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COMPUESTOS ORGANOCLORADOS Y CÁNCER DE PÁNCREAS EXOCRINO

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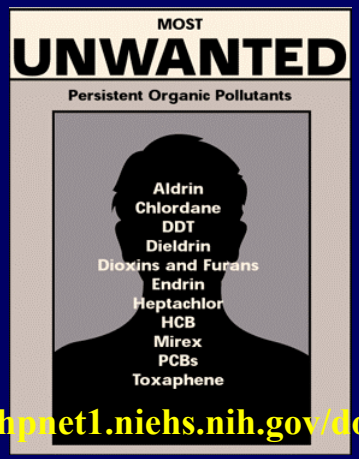
Background

- Relationship between exposure to organochlorine compounds and risk of several major types of cancer is receiving abundant attention, yet
- No data on internal concentration of organochlorine compounds and risk of exocrine pancreatic cancer.



http://ehpnet1.niehs.nih.gov/docs/1999

"The DDT Debacle"

Env Health Perspect 1999; 107: A24-A25.

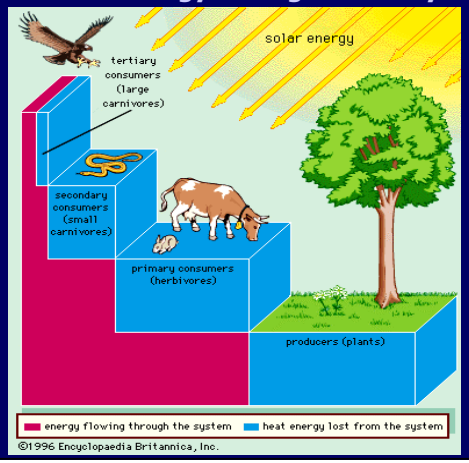
"The DDT Debacle"

"… 30,000 metric tons of DDT were produced by six countries in 1995 for use against malaria…"

"…tackling continued DDT use is the most pressing issue…"

Env Health Perspect 1999; 107: A24-A25.

Transfer of energy through an ecosystem



- **"In spite of the 1972 U.S. ban of DDT, human exposure to DDT potentially is great because of its extensive former use and the persistence of the compound and its metabolites in the environment."**

National Toxicology Program
8th. Report on Carcinogens (1998)
http://ntp-server.niehs.nih.gov/Main_pages/NTP_8RoC_pg.html

- **DDT continues to be used. Total global use (worldwide) may be as great in the 1990s as it was in the 1970s.**

– Smith D. *Int J Epidemiol* 1999.

– Lindström G et al. *Env Health Perspect* 1995.

Surveys in Spain:

- **83% of lamb samples contained DDT. HCB and HCH were detected in 100% of lamb and pork. PCBs in 50% of fish (congeners 138, 153 and 180).**

– Herrera A et al. *J Food Protect* 1994, 1999; *J Agricult Food Chem* 1996, 1998; *Food Addit Contam* 1995.

- **Lazaro R, et al. Levels of selected polychlorinated biphenyl congeners in total diet samples from Aragón, Spain. *J Food Protect* 1999; 62: 1054-8.**
- **Ariño A, et al. The effect of commercial processing on incurred residues of DDE in meat products. *Food Addit Contam* 1995; 12: 559-66.**

Spain:

- **Highest DDT levels in human breast milk of Western Europe during `60s to `80s.**

– Smith D. *Int J Epidemiol* 1999

IARC Evaluation of Carcinogenicity

Agent	Overall evaluation		Evidence	
	Group	Carcinogenic to humans?	Animals	Humans
DDT*	2B	Possibly	Sufficient	Inadequate
PCBs*	2A	Probably	Sufficient	Limited

* Reasonably anticipated to be a human carcinogen (8th Report on Carcinogens, 1998)

- **androgen and estrogen receptors have been demonstrated in normal and neoplastic pancreas, and polypeptide and steroid hormones modulate pancreatic carcinogenesis in rodents.**

– Longnecker DS. *Int J Pancreatol* 1991.

– Andrén-Sandberg A. In: Beger HG et al, eds. *The pancreas*. Blackwell, 1998.

Even if role as "tumor promoters" remains more widely accepted...

- **Some estrogen metabolites can be complete carcinogens (able to covalently bind to DNA, cause the initiating mutations).**
- **Hormonal effects may complete the development of tumors.**

– Roy & Liehr. *Mutat Res* 1999.
– Service RF. *Science* 1998.
– Yager & Liehr *Annu Rev Pharcol Toxicol* 1996.

- **Some epidemiologic studies observed that *occupational* exposure to DDT, PCBs and other OCs increased risk EPC.**
- **But epi studies generally negative.**

– **Weiderpass E et al. *Scand J W Env Health* 1998.**
– **Anderson KE et al. In: Schottenfeld D, Fraumeni JF Jr, eds. *Cancer E & P... 2nd. ed.* OUP, 1996.**
– **Longnecker MP et al. *Annu Rev Public Health* '97**

DDT and related compounds and risk of pancreatic cancer

Garabrant DH, Held J et al. *JNCI 1992; 84: 764-71.*

	DDT family	DDT	Ethylan	DDD
All subjects	3.3*	4.8*	5.0*	4.3*

*$P \leq 0.02$

DDT and related compounds and risk of pancreatic cancer

Malats N, Real FX, Porta M.
+ Garabrant DH, Held J, Homa D. *JNCI* 1993; 85: 328-9.

	DDT family	DDT	Ethylan	DDD
All subjects	3.3*	4.8*	5.0*	4.3*
Cytologically confirmed	21.0*	∞*	∞*	15.4*
Death certificate	0.8	1.0	2.6	1.4

*$P \leq 0.02$

Classical epidemiological approach: Occupation and EPC

Agent	MRR	95% CI
Chlorinated hydroc. solvents	1.3	1.0 – 1.8
Insecticides	1.5	0.6 – 3.7
Nickel	1.9	1.2 – 3.2
PAHs	1.5	0.9 – 2.5

Ojajärvi A, Partanen T, Ahlbom A, et al. 2000.

- But epidemiologic studies generally been negative…

Probably because of difficulty of estimating cumulative personal exposure to organochlorines.

Serum levels provide accurate and specific estimates of individual internal dose.

PANKRAS II Study

Designed in 1990-91, 5 centers, prospective, one of the primary aims was to assess interactions between specific genetic alterations (notably, K-*ras* mutations) and environmental, occupational and lifestyle factors.

Porta M et al. *J Epidemiol Community Health* 1999; 53: 702-9.

PANKRAS II Study: Subjects included

Diagnostic Group	N
Exocrine Pancreatic Cancer	185
Cancer Extrahepatic Biliary System	128
Nonmalignant Diseases Pancreas	166
Benign Biliary Diseases	54
Other Benign Pathologies	22
Other Neoplasms	47
EPC Controls (1 hospital)	29
Total PANKRAS II	631

Exocrine pancreatic cancer	N	(%)
Total number of patients	185	(100)
With K-*ras* status established	121	(65)
With serum OCs measured	51	(28)

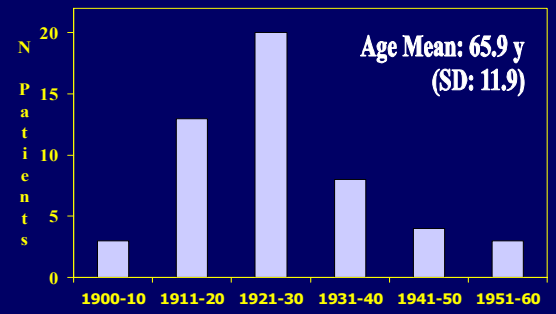
51 vs. 134 rest of EPC cases

	51	134	P-value
Males (%)	54.9	61.2	0.541
Age *	67.0	67.7	0.599
Interview minutes*	25	25	0.565
Smokers (%)	56.9	55.3	0.983
Alcohol drink. (%)	70.6	75.2	0.665
Coffee drink. (%)	78.4	88.5	0.147

*median

- Prospective collection of tumour cytohistological material during hospital stay.
- Respect for usual clinical practice.
- Independent review by 2 pathologists.
- Prospective collection of biologic samples: serum, plasma, leucocytes, hematies, urine, hair, eyebrows, nails.

"Because of the ubiquity of DDT, everyone born since the mid-1940s has had a lifetime of exposure to DDT and storage of it in fatty tissues."



- **Serum levels of organochlorine compounds were measured by gas chromatography with electron-capture detection and negative ion chemical ionization mass spectrometry.**

– Grimalt J, Sunyer J, Sala M et al.
Environ Health Perspect 1997
J Chromatogr A 1997
J Chromatogr A 1998
Occup Environ Med 1999
Arch Environ Health 1999

- **Individual adjustment by total lipids :**

TL = 2.27*(total cholesterol [mg/100 mL]) + (triglycerides [mg/100 mL]) + 62.3

OC adjusted by TL [μg / g lipid] = (OC [ng/mL] * 100) / (TL [mg/100 mL])

– Phillips DL et al. *Arch Environ Contam Toxicol* 1989; 18: 495-500.

Characteristics of cases and controls

	CASES (n = 51)	CONTROLS (n = 26)
Age (mean±SD)	65.9±11.9	73.2±9.8
Males (%)	54.9	46.1
Ever-smokers (%)	56.9	34.6
Reg. coffee drinkers (%)	78.4	80.8
Cholesterol (mean±SD)	214.1±110.7	203.6±52.8
median	188	209
Triglycerides (mean±SD)	179.9±101.7	159.8±151.2
median	153	119

Lipid mobilisation ➔ serum Ocs ?
OCs by stage at diagnosis

(N=51)	I	II	III	IV	P-value
Number of cases	9	9	9	24	-----
Mutated (%)	55.6	88.9	77.8	58.3	0.613
Total Lipids	668.4	887.4	718.3	694.6	0.451
ppDDE [crude]	17.9	26.1	15.9	17.5	0.683
ppDDE [lipid-adjusted]	2.48	3.03	2.85	2.68	0.979
Total PCB [crude]	5.99	9.65	9.55	9.49	0.278
Total PCB [lipd-adj.]	0.90	1.11	1.38	1.56	0.119

Potential confounders? (n=51)

	MALES	SMOKERS	COFFEE
AGE	±young	±young	≈
TOT LIPIDS	↑	↑	≈
3 PCBs	↑	≈	↑
DDE	≈	↓	↑
DDT	↓	↓	↑

➲ Low or null confounding by sex, smoking or coffee drinking.

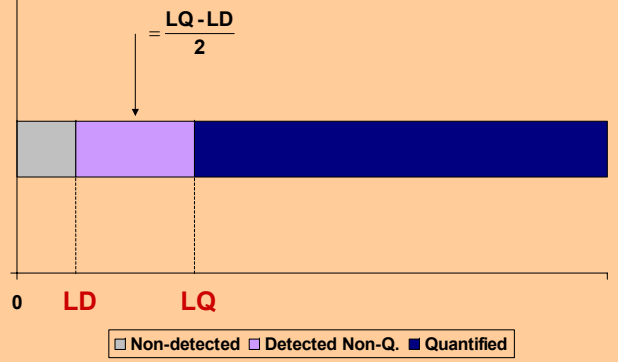
Detection and Quantification Limits

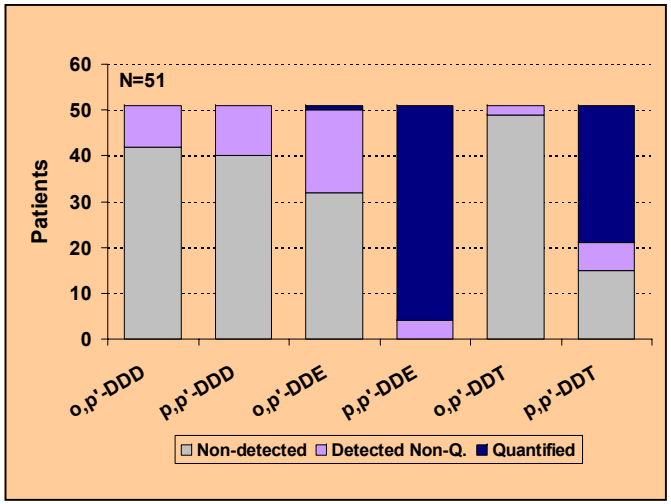
	Detection Limit	Quantific. Limit	
PCB 28	0.14	0.48	
PCB 52	0.24	0.81	
PCB 101	0.25	0.83	
PCB 118	0.24	0.81	
PCB 138	0.1	0.33	
PCB 153	0.24	0.79	
PCB 170	0.4	1.3	
PCB 180	0.4	1.3	
PCB 187	0.4	1.3	
PCB 194	0.4	1.3	(ng / mL)

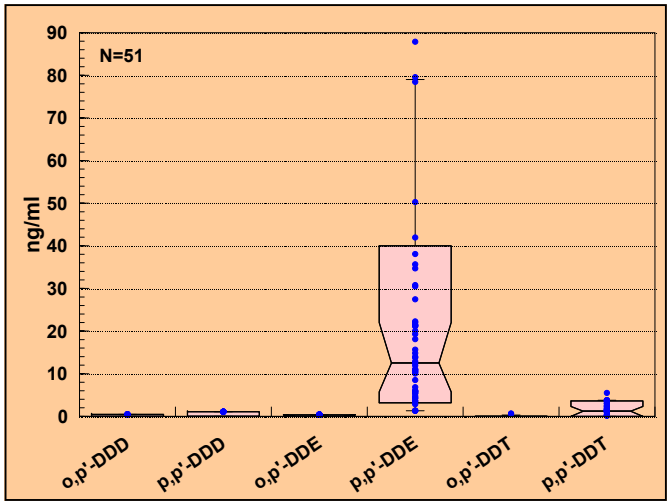
Detection and Quantification Limits

	Detection Limit	Quantification Limit	
α-HCH	0.2	0.6	
β-HCH	0.6	2.1	
γ-HCH	0.2	0.8	
HCB	0.23	0.76	
PENTACB	0.12	0.4	
OCE	0.26	0.84	
p,p'-DDE	0.6	2	
p,p'-DDT	0.09	0.3	
p,p'-DDD	0.54	1.6	
o,p'-DDT	0.28	0.94	
o,p'-DDE	0.17	0.5	
o,p'-DDD	0.2	0.68	(ng / mL)

LOD and LOQ / inferred values




N=51
Patients
60
50
40
30
20
10
0
o,p'-DDD
p,p'-DDD
o,p'-DDE
p,p'-DDE
o,p'-DDT
p,p'-DDT
Non-detected
Detected Non-Q.
Quantified


N=51
ng/ml
90
80
70
60
50
40
30
20
10
0
o,p'-DDD
p,p'-DDD
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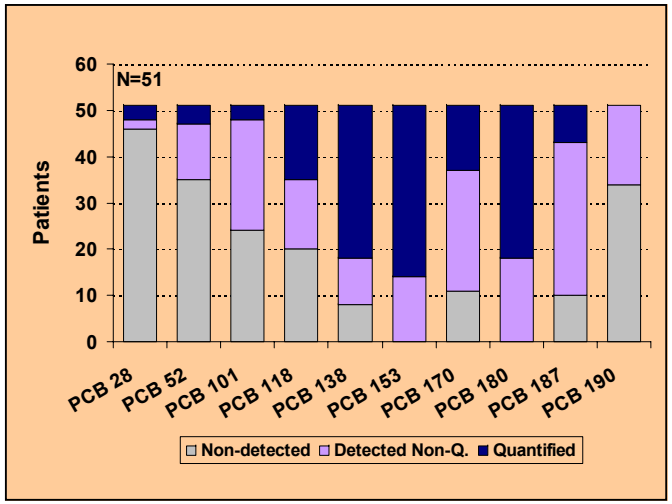
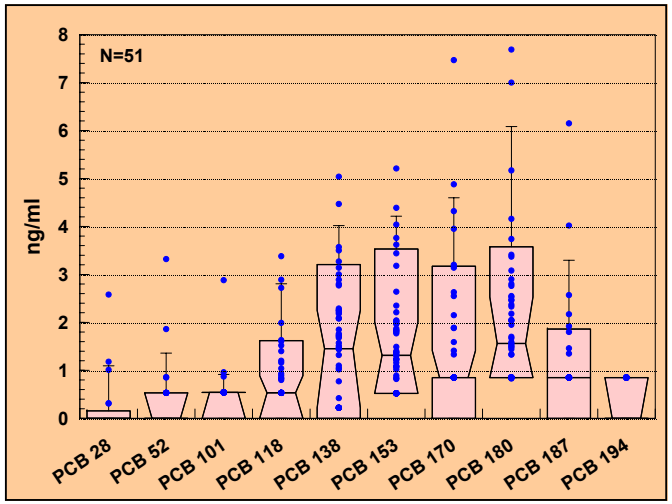
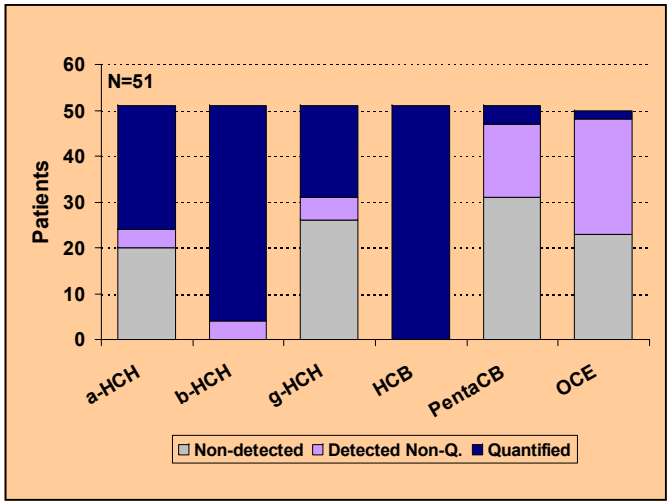
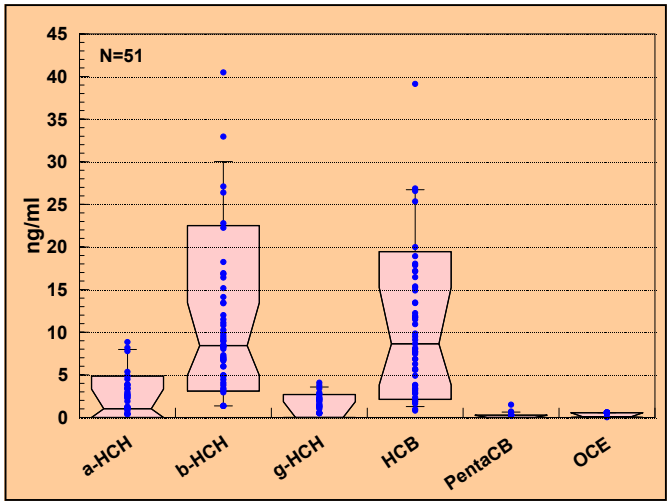
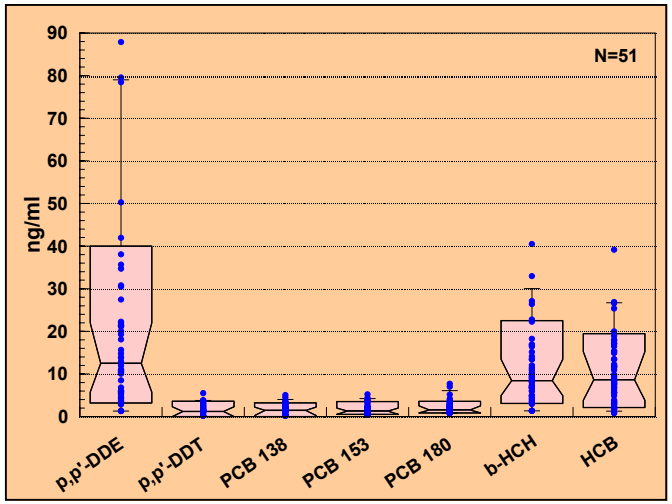
p,p'-DDE
o,p'-DDT
p,p'-DDT


N=51
Patients
60
50
40
30
20
10
0
PCB 28
PCB 52
PCB 101
PCB 118
PCB 138
PCB 153
PCB 170
PCB 180
PCB 187
PCB 190
Non-detected
Detected Non-Q.
Quantified


N=51
ng/ml
8
7
6
5
4
3
2
1
0
PCB 28
PCB 52
PCB 101
PCB 118
PCB 138
PCB 153
PCB 170
PCB 180
PCB 187
PCB 194







Spearman correlation coefficients

(n=51)

	DDT	DDE	PCB138	PCB153	PCB180
AGE	0.322*	0.195	–0.062	0.068	0.067
TL	0.183	0.223	0.299*	0.312*	0.402*

*P<0.05 TL = Total Lipids

Spearman correlation coefficients

(n=51)

	TOTAL PCBs	PCB138	PCB153	PCB180
DDT	0.199	0.088	0.255	0.175
DDE	0.303*	0.262	0.434*	0.261

*P<0.05

p,p'-DDT

	Cases (n=51)	Controls (n=26)	P-value
Mean±SD (ng/ml)	1.35±1.40	0.53±0.67	0.001*
Median	1.20	0.20	0.047§
			<0.001¶

*Student's *t*-test. §Mann-Whitney's U test. ¶Covariance analysis, adjusting by age, sex, total lipids, smoking, alcohol and coffee drinking.

p,p'-DDE

	Cases (n=51)	Controls (n=26)	P-value
Mean±SD (ng/ml)	18.80±19.65	9.41±7.25	0.003*
Median	12.49	7.59	0.030§
			0.009¶

*Student's *t*-test. §Mann-Whitney's U test. ¶Covariane analysis, adjusting by age, sex, total lipids. smoking, alcohol and coffee drinking.

Cases of EPC vs. controls, by tertiles.

Tertiles (µg / g lipid)		Crude OR	Crude P for trend (OR 95%CI)	Adjusted * OR	Adjusted * P for trend (OR 95%CI)
p,p'-DDT	Nd+DNq	1.00	0.040		
	≤ 0.225	1.41	(0.46-4.36)		
	> 0.225	4.32	(1.08-17.31)		
p,p'-DDE	≤ 0.950	1.00	0.052		
	≤ 2.350	1.00	(0.33-3.01)		
	> 2,350	3.85	(1.03-14.44)		

Tertiles based on distribution among 77 patients
ORs derived from values individually-adjusted by total lipids

Cases of EPC vs. controls, by tertiles.

Tertiles (µg / g lipid)		Crude OR	Crude P for trend (OR 95%CI)	Adjusted * OR	Adjusted * P for trend (OR 95%CI)
p,p'-DDT	Nd+DNq	1.00	0.040	1.00	0.002
	≤ 0.225	1.41	(0.46-4.36)	2.99	(0.69-12.89)
	> 0.225	4.32	(1.08-17.31)	15.77	(2.68-92.89)
p,p'-DDE	≤ 0.950	1.00	0.052	1.00	0.025
	≤ 2.350	1.00	(0.33-3.01)	1.19	(0.34-4.09)
	> 2.350	3.85	(1.03-14.44)	5.56	(1.26-24.61)

Tertiles based on distribution among 77 patients
ORs derived from values individually-adjusted by total lipids
*Adjusted by age, gender, and tobacco, coffee and alcohol use.

PCB 180

	Cases (n=51)	Controls (n=26)	P-value
Mean±SD (ng/ml)	2.01±1.49	1.30±0.58	0.004*
Median	1.56	0.85	0.040§
			0.009¶

*Student's *t*-test. §Mann-Whitney's U test. ¶Covariane analysis, adjusting by age, sex, total lipids. smoking, alcohol and coffee drinking.

methodologic issues

1. Selection of subjects / samples
2. Matching in the case-case design
3. Potential confounders
4. LOD and LOQ / inferred values
5. "Total PCBs"
6. Lipid mobilisation → serum Ocs ?
7. Conditional vs. unconditional logistic regression

GRACIAS POR SU ATENCIÓN

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