

Table S1. Differences between Spanish children included in the main analyses (N=1342) and Spanish children excluded (N=569).

Characteristics	Inclusion		p-value
	Not included in main analysis (N=569)	Included in main analysis (N=1342)	
Characteristics of the children			
Male Sex (%)	48.1	51.8	0.18
N missing	157	3	
Preterm (<37 weeks, %)	6.0	3.8	0.05
N missing	84	2	
Low birth-weight (<2500g, %)	7.9	5.3	0.04
N missing	89	4	
Predominant breastfeeding (%)			<0.001
0 weeks	26.8	19.2	
1-16 weeks	37.5	32.7	
17-24 weeks	27.7	36.1	

>24 weeks	7.9	12.1	
N missing	241	47	
			<0.001
Day-care attendance	22.5	34.3	
N missing	267	14	
Region (%)			<0.001
Gipuzkoa (N=638)	19.3	37.3	
Sabadell (N=657)	20.7	33.9	
Valencia (N=855)	59.9	28.8	
N missing	0	0	
LRTIs [†] at 12/14 months (%)	32.1	35.4	0.32
N missing	329	0	
Wheeze at 12/14 months (%)	24.6	33.6	<0.001
N missing	228	0	

Characteristics of the mother

Organochlorine concentrations in

maternal serum			
DDE (GM, GSD)	111.6 (2.2)	119.4 (2.2)	0.21
HCB (GM, GSD) *	36.8 (2.3)	44.3 (2.3)	<0.001
ΣPCBs (GM, GSD) [‡]	101.3 (1.8)	112.4 (1.8)	<0.001
N missing	314	0 (2)	
Age, years (mean, SD)	29.8 (4.6)	30.9 (4.0)	<0.001
N missing	0	0	
Pre-pregnancy weight, kg (mean, SD)	61.8 (13.2)	62.7 (11.7)	<0.001
N missing	0	0	
Social class (%)			0.08
Non-manual jobs	71.5	76.2	
Manuals jobs	27.2	23.0	
Unknown or unclassifiable	1.2	0.8	
N missing	0	0	
Education (%)			<0.001

Primary school	33.1	23.6	
Secondary	42.3	39.7	
University	24.7	36.7	
N missing	1	3	
Smoking during pregnancy (%)	26.9	16.8	<0.001
N missing	85	19	
Smoking during the first year (%)	35.4	26.6	0.02
N missing	267	17	
Maternal allergy and/or asthma (%)	27.0	27.2	0.92
N missing	2	1	
Parity (First child, %)	57.3	55.1	0.38
N missing	0	1	
Diet of the mother (g/day, mean, SD)			
Meat	116.4 (48.7)	113.2 (42.0)	0.14
Fish	60.7 (32.1)	66.8 (30.0)	<0.001

Vegetables & fruit	484.4 (240.3)	516.3 (212.9)	0.004
N missing	0	0	

DDE= dichlorodiphenyldichloroethylene, HCB= hexachlorobenzene, PCBs= polychlorinated biphenyls.

GM= Geometric Mean, SD=standard deviation.

The percentage of missing values within the non-included population is much higher than in the included population because in non-included already a 34.2% of the children either died or withdrew the study at birth or either did not attend the visit at 12/14 months.

[†]This is according to the final definition of having LRTI used in this study.

*One child was excluded from the analysis with HCB because it was an outlier (N=1341).

[‡]Two children had no information for PCBs within the Spanish population and one was excluded from the analysis with ΣPCBs because it was an outlier (N=1339).

Table S2. Associations between confounders and LRTIs and wheezing after adjusting for all confounders.

	DDE (N=1342)			sumPCBs (N=1339)		
	RR	95%CI	p-value	RR	95%CI	p-value
LRTIs						
Q1	1.16	(0.94, 1.43)	0.16	0.98	(0.80, 1.20)	0.83
Q2	1.33	(1.08, 1.62)	0.01	0.94	(0.75, 1.17)	0.56
Q3	1.20	(0.96, 1.51)	0.11	0.84	(0.65, 1.08)	0.17
Gipuzkoa region	0.93	(0.79, 1.10)	0.40	0.94	(0.79, 1.13)	0.52

Valencia region	0.72	(0.59, 0.88)	0.00	0.78	(0.64, 0.96)	0.02
Male sex	1.29	(1.12, 1.49)	0.00	1.27	(1.10, 1.47)	0.00
Age of the mother	0.98	(0.96, 1.00)	0.06	0.99	(0.97, 1.01)	0.51
Pre-pregnancy weight of the mother	1.00	(1.00, 1.01)	0.10	1.00	(1.00, 1.01)	0.19
Allergic or asthmatic mother	1.25	(1.08, 1.45)	0.00	1.26	(1.09, 1.46)	0.00
Multiparous	1.69	(1.45, 1.97)	0.00	1.66	(1.42, 1.94)	0.00
Maternal smoking during the 1st year of life	1.08	(0.88, 1.32)	0.48	1.08	(0.88, 1.32)	0.48
Maternal smoking during pregnancy	1.05	(0.83, 1.34)	0.69	1.05	(0.82, 1.33)	0.72
Manual jobs	1.09	(0.92, 1.29)	0.33	1.07	(0.90, 1.28)	0.42
Unclassifiable	1.06	(0.46, 2.42)	0.89	1.03	(0.46, 2.35)	0.93
Breastfeeding 1-16 weeks	0.99	(0.81, 1.21)	0.91	0.97	(0.80, 1.19)	0.80
Breastfeeding 17-24 weeks	0.89	(0.73, 1.09)	0.28	0.88	(0.72, 1.07)	0.21
Breastfeeding >24 weeks	1.04	(0.81, 1.33)	0.76	1.03	(0.81, 1.32)	0.79
Day care attendance	1.43	(1.24, 1.67)	0.00	1.45	(1.25, 1.69)	0.00

Wheezing

Q1	1.10	(0.88, 1.36)	0.41	1.02	(0.84, 1.25)	0.83
Q2	1.30	(1.06, 1.59)	0.01	0.96	(0.78, 1.19)	0.73
Q3	1.11	(0.89, 1.40)	0.35	0.85	(0.67, 1.07)	0.17
Gipuzkoa region	0.97	(0.81, 1.15)	0.70	0.99	(0.82, 1.18)	0.89

Valencia region	0.69	(0.56, 0.85)	0.00	0.73	(0.59, 0.90)	0.00
Male sex	1.31	(1.13, 1.52)	0.00	1.29	(1.11, 1.50)	0.00
Allergic or asthmatic mother	1.16	(0.99, 1.35)	0.07	1.17	(1.00, 1.38)	0.05
Multiparous	1.59	(1.37, 1.84)	0.00	1.61	(1.39, 1.88)	0.00
Maternal smoking during the 1st year of life	1.08	(0.87, 1.33)	0.48	1.07	(0.86, 1.32)	0.55
Maternal smoking during pregnancy	1.30	(1.03, 1.65)	0.03	1.30	(1.02, 1.65)	0.03
Manual jobs	1.23	(1.04, 1.46)	0.02	1.22	(1.03, 1.44)	0.02
Unclassifiable	0.55	(0.15, 2.09)	0.38	0.57	(0.15, 2.15)	0.40
Breastfeeding 1-16 weeks	1.05	(0.86, 1.28)	0.66	1.02	(0.83, 1.24)	0.86
Breastfeeding 17-24 weeks	0.78	(0.63, 0.97)	0.02	0.77	(0.62, 0.94)	0.01
Breastfeeding >24 weeks	0.88	(0.67, 1.15)	0.34	0.87	(0.66, 1.14)	0.31
Day care attendance	1.50	(1.28, 1.75)	0.00	1.52	(1.30, 1.78)	0.00

DDE= dichlorodiphenyldichloroethylene, PCBs= polychlorinated biphenyls.

Table S3. Number of children (N), cases of LRTIs during the first 12-14 months of life (%) and adjusted relative risk (RR (95% Confidence Interval)) for continuous exposure and for each quartile of DDE exposure within the Spanish study population by region (N=1342^{*†}).

Gipuzkoa (N=500)			Sabadell (N=455)			Valencia (N=387)		
N	Adjusted	p-	N	Adjusted	p-	N	Adjusted	p-
(% LRTI	RR (95%CI)	value	(% LRTI	RR (95%CI)	value	(% LRTI	RR (95%CI)	value
cases)			cases)			cases)		

DDE

Continuous	500 (36.4)	1.16 (0.98, 1.37)	0.08	455 (39.6)	1.08 (0.92, 1.27)	0.35	387 (29.2)	1.01 (0.82, 1.26)	0.9
<72.6	172 (31.4)	1		129 (34.9)	1		35 (28.6)	1	
72.6-115.9	149 (38.3)	1.25 (0.93, 1.69)	0.14	109 (38.5)	1.09 (0.80, 1.49)	0.57	77 (26.0)	0.99 (0.52, 1.87)	0.97
115.5-191.7	107 (40.2)	1.35 (0.98, 1.86)	0.07	127 (43.3)	1.15 (0.85, 1.56)	0.37	102 (35.3)	1.34 (0.76, 2.35)	0.31
>191.7	72 (38.9)	1.45 (1.01, 2.08)	0.04	90 (42.2)	1.17 (0.83, 1.66)	0.36	173 (27.2)	0.94 (0.53, 1.66)	0.83

HCB*

Continuous	500 (36.4)	1.10 (0.93, 1.31)	0.28	455 (39.6)	1.02 (0.85, 1.23)	0.82	386 (29.3)	1.02 (0.85, 1.22)	0.84
<26.4	166 (36.1)	1		114 (39.5)	1		56 (25.0)	1	
26.4-46.4	152 (34.2)	0.98 (0.73, 1.33)	0.92	137 (37.3)	0.94 (0.70, 1.26)	0.66	46 (30.4)	1.09 (0.57, 2.07)	0.79

46.4-79.0	118	1.26	0.13	122	0.91	0.57	95	1.13	0.66
	(42.4)	(0.93, 1.71)		(36.9)	(0.65, 1.26)		(30.5)	(0.65, 1.94)	
>79.0	64	1.05	0.82	82	1.01	0.94	189	1.02	0.93
	(31.3)	(0.68, 1.26)		(47.6)	(0.70, 1.46)		(29.6)	(0.60, 1.74)	
ΣPCBs[†]									
Continuous	498	0.86	0.31	455	0.99	0.97	386	1.13	0.38
	(36.4)	(0.65, 1.14)		(39.6)	(0.74, 1.33)			(0.86, 1.48)	
<79.4	69	1		204	1		62	1	
	(42.0)			(37.3)			(35.5)		
79.4-113.7	126	0.96	0.83	129	0.95	0.74	80	0.70	0.16
	(36.5)	(0.67, 1.38)		(41.9)	(0.72, 1.27)		(26.3)	(0.43, 1.15)	
113.7-158.6	134	1.03	0.86	86	0.95	0.75	115	0.63	0.07
	(41.0)	(0.71, 1.50)		(41.9)	(0.67, 1.33)		(24.4)	(0.38, 1.04)	
>158.6	169	0.78	0.26	36	0.91	0.69	129	0.77	0.27
	(30.2)	(0.51, 1.20)		(38.9)	(0.58, 1.43)		(31.8)	(0.49, 1.23)	

DDE= dichlorodiphenyldichloroethylene, HCB= hexachlorobenzene, PCBs= polychlorinated biphenyls.

LRTIs model adjustment: sex of the child, age and pre-pregnancy weight of the mother, allergic or asthmatic mother, parity (first child) and social class, predominant breastfeeding, maternal smoking status (during pregnancy and during the 1st year of life of the child) and day-care attendance during the first year of life.

*One child within the Valencia region was excluded from the analysis with HCB because it was an outlier.

†Two children had no information for PCBs within the Gipuzkoa region and one from the Valencia region was excluded from the analysis with ΣPCBs because it was an outlier.

Table S4. Results of the linear splines using log-transformed exposures and comparison between pooled-analysis and meta-analysis results for the association between DDE exposure (continuous and by quartiles) and LRTIs.

DDE			HCB			PCB		
Knots	(N)	RR (95%CI)	Knots	(N)	RR (95%CI)	Knots	(N)	RR (95%CI)
< 3.61	55	0.91 (0.40, 2.08)	< 3.75	617	0.93 (0.71, 1.23)	< 3.92	105	2.95 (0.66, 13.18)
3.61-5.82	1174	1.37 (0.55, 3.40)	>= 3.75	724	1.38 (0.84, 2.27)	3.92-4.84	679	0.27 (0.05, 1.6)
> 5.82	113	1.10 (0.50, 2.42)				>4.84-5.75	502	1.05 (0.4, 2.77)
						> 5.75	53	6.77 (0.72, 63.8)

Adjustment of all models: region, sex of the child, allergic or asthmatic mother, parity (first child) and social class, predominant breastfeeding, maternal smoking status (during pregnancy and during the 1st year of life of the child) and day-care attendance during the first year of life.

	DDE (N=1342)		HCb[#] (N=1341)		ΣPCBs[†] (N=1339)	
	RR	p-value	RR	p-value	RR	p-value
	(95%CI)	Heterogeneity	(95%CI)	Heterogeneity	(95%CI)	Heterogeneity
		(meta-analysis)		(meta-analysis)		(meta-analysis)
			Continuous			
Pooled-analysis	1.11		1.06		1.00	
	(1.00, 1.22)		(0.95, 1.17)		(0.86, 1.18)	
Meta-analysis	1.09	0.66	1.05	0.81	0.97	0.39
	(0.98, 1.2)		(0.94, 1.15)		(0.81, 1.13)	
			Quartiles			
Pooled-analysis						
Q2	1.16		0.96		0.98	
	(0.94, 1.43)		(0.79, 1.18)		(0.80, 1.20)	

Q3	1.33		1.08		0.94	
	(1.08, 1.62)		(0.88, 1.32)		(0.75, 1.17)	
Q4	1.20		1.06		0.84	
	(0.96, 1.51)		(0.84, 1.33)		(0.65, 1.08)	
Meta-analysis						
Q2	1.14	0.78	0.97	0.92	0.88	0.34
	(0.9, 1.37)		(0.77, 1.16)		(0.70, 1.06)	
Q3	1.24	0.84	1.04	0.39	0.83	0.09
	(0.98, 1.49)		(0.82, 1.26)		(0.63, 1.02)	
Q4	1.17	0.52	1.03	0.99	0.81	0.81
	(0.90, 1.45)		(0.77, 1.28)		(0.60, 1.02)	

Adjustment of all models: region, sex of the child, allergic or asthmatic mother, parity (first child) and social class, predominant breastfeeding, maternal smoking status (during pregnancy and during the 1st year of life of the child) and day-care attendance during the first year of life.

[#]One child was excluded from the analysis with HCB because it was an outlier (N=1341).

†Two children had no information for PCBs within the Spanish population and one was excluded from the analysis with Σ PCBs because it was an outlier (N=1339).