



Protecting farm workers and citizens in rural areas against pesticides



Long-term health effects of pesticides on citizens

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INMA Spanish birth cohort



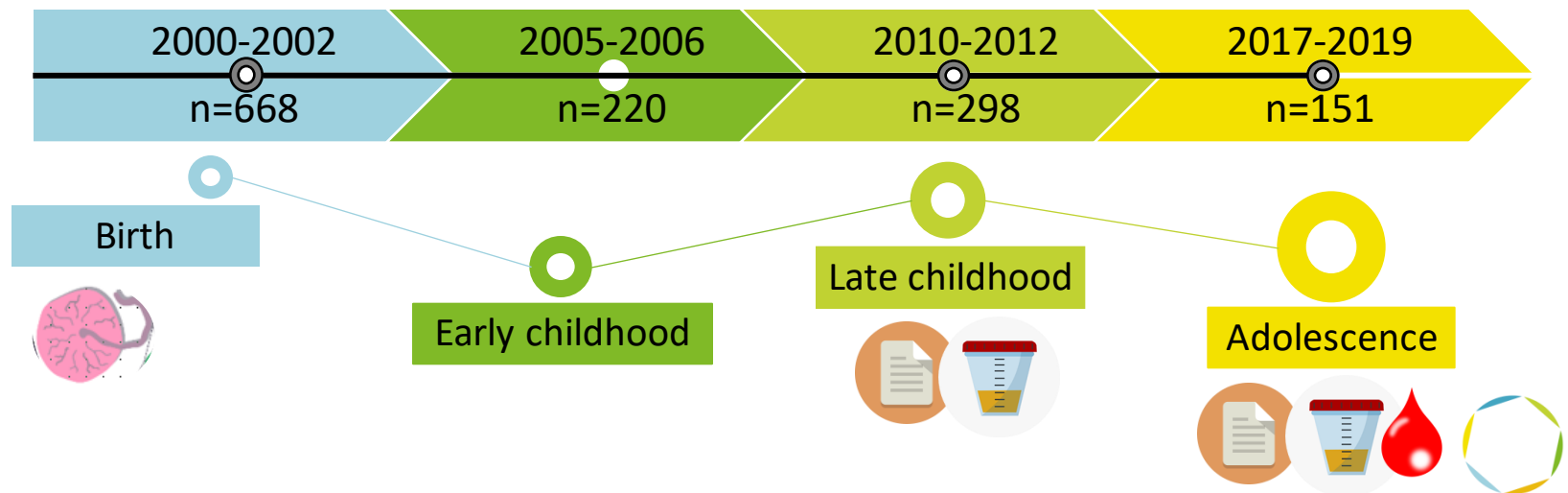
Population-based cohorts

The INMA Project study population consists of almost **4,000 mother-child pairs** residing in one of the seven study areas

Objective:

To study the role of the most important environmental pollutants in air, water and diet during pregnancy and early life, and their effects on child-adolescent growth and development.

The Environment and Childhood (INMA)-Granada Cohort.



INMA Results



Ribera d'Ebre (Flix)
ERCROS
Funded in 1897
Production of
chlorinated solvents -
HCB released in the
environment



Menorca island

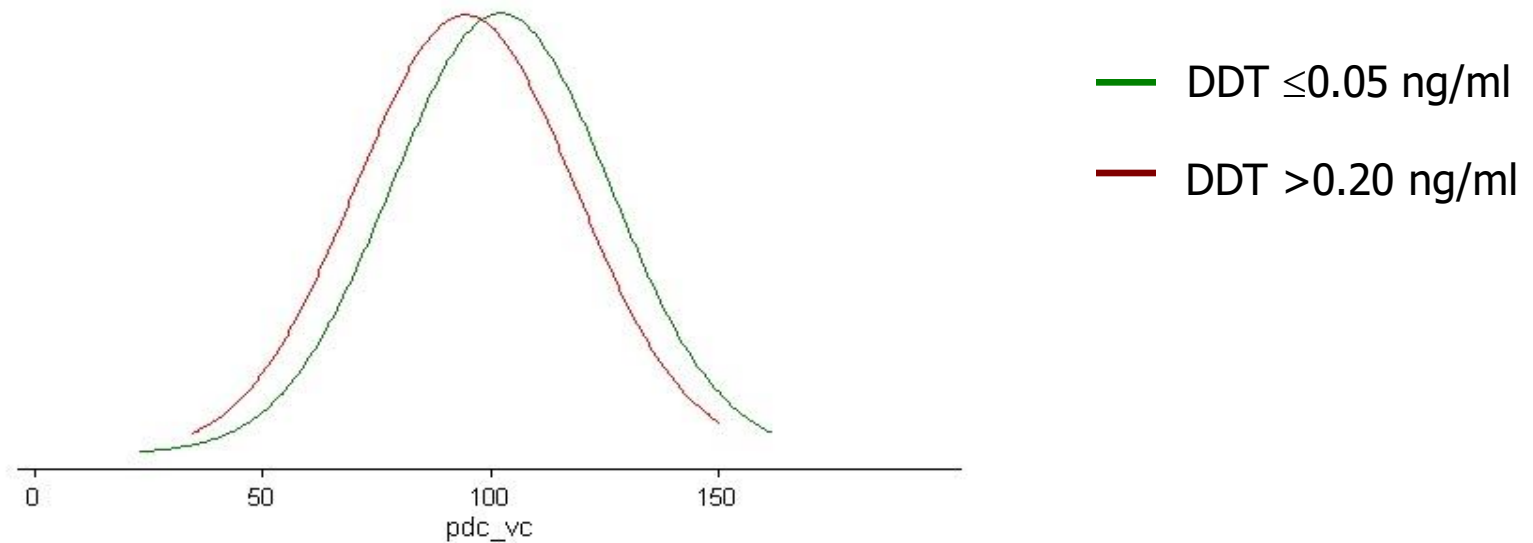
Neurodevelopment
4 years



Bayley's test

INMA Results

Association between *in utero* exposure to *p,p'*-DDT and neurodevelopment in Ribera d'Ebre and Menorca at age 4 years



Executive
function

Ribas-Fitó et al, Am J Epidemiol 2006, 2007

Biomarkers of *exposure*: non-persistent pesticides

Prioritized HBM4EU chemicals

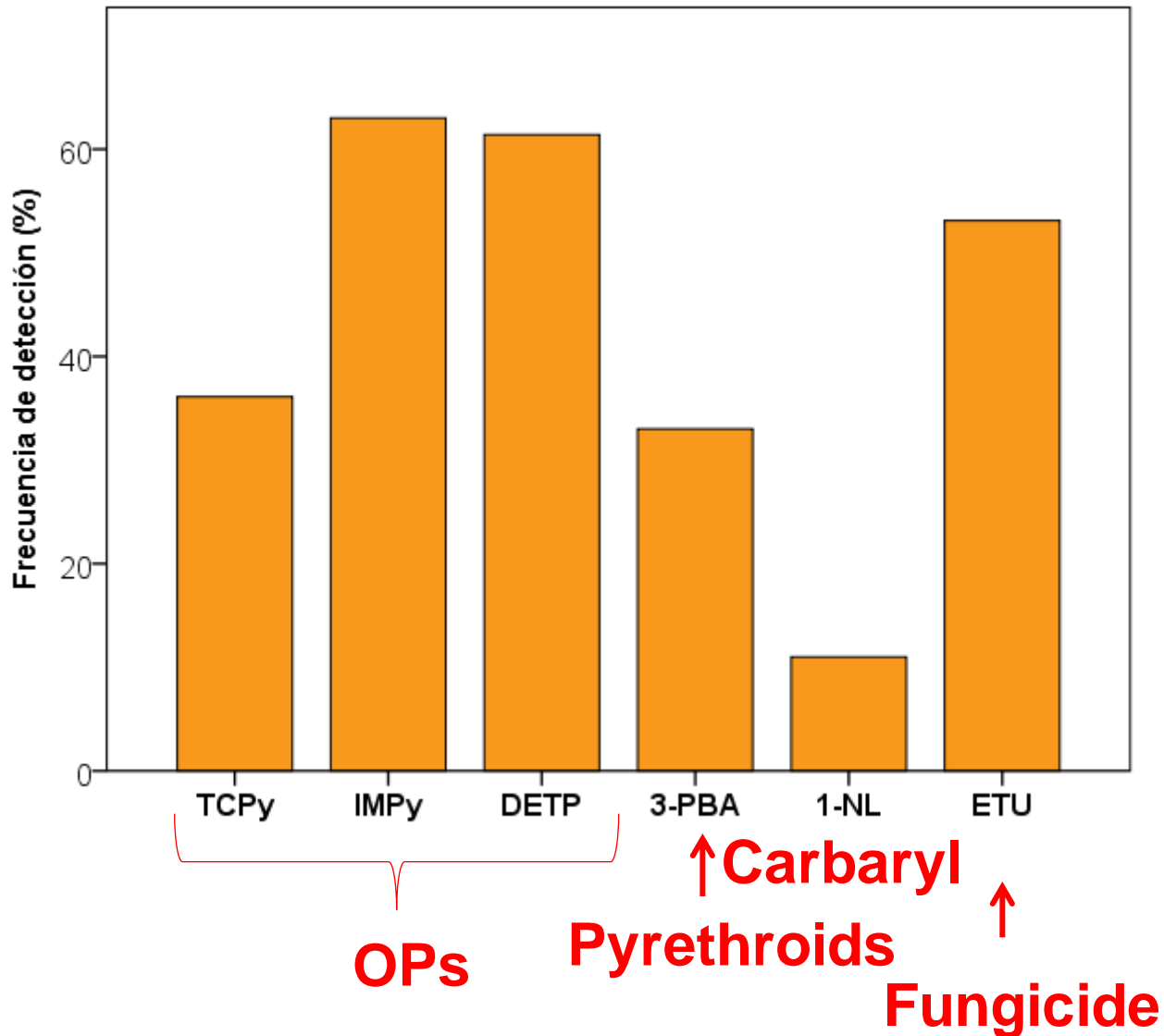
Chlorpyrifos

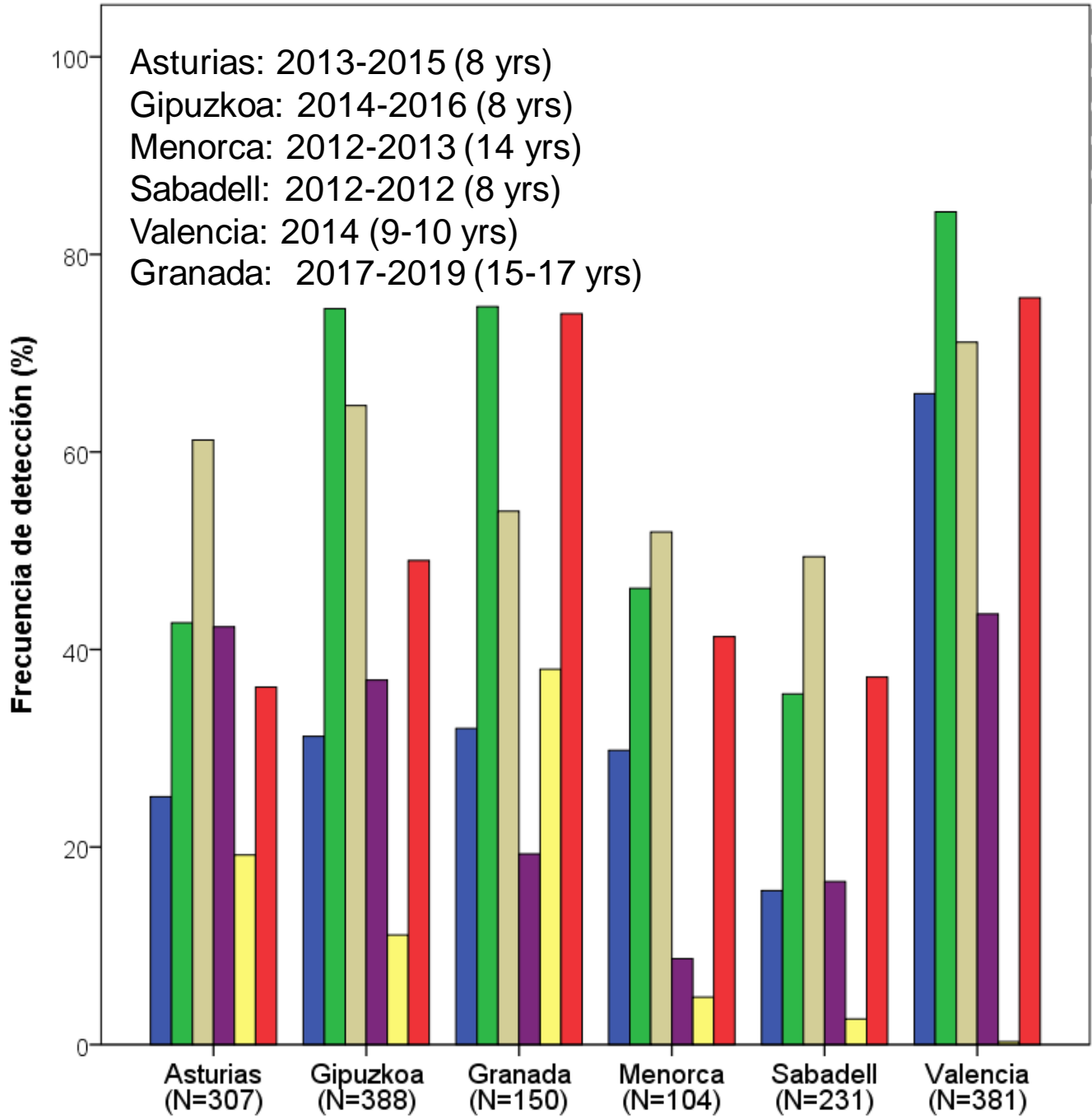
Pyrethroids

- **Organophosphate (OP) insecticide metabolites:** 3,5,6-trichloro-2-pyridinol (TCPy), 2-isopropyl-4-methyl-6-hydroxypyrimidine (IMPy), malathion diacid (MDA), and diethyl thiophosphate (DETP) + Σ OPs
- **Pyrethroids (PYR) metabolites:** 3-phenoxybenzoic acid (3-PBA) and dimethylcyclopropane carboxylic acid (DCCA) + Σ PYR
- **Carbaryl metabolite:** 1-naphthol (1N)
- **Ethylene-bis-dithiocarbamate fungicides (EBDC):** ethylene thiourea (ETU)



Non-persistent pesticide residues in the urine of 1,561 Spanish children (INMA cohort)





- TCPy
- IMPy
- DETP
- 3-PBA
- 1-NP
- ETU

Pesticide metabolites
n=1,561 Spanish children
 (INMA birth cohort)
 (4 new cohorts +
 INMA-Granada +
 INMA-Menorca)

2012-2029

Consequences of non-persistent pesticides exposure

Science of the Total Environment 769 (2021) 144563



Contents lists available at ScienceDirect

Science of the Total Environment

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

Organophosphate pesticide exposure, hormone levels, and interaction with PON1 polymorphisms in male adolescents

Beatriz Suárez^{a,b,c,1}, Fernando Vela-Soria^{a,1}, Francesca Castiello^{a,e}, Alicia Olivas-Martinez^{a,c}, Dario Acuña-Castroviejo^{a,c,d}, José Gómez-Vida^e, Nicolás Olea^{a,b,c,f}, Mariana F. Fernández^{a,b,c,f}, Carmen Freire^{a,b,c,*}

Environmental Research 197 (2021) 111016



Contents lists available at ScienceDirect

Environmental Research

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



Urinary metabolites of non-persistent pesticides and serum hormones in Spanish adolescent males

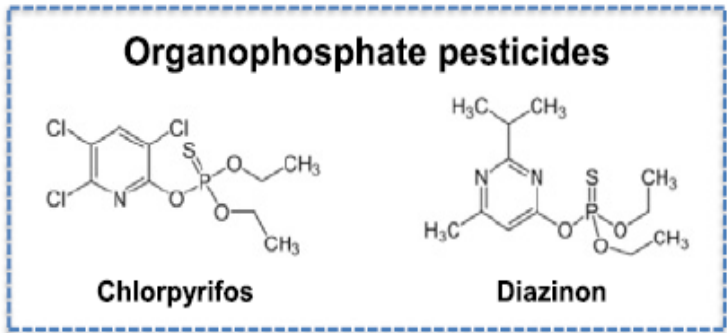
Carmen Freire^{a,b,c,*}, Beatriz Suárez^{a,b,c}, Fernando Vela-Soria^a, Francesca Castiello^{a,d}, Iris Reina-Pérez^{c,e}, Helle R. Andersen^f, Nicolás Olea^{a,b,c,e}, Mariana F. Fernández^{a,b,c,e}



Reproductive
development:
adverse effects
on **thyroid and**
reproductive
hormones



Sexual hormones – **INMA-Granada** birth cohort: follow up (15-17 yrs.)

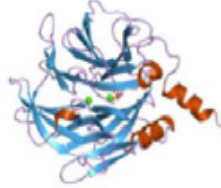


Susceptibility biomarkers

PON1 polymorphisms:

Q192R

L55M



Paraoxonase 1 gene

X



Male adolescents



Urinary metabolites

TCPy

IMPy

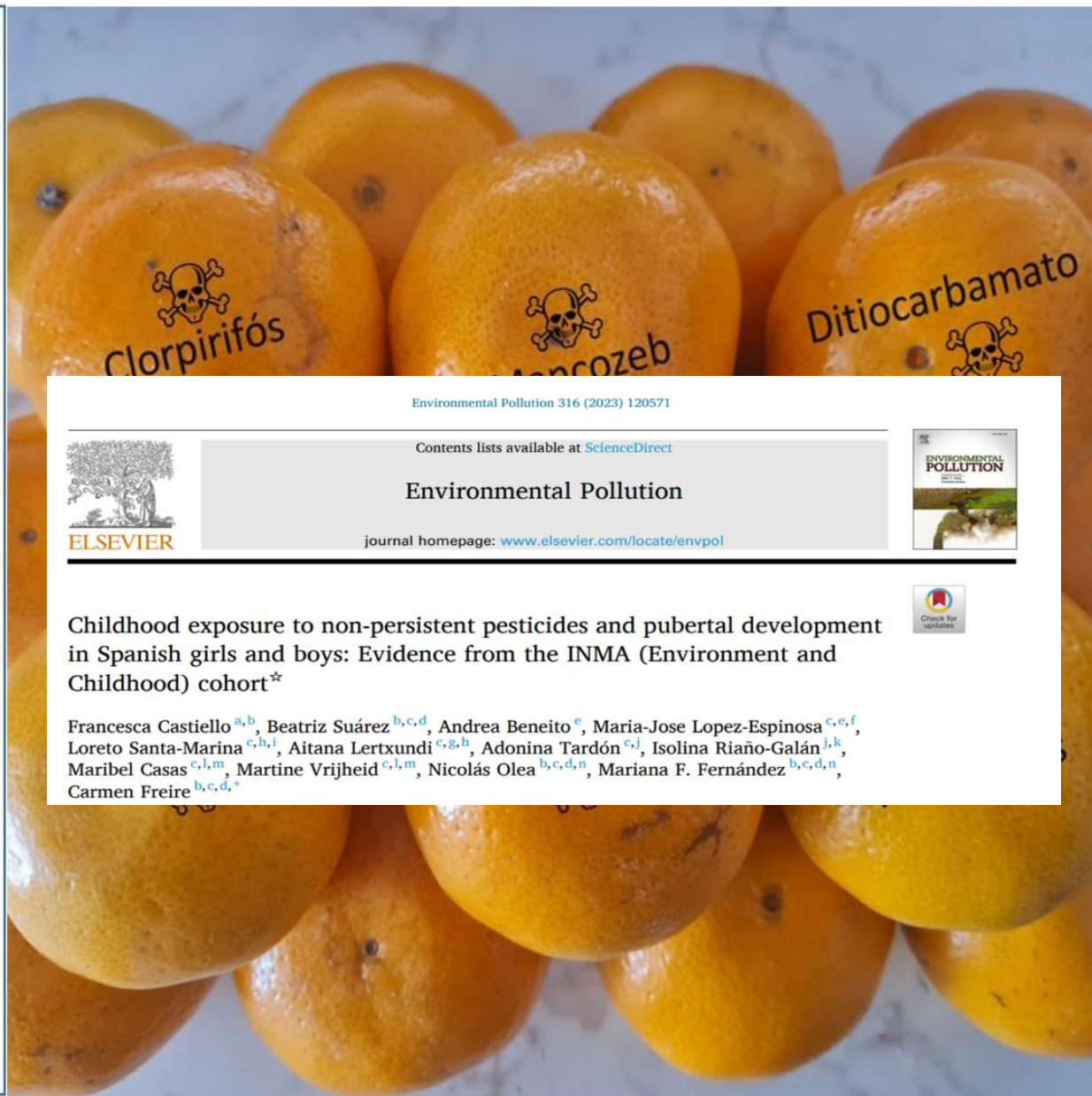
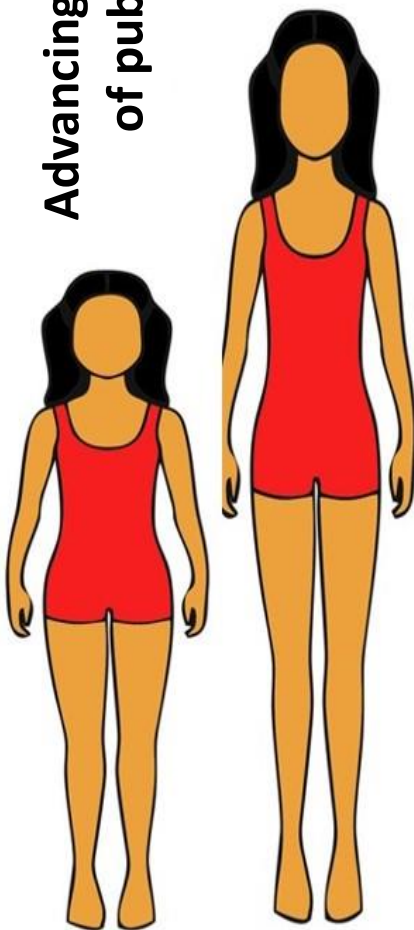
DETP

TCPy:	↑ DHEAS	↓ E ₂ , FSH, AMH
IMPy:	↑ E ₂ , DHEAS, FSH, AMH, prolactin	↓ SHBG, LH
DETP:	↓ FSH, AMH, prolactin	
IMPy → DHEAS, FT4	TCPy → FT4	} ↑ 55MM carriers
DETP → TT, TSH		
DETP → TT3		

PON1: a key enzyme in the hydrolysis of OP pesticides

Polymorphisms in genes encoding enzymes involved in xenobiotic metabolism may contribute to inter-individual variance in susceptibility to the toxicity of environmental chemicals

Advancing the age of puberty



Environmental Pollution 316 (2023) 120571

Contents lists available at [ScienceDirect](https://www.sciencedirect.com)



ELSEVIER

Environmental Pollution

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



Childhood exposure to non-persistent pesticides and pubertal development in Spanish girls and boys: Evidence from the INMA (Environment and Childhood) cohort[☆]

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Neurocognitive Development

To investigate the relationship between exposure to various non-persistent pesticides, BDNF, and behavioral function among Spanish adolescent males from the INMA-Granada cohort.



Rodríguez-Carrillo, A., et al. Environ Res. 2022;211:113115 (open access)



Results & Discussion

Study design	Exposure	Outcome	Statistical Method	Covariates
Cross-sectional	Non-persistent pesticides metabolites (ng/mL)	Behavior (CBCL)	Multivariate linear regression models Weighted quintile sum (WQS) Mediation analysis	Age, BMI, alcohol consumption, season of urine collection, urine creatinine, maternal education

BDNF

n=140 participants urinary pesticides & CBCL data

n=130 participants serum BDNF protein levels, pesticides & CBCL

n=118 participants BDNF gene DNA methylation, pesticides & CBCL

Pesticide metabolites	Non-persistent pesticide concentrations										
	IMPy	MDA	TCPy	DETP	ΣOPs	DCCA	3-PBA	ΣPYR	1-N	ETU	
% Detection	74.8	83.0	32.5	54.3	-	100	19.9	-	38.0	74.2	
25	0.08	0.14	<LOD	<LOD	0.67	0.12	<LOD	0.21	<LOD	0.05	
Percentiles	50	0.25	0.30	<LOD	0.25	1.29	1.06	<LOD	1.17	<LOD	0.26
75	0.81	0.50	0.08	0.74	2.27	3.45	0.083	3.53	0.34	0.70	

IMPy, MDA, DCCA, and ETU selected for WQS analysis



Table. Pesticide metabolites and CBCL behavior scoring (β , 95% CI)

		Syndrome Scores			Composite scores			
		Social problems	Thought problems	Rule-breaking behavior	Aggressive behavior	Internalizing problems	Externalizing problems	Total problems
IMPy	T2	1.47	2.33	0.76	2.47	2.19	2.46	2.54
		(-1.19,4.13)	(-0.24,4.90)	(-1.90,3.43)	(-0.20,5.13)	(-1.83,6.21)	(-1.43,6.34)	(-1.34,6.42)
IMPy	T3	3.34	2.56	3.76	3.77	1.13	5.50	4.60
		(0.65,6.02)	(-0.04,5.16)	(1.06,6.45)	(1.07,6.46)	(-2.93,5.20)	(1.58,9.42)	(0.68,8.52)
TCPy	D	2.13	2.48	-0.61	0.21	-0.09	-0.74	0.58
	vs ND	(-0.16,4.42)	(0.29,4.67)	(-2.95,1.74)	(-2.13,2.56)	(-3.53,3.36)	(-4.14,2.67)	(-2.80,3.95)
ΣOPs	T2	1.87	1.62	1.19	1.42	1.61	2.44	2.01
		(-0.87,4.61)	(-1.04,4.27)	(-1.55,3.93)	(-1.35,4.19)	(-2.50,5.72)	(-1.56,6.45)	(-1.98,6.00)
ΣOPs	T3	2.25	2.21	3.40	2.47	2.53	4.33	3.61
		(-0.49,4.99)	(-0.44,4.86)	(0.67,6.14)	(-0.30,5.23)	(-1.58,6.63)	(0.33,8.33)	(-0.38,7.59)
ETU	T2	3.18	1.59	-0.56	1.15	-0.87	0.10	0.28
		(0.64,5.71)	(-1.25,4.44)	(-3.18,2.07)	(-1.46,3.76)	(-4.69,2.96)	(-3.69,3.89)	(-3.47,4.02)
ETU	T3	0.48	-0.15	-1.16	-0.78	-3.00	-2.60	-2.75
		(-2.12,3.07)	(-3.06,2.77)	(-3.85,1.53)	(-3.45,1.89)	(-6.91,0.92)	(-6.48,1.27)	(-6.58,1.09)

p<0.05; p<0.10

Model adjustment: Age, BMI, alcohol consumption, season of urine collection, urine creatinine, maternal education

Increased behavioral problems: higher concentration of IMPy, TCPy and ΣOPs is associated with increased externalizing and internalizing problems.

Take Home Messages

Our results over the last 25 years show that the population is exposed to low concentrations of many environmental pollutants that are relevant from a public health point of view. It is necessary to control the production and distribution of these endocrine active chemicals.

Exposure/effect combined biomarkers strengthen the concern that the **internal exposure to some endocrine disrupting chemicals** are linked to a **variety of human reproductive and neurocognitive health outcomes**

We should measure the effects of combined EDC exposure (actual exposure scenario) rather than relating health outcomes to individual chemicals.

When we assess the findings gathered in different areas of endocrinology together with the present results, we observe a full and coherent cycle.