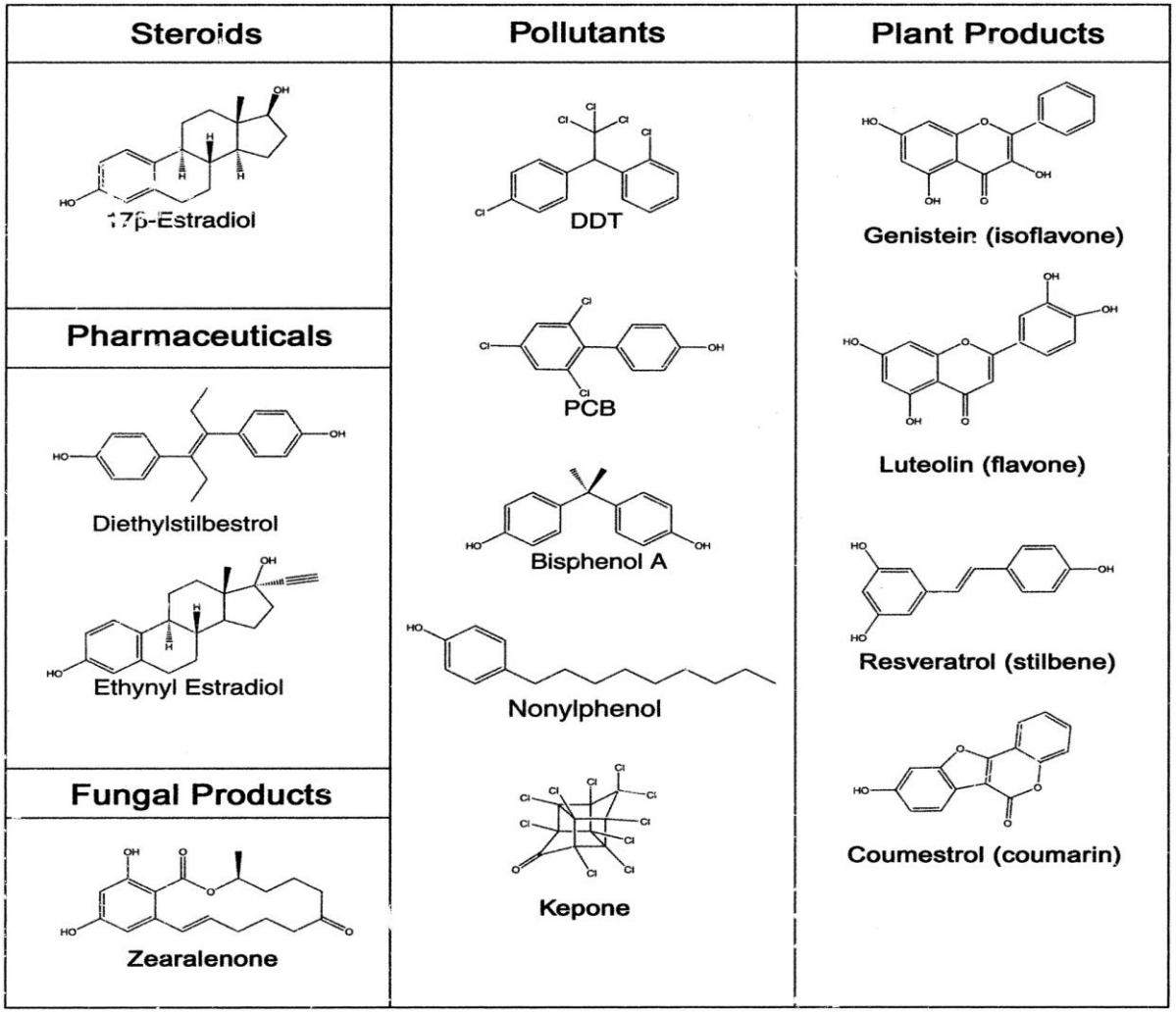
- *le développement d'un goitre*, rapporté chez l'enfant, n'ont pas été démontré chez l'adulte au cours de la consommation de soja
- *cet effet goitrigène* semble disparaître si l'apport de iodures recommandé est respecté
- *le principal risque de la consommation d'isoflavones* pourrait être d'augmenter les besoins en hormones thyroïdiennes chez les patients hypothyroïdiens substitués ou freinés par thyroxine, comme cela a été documenté chez l'enfant.

Classification des perturbateurs endocriniens

- Origine industrielle



Produits chimiques de l'environnement possédant des activités hormonales: perturbateurs endocriniens

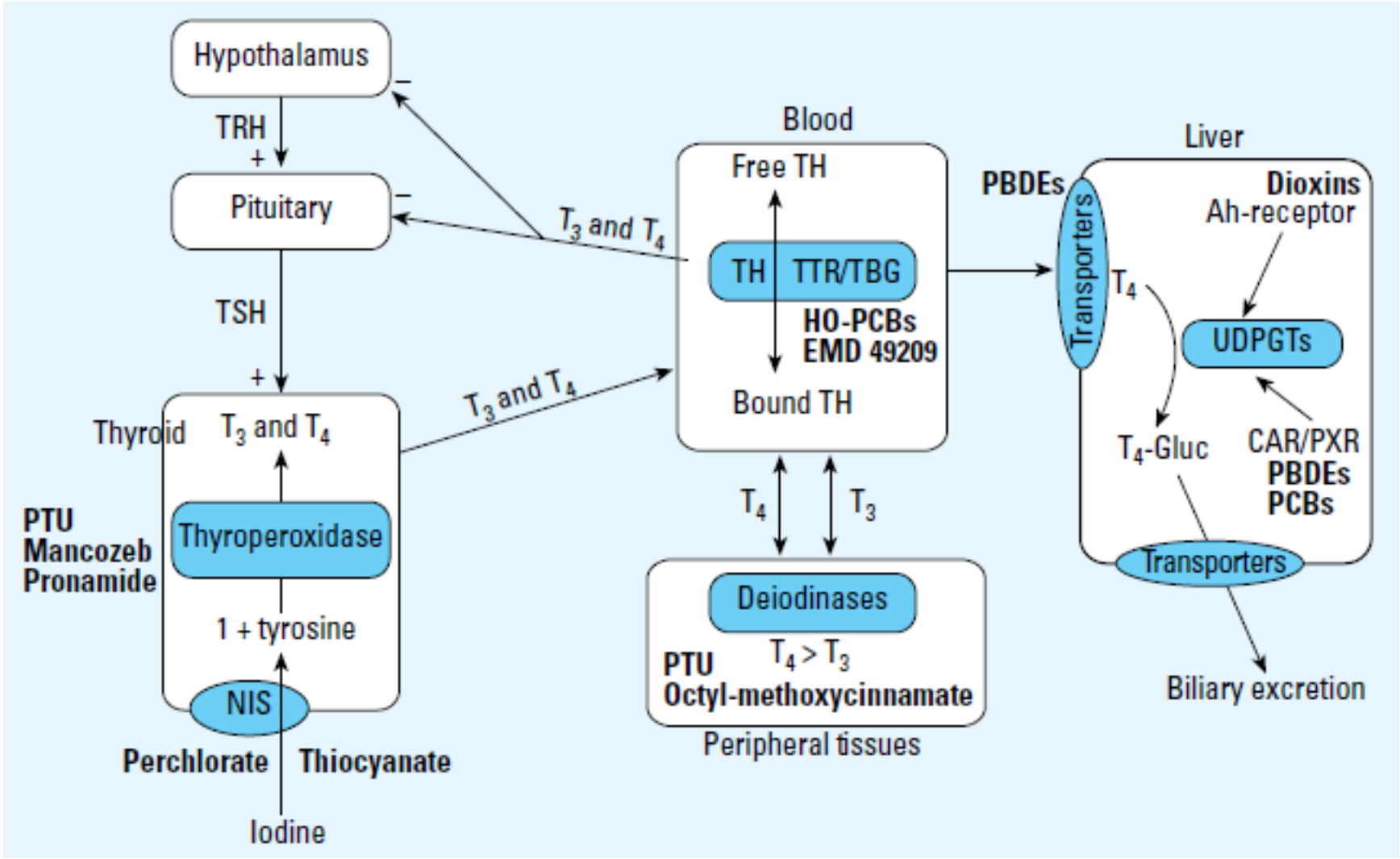


Sources des produits chimiques de l'environnement possédant une activité de perturbateur thyroïdien

Agent	*Example of sources*	*Mode of action*	*Associated as a trigger or accelerating autoimmune thyroid disease*
PCBs	Found in coolants and lubricants, multiple cogeners, lipophilic	TR agonist/antagonist, can alter levels of T4 and TSH	Possible increase in TSH, thyroid autoantibodies, thyroid volume
Organochlorine pesticides	Used as pesticide on crops	Induce hepatic UDPGTs and glucuronidate T4, accelerating metabolism	No human studies establishing association
PBDEs	Found in flame retardants	Bind to TRs, displaces T4 from binding proteins	Increase in HT in some studies
BPA	Used in plastic bottles	Antagonize TR	No human studies establishing association
Perchlorate, thiocyanate	Rocket fuel, fertilizer, smoking	Inhibits iodine uptake	No human studies establishing association
Triclosan	Antibacterial in soaps	Reduce serum T4, disrupt amphibian development	No human studies establishing association
Isoflavones	Soy products	Inhibits TPO activity	Possible increase in HT

PCBs, polychlorinated biphenyls; TR, thyroid hormone receptor; T4, thyroxine; TSH, thyrotropin; UDPGTs, uridine diphosphate glucuronyltransferase; PBDE, polybrominated diphenylethers; HT, Hashimoto's thyroitidits; BPA, Bisphenol-A; TPO, thyroid peroxidase.

Régulation, sécrétion et métabolisme des HT et l'impact des perturbateurs



Abbreviations: Gluc, glucose; HO-PCBs, hydroxyl-PCBs; NIS, sodium/iodide symporter; PBDE, polybrominated diphenyl ether; PTU, propylthiouracil; T4-Gluc, T4-glucuronide; TBG, thyroid-binding globulin; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; TTR, transthyretin; UDPGT, uridine diphosphate glucuronyltransferase. Sites or processes where xenobiotics are known or hypothesized to act as TDCs are indicated in the boxes and ovals. Xenobiotics that block, inhibit, or up-regulate these processes are shown in bold (modified from Crofton 2008).

Mécanismes d'action de perturbateurs thyroïdiens

Mechanisms of action	Group of chemicals	References
Inhibition of the iodide uptake	Perchlorate, phthalates	114, 115
Thyroperoxidase	NP	61
Inhibition of the function of the TSH receptor	DDT, PCB	116
Binding to transport proteins	PCB, phthalates, phenols, flame retardants, HCB	18, 117–123
Cellular uptake of thyroid hormones	Phthalates, chlordanes	125
Binding to thyroid hormone receptor and gene expression	PCB, phenols, flame retardants, BPA, HCB	56, 70, 126, 129, 130, 132–137
Iodothyronine deiodinases	Methoxychlor, MBC	61, 142, 143
Excretion/clearance of thyroid hormones	PCB, dioxin, phenols, flame retardants, HCB, BPA	45–47,67,68,144–146

Etudes rapportant chez l'homme un effet des PCBs sur la fonction thyroïdienne

Author	Year	No. of subjects	Effect	Reference
Hsu *et al.*	2005	60 boys	No effects	43
Takser *et al.*	2005	101 mothers 92 cord blood	Mothers: ↓TT3, ↑TSH Cord blood: No significant correlations	39
Schell *et al.*	2004	115 adults	↓FT4, ↓T4, ↑TSH	33
Bloom *et al.*	2003	66 adults	No effects	35
Ribas-Fito *et al.*	2003	98 infants	No significant effects (trend toward ↑TSH)	38
Langer *et al.*	2003	101 adults	Higher thyroid volume in highly exposed subjects	36
Persky *et al.*	2001	229 adults	↓T4, FTI (females); ↑T3-uptake (men)	31
Matsuura *et al.*	2001	337 breastfed infants[a]	No effects	42
Sala *et al.*	2001	192 (608) adults	No significant effects (trend toward ↑TSH)	105
Hagmar *et al.*	2001	110 adults (men)	No effects	34
Hagmar *et al.*	2001	182 adults (women)	↓TT3	30
Steuerwald *et al.*	2000	182 children	No effects	37
Longnecker *et al.*	2000	160 cord blood	No effects	41
Osius *et al.*	1999	320 children	↓FT3, ↑TSH	32
Koopman-Esseboom *et al.*	1994	105 mothers and Infants[a]	Mothers: ↓TT3, ↓TT4 Infants: ↑TSH (2 weeks and 3 months age)	40

[a]PCB measured in breast milk.

Résumé des effets thyroïdiens potentiels des perturbateurs endocriniens chez le rongeur

- Hypothyroïdie: dioxines, furanes et PCBs
- Baisse des hormones thyroïdiennes : retardeur de flamme, effet inconsistant des phtalates (éventuellement stimulant)

American Journal of Epidemiology

Vol. 171, No. 4
DOI: 10.1093/aje/kwp404
Advance Access publication:
January 8, 2010

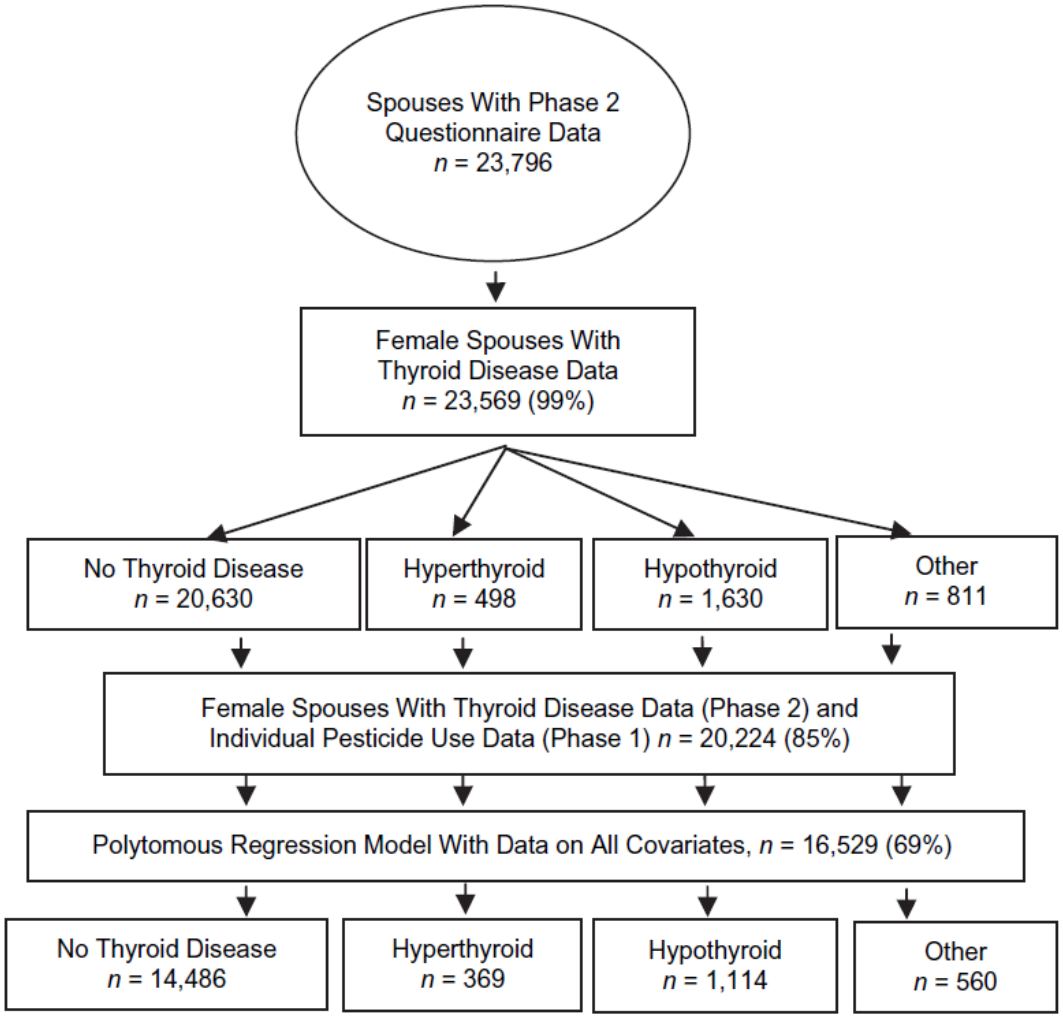
Original Contribution

Pesticide Use and Thyroid Disease Among Women in the Agricultural Health Study

Whitney S. Goldner*, Dale P. Sandler, Fang Yu, Jane A. Hoppin, Freya Kamel, and Tricia D. LeVan

* Correspondence to Dr. Whitney S. Goldner, University of Nebraska Medical Center, 983020 Nebraska Medical Center, Omaha, NE 68198-3020 (e-mail: wgoldner@unmc.edu).

Inclusions des patients dans l'étude Agricultural Health Study, 1993–1997.



Female spouses of licensed pesticide applicators in Iowa and North Carolina who were part of the Agricultural Health Study and who also had thyroid disease and pesticide use data were included. For further analysis, the population was then divided into 4 groups: no thyroid disease, hyperthyroid, hypothyroid, and other.

Am J Epidemiol 2010;171:455–464

General Farm Characteristics and Pesticide Use Among Female Spouses by Thyroid Disease Status, Agricultural Health Study, 1993–2003a

Exposure	No Thyroid Disease (n = 14,486; 88%)		Hyperthyroid (n = 369; 2%)				Hypothyroid (n = 1,114; 7%)				Other (n = 560; 3%)			
	No.	% Exposed	No.	% Exposed	OR	95% CI	No.	% Exposed	OR	95% CI	No.	% Exposed	OR	95% CI
Worked/lived on a farm, years														
Never	460	3.2	13	3.6	1.0		25	2.3	1.0		17	3.1	1.0	
≤25	5,352	37.3	111	30.7	0.87	0.49, 1.6	357	32.4	1.5	0.95, 2.2	155	27.9	0.95	0.57, 1.6
26–40	4,111	28.7	94	26.1	0.78	0.43, 1.4	299	27.1	1.4	0.89, 2.1	145	26.1	0.93	0.56, 1.6
>40	4,416	30.8	143	39.6	0.76	0.42, 1.4	422	38.2	1.3	0.87, 2.0	238	42.9	0.92	0.55, 1.5
Lifetime pesticide application, years														
Never	6,983	56.0	178	56.2	1.0		530	54.4	1.0		267	55.7	1.0	
≤5	2,064	16.6	50	15.8	1.1	0.79, 1.5	149	15.3	0.99	0.82, 1.2	72	15.0	1.1	0.82, 1.4
6–16	2,385	19.1	47	14.8	0.80	0.58, 1.1	188	19.3	1.0	0.84, 1.2	86	18.0	0.99	0.77, 1.3
≥17	1,032	8.3	42	13.2	1.2	0.85, 1.7	107	11.0	1.0	0.82, 1.3	54	11.3	1.0	0.75, 1.4
Mixed/applied pesticides, days/year														
Never	6,983	56.0	178	56.5	1.0		530	54.3	1.0		267	55.5	1.0	
≤3	2,824	22.7	63	20.0	0.91	0.68, 1.2	210	21.5	0.95	0.80, 1.1	92	19.1	0.89	0.70, 1.1
4–7	1,228	9.9	40	12.7	1.2	0.87, 1.8	114	11.7	1.1	0.91, 1.4	50	10.4	1.0	0.76, 1.4
≥8	1,429	11.4	34	10.8	0.89	0.61, 1.3	122	12.5	1.0	0.84, 1.3	72	15.0	1.3	0.98, 1.7

Am J Epidemiol 2010;171:455–464

Original Contribution

Pesticide Use and Thyroid Disease Among Women in the Agricultural Health Study

- Cette étude montre une augmentation de 12% d'événements thyroïdiens dans la population exposése aux pesticides en comparaison de la population générale.
- L'événement le plus fréquent est l'hypothyroïdie notamment associé à l'exposition aux
  - organochlorés insecticides OR ajusté de 1,2 (95% intervalle de confiance (IC): 1.0, 1.6)
  - fongicides (ORadj 1.4 (95% CI: 1.1, 1.8)
  - mais non associés aux herbicides, organophasphatés, pyethroides et carbamates
- Le chlordane un organochloré (ORadj ¼ 1.3 (95% CI: 0.99, 1.7), le benomyl (ORadj ¼ 3.1 (95% CI: 1.9, 5.1) le maneb/mancozeb (ORadj ¼ 2.2 (95% CI: 1.5, 3.3) fongicides et le paraquat, un herbicide (ORadj ¼ 1.8 (95% CI: 1.1, 2.8) sont les produits avec l'OR le plus élevé vis à vis du risque d'hypothyroïdie.
- Le Maneb/mancozeb est le seul pesticides associé au duble risque d'hypo et d'hyperthyroïide (ORadj ¼ 2.3 (95% CI: 1.2, 4.4) and hypothyroidism.

Am J Epidemiol 2010;171:455–464

American Journal of Epidemiology

Vol. 171, No. 4
DOI: 10.1093/aje/kwp404
Advance Access publication:
January 8, 2010

Original Contribution

Pesticide Use and Thyroid Disease Among Women in the Agricultural Health Study

Conclusions : Ces résultats suggèrent un rôle des organochlorés et des fongicides dans l'étiologie des maladies thyroïdiennes

THYROID
Volume 20, Number 7, 2010

DOI: 10.1089/thy.2010.1636

Environmental Exposures and Autoimmune Thyroid Disease

Gregory A. Brent

Risk Reduction of Thyroid Autoimmunity in the Individual Patient

Susceptibility factor	*Mechanism*	*Reduce or monitor risk*
Genetic background: family history of thyroid disease	Increases genetic susceptibility to environmental triggers	Awareness/avoidance of triggers; low clinical threshold for thyroid function testing
Dietary iodine	Increased immunogenicity of thyroglobulin, thyroid cell destruction	Maintain regular and sufficient intake, especially during pregnancy
Dietary selenium	Interaction with immune response	Avoid deficiency, benefit of supplements not established, but may reduce antibody production in specific settings
Cigarette smoking	May increase cytokines in orbit and thyroid, complex interactions with the immune system	Increased risk of Graves' disease and Graves' ophthalmopathy; reduced risk of Hashimoto's disease
Medical radiation	Increases thyroid antigens, inflammation	Awareness of increased incidence of Hashimoto's and Graves' disease, thyroid function test monitoring
Nuclear incident	Direct thyroid destruction, increased thyroid antigens	Potassium iodine ingestion at time of incident
Medications	Stimulation of immune response at multiple sites	Thyroid function tests and thyroid autoantibodies in susceptible individuals, thyroid function test monitoring
Environmental toxicants/chemicals	Promote autoimmune thyroiditis in susceptible animal models	Monitoring thyroid function tests and thyroid autoantibodies, test well water for contaminants

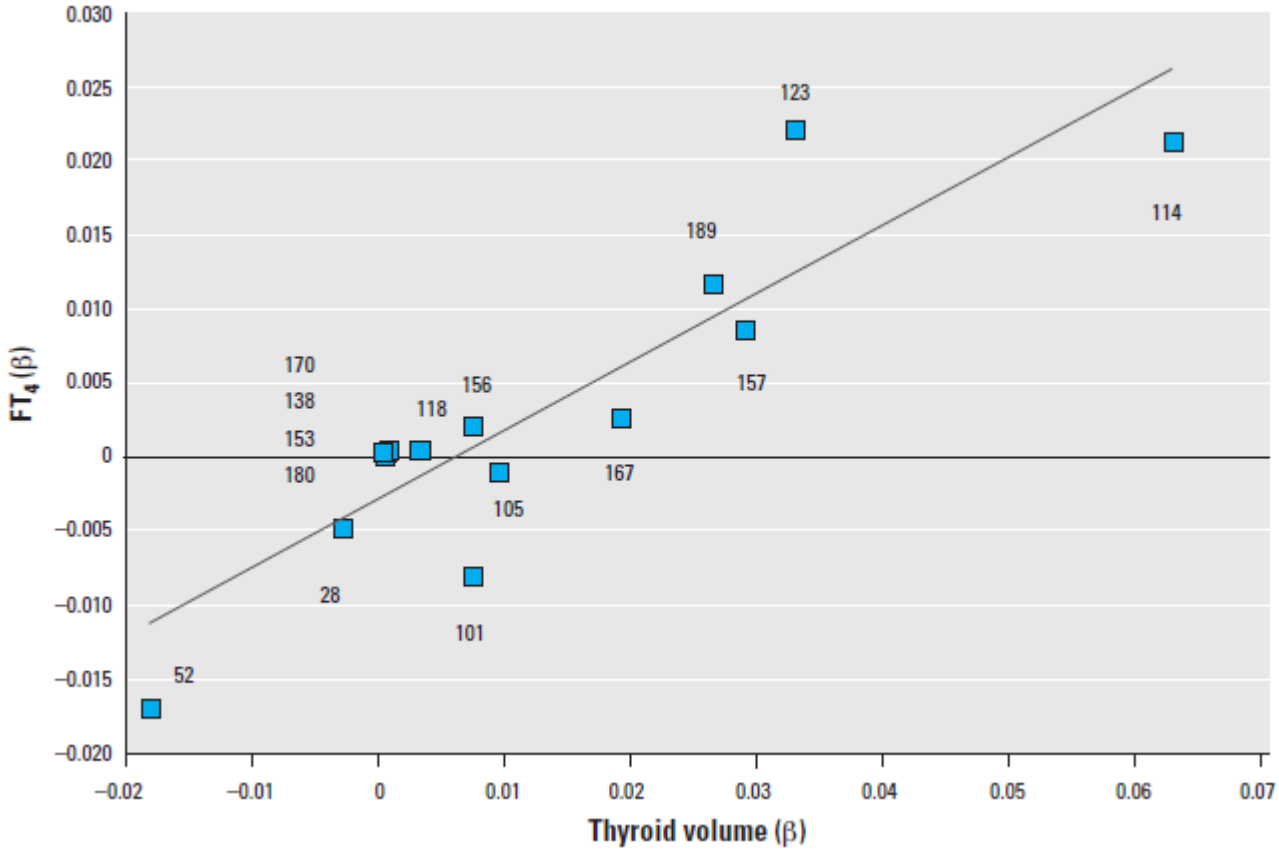
Research

Relative Effect Potency Estimates of Dioxin-like Activity for Dioxins, Furans, and Dioxin-like PCBs in Adults Based on Two Thyroid Outcomes

Tomáš Trnovec,[1] Todd A. Jusko,[2] Eva Šovčíková,[1] Kinga Lancz,[1] Jana Chovancová,[1] Henrieta Patayová,[1] Ľubica Palkovičová,[1] Beata Drobná,[1] Pavel Langer,[3] Martin Van den Berg,[4] Ladislav Dedik,[5] and Soňa Wimmerová[1]

[1]Slovak Medical University, Bratislava, Slovakia; [2]Epidemiology Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, North Carolina, USA; [3]Institute of Experimental Endocrinology, Slovak Academy of Sciences, Bratislava, Slovakia; [4]Institute for Risk Assessment Sciences, Utrecht University, Utrecht, the Netherlands; [5]Faculty of Mechanical Engineering, Slovak University of Technology in Bratislava, Bratislava, Slovakia

Plot of regression coefficients [for thyroid volume vs. PCB congener concentration (*x*-axis) against those for FT4 serum concentration vs. PCB congener concentration (*y*-axis)



Relative Effect Potency Estimates of Dioxin-like Activity for Dioxins, Furans, and Dioxin-like PCBs in Adults Based on Two Thyroid Outcomes

Tomáš Trnovec,[1] Todd A. Jusko,[2] Eva Šovčíková,[1] Kinga Lancz,[1] Jana Chovancová,[1] Henrieta Patayová,[1] Ľubica Palkovičová,[1] Beata Drobná,[1] Pavel Langer,[3] Martin Van den Berg,[4] Ladislav Dedik,[5] and Soňa Wimmerová[1]

Conclusions: Cette approche expérimentale et statistique montre que chez l'homme l'augmentation des taux circulants de Dioxine-like et PCBs influence la corrélation entre les taux de T4 libre et le volume de la thyroïde.

American Journal of Epidemiology

Vol. 168, No. 3
DOI: 10.1093/aje/kwn136
Advance Access publication June 10, 2008

Original Contribution

Effects of Exposure to Polychlorinated Biphenyls and Organochlorine Pesticides on Thyroid Function during Pregnancy

Jonathan Chevrier[1,2], Brenda Eskenazi[1,2], Nina Holland[1,3], Asa Bradman[1], and Dana B. Barr[4]

[1] Center for Children's Environmental Health Research, School of Public Health, University of California, Berkeley, Berkeley, CA.
[2] Division of Epidemiology, School of Public Health, University of California, Berkeley, Berkeley, CA.
[3] Division of Environmental Health Sciences, School of Public Health, University of California, Berkeley, Berkeley, CA.
[4] National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, GA.

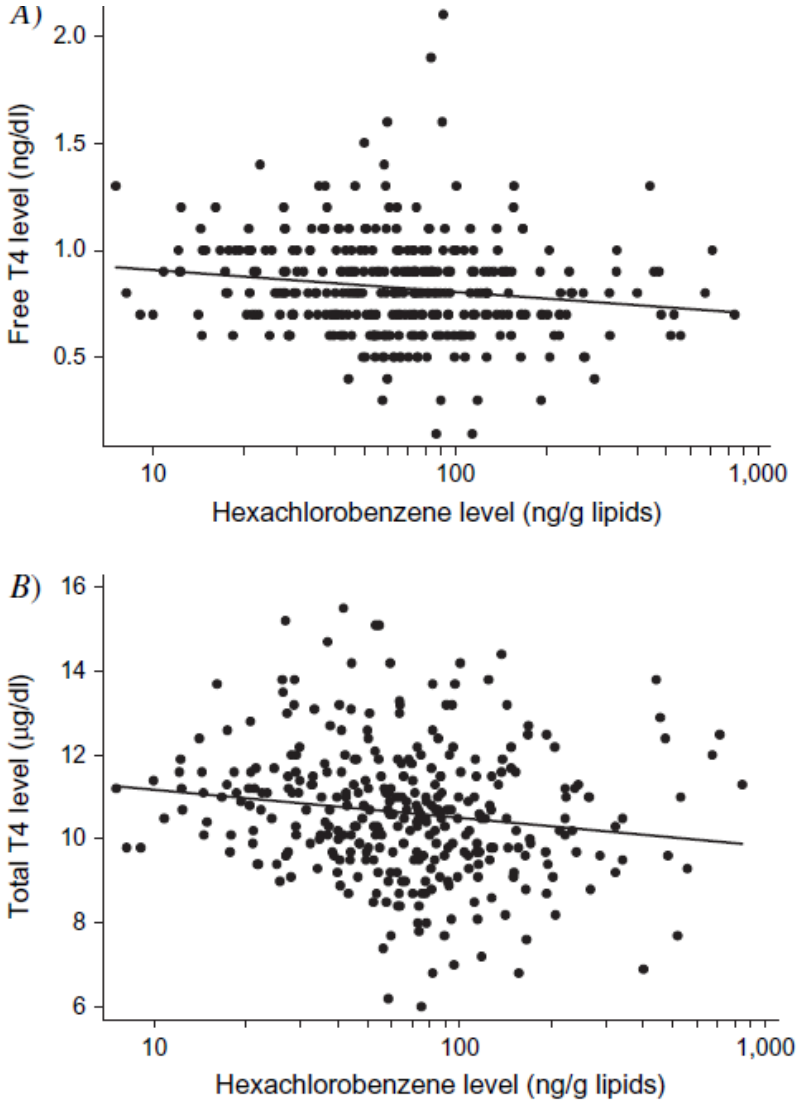
Objective: to determine whether serum concentrations of polychlorinated biphenyls (PCBs), hexachlorobenzene, p,p#-dichlorodiphenyl trichloroethane (DDT), o,p#-DDT, and p,p#-dichlorodiphenyl dichloroethylene (DDE) are associated with thyroid function during pregnancy.

Methods : These compounds, as well as thyroid-stimulating hormone, total thyroxine, and free thyroxine, were measured in serum samples collected between October 1999 and October 2000 from 334 pregnant women living in the Salinas Valley, California. Data were analyzed by multivariate linear regression.

Results: After adjustment for covariates,

- seven of the 19 PCB congeners detected in more than 75% of participants and the sum of those congeners were negatively associated with free thyroxine concentrations but not with TSH
- exachlorobenzene concentrations were negatively associated with both free thyroxine and total thyroxine.
- PCB and hexachlorobenzene concentrations were strongly correlated, which hampered the authors' ability to identify their independent associations with thyroid function.

FIGURE 1. Association between hexachlorobenzene and *A*) free and *B*) total thyroxine (T4) concentrations in pregnant women ($n = 333$), Salinas Valley, California, 1999–2000.



American Journal of Epidemiology

Vol. 168, No. 3
DOI: 10.1093/aje/kwn136
Advance Access publication June 10, 2008

Original Contribution

Effects of Exposure to Polychlorinated Biphenyls and Organochlorine Pesticides on Thyroid Function during Pregnancy

Conclusions

Les résultats de cette étude suggère que l'exposition aux PCBs

et à l'hexachlorobenzène perturbe la fonction thyroïdienne durant la

grossesse.

Prenatal exposure to endocrine disrupting chemicals in relation to thyroid hormone levels in infants – a Dutch prospective cohort study

Marijke de Cock[1*], Michiel R de Boer[1], Marja Lamoree[2], Juliette Legler[2] and Margot van de Bor[1]

de Cock *et al. Environmental Health* 2014, **13**:106
http://www.ehjournal.net/content/13/1/106

Regression coefficients for PCB-153 (<LOQ vs. >LOQ) and T4 (nmol/L), stratified for gender

	N	<LOQ	>LOQ	
			β (95% CI)	P-value
Male				
Crude	48	Ref.	3.3 (−9.58, 16.20)	0.607
Model A[1]	45	Ref.	4.2 (−9.63, 18.05)	0.542
Model B[2]	42	Ref.	−0.6 (−19.02, 17.79)	0.945
Female				
Crude	48	Ref.	−4.5 (−22.54, 13.55)	0.618
Model A[1]	45	Ref.	−7.4 (−28.59, 13.78)	0.483
Model B[2]	42	Ref.	−17.2 (−43.52, 9.04)	0.188

1 Adjusted for thyroid gland problems, use of thyroid medication, and birth weight. Caesarean section was constant and not included in the model.
2 Model A + additionally adjusted for gestational weight gain, gestational age, parity, smoking, alcohol, maternal BMI, and maternal age at birth.

Prenatal exposure to endocrine disrupting chemicals in relation to thyroid hormone levels in infants – a Dutch prospective cohort study

Marijke de Cock[1*], Michiel R de Boer[1], Marja Lamoree[2], Juliette Legler[2] and Margot van de Bor[1]

Conclusions

This study showed that DDE and PFAAs may be associated with T4 in a sex-specific manner. The study population was relatively small, therefore results should be interpreted with caution, and confirmation from larger studies is warranted.

Vulnérabilité des enfants à l'effet des pesticides

- vulnérabilité des enfants qui ne sont pas de « petits adultes »
- sources: milieu urbain – alimentation – proximité du sol
- concentrations plus élevées des principaux pesticides dans les urines (organophophorés, et métabolites diethylthophosphate et dimethylthiophosphate que chez les adultes
- conséquences connues sur les fonctions endocrines:
  - *prématurе pubarche ou puberté précoce*
  - *cryptorchidies plus fréquentes* (Hosie, 2000 – Longnecker 2002)
  - cancers : tumeurs du SNC (RR = 2,4)
  - dysfonction de la thyroïde

Vincent Garry *Tox and Applid Pharmac* 2004;198:152

Fonction thyroïdienne et perturbateurs endocriniens

Remarques et conclusions

- Le niveau de preuve d'une relation entre exposition aux polluants

et pathologie de la thyroïde repose sur des analyses transversales de population

avec un niveau de preuve épidémiologiques encore faible

- Des études d'intervention devront être menées pour confirmer

le risque d'exposition aux polluants

- En attendant, comme pour le Bisphénol A le principe de précaution

devrait être appliqué sans attendre les réglementations européennes

pour la mère et l'enfant

Le principe de précaution