



Review

Effects of persistent organic pollutants on the developing respiratory and immune systems: A systematic review

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ABSTRACT

Background: Disruption of developing immune and respiratory systems by early-life exposure to persistent organic pollutants (POPs) could result into reduced capacity to fight infections and increased risk to develop allergic manifestations later in life.

Objectives: To systematically review the epidemiologic literature on the adverse effects of early-life exposure to POPs on respiratory health, allergy and the immune system in infancy, childhood and adolescence.

Methods: Based on published guidelines for systematic reviews, two independent researchers searched for published articles in MEDLINE and SCOPUS using defined keywords on POPs and respiratory health, immune function and allergy. Study eligibility criteria were defined to select the articles.

Results: This review of 41 studies finds limited evidence for prenatal exposure to DDE, PCBs and dioxins and risk of respiratory infections. Evidence was limited also for postnatal exposure to PCBs, specifically ndl-PCBs, and reduced immune response after vaccination in childhood. The review indicates lack of association between postnatal exposure to PCBs/ndl-PCBs and risk of asthma-related symptoms. For the other exposure–outcome associations reviewed evidence was inadequate.

Discussion and conclusion: Current epidemiological evidence suggests that early-life exposure to POPs can adversely influence immune and respiratory systems development. Heterogeneity between studies in exposure and outcome assessment and the small number of studies for any given exposure–outcome relationship currently make comparisons difficult and meta-analyses impossible. Also, mechanisms remain largely unexplored. Recommendations for significantly improving our understanding thus include harmonization of exposure and outcome assessment between studies, conduct of larger studies, long-term assessment of respiratory infections and asthma symptoms in order to identify critical periods of susceptibility, integration of the potential immunotoxic mechanisms of POPs, and use of new statistical tools to detangle the role of multiple exposures on multiple outcomes.

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Abbreviations: Ab, antibody; AOM, acute otitis media; BPA, bisphenol A; COX-2, cyclooxygenase-2; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; GIs, gastrointestinal infections; HCB, hexachlorobenzene; HCH, hexachlorohexane; HCE, heptachlor epoxide; HDM, house dust mite; Ig, immunoglobulin; IL, interleukin; INF- γ , interferon- γ ; LRTIs, lower respiratory tract infections; NK-cells, natural killer cells; PBDEs, polybromodiphenyl ethers; PCBs, polychlorinated biphenyls; dl-PCBs, dioxin-like polychlorinated biphenyls; ndl-PCBs, non-dioxin-like polychlorinated biphenyls; PCDD, polychlorinated dibenzo-*p*-dioxins; PCDFs, polychlorinated dibenzofurans; PFCs, perfluorinated compounds; PFDA, perfluorodecanoate; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate; PFNA, perfluorononanoic acid; PFHxS, perfluorohexane sulfonic acid; POPs, persistent organic pollutants; PPAR α , peroxisome proliferator-activated receptor; RAST, radioallergosorbent test; SEM, structural equation models; SOB, shortness of breath; SPT, skin prick test; TDAR, T-cell-dependent IgM antibody responses; TEQ, toxic equivalent factor; TNF- α , tumor necrosis factor α ; URTIs, upper respiratory tract infections; WBC, white blood-cell count.

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1. Introduction

Acute respiratory infections in under 5-year olds are a worldwide cause of morbidity and mortality, accounting for about 20% of all childhood deaths, mostly in developing countries (Nair et al., 2010; Rudan et al., 2004). Further, the prevalence of asthma and allergy in children is more than 20% in some countries and still rising (Bousquet et al., 2011; Burr et al., 2006; Chad, 2001). Diverse studies have pointed environmental pollutants, including persistent organic pollutants (POPs), as important factors that can impact susceptibility to infections and the development of allergy and asthma during the first years of life (Winans et al., 2011). POPs are lipophilic synthetic compounds that persist in the environment and bioaccumulate through the food chain in human and animal fatty tissues and include a wide range of compounds, such as polychlorinated biphenyls (PCBs), dioxins, dichlorodiphenyldichloroethylene (DDE), hexachlorobenzene (HCB), and many other chemicals. Human exposure to POPs begins in the uterus, since most POPs cross the placental barrier (Covaci et al., 2002; Lackmann et al., 1999; Sala et al., 2001). After birth, newborns are exposed to POPs through breastfeeding, diet or by direct contact with materials containing these compounds (Aliyu et al., 2010; Fischer et al., 2006; LaKind et al., 2004). Poisoning incidents in the 1970s provided the first evidence of potential adverse health effects of exposure to high concentrations of PCBs on human respiratory and immune systems (Aoki, 2001; Guo et al., 2004); these studies revealed altered levels of immune markers, as well as higher frequencies of respiratory infections among both children and adults.

Because immune and respiratory systems develop and mature during pre and postnatal early life, these periods may be particularly susceptible to the effects of POPs. All major respiratory elements, including the bronchioles and alveolar ducts, appear before birth, alveoli proliferation continues after birth, and full maturation of the respiratory system is not complete until late adolescence (Dietert et al., 2000; Pinkerton and Joad, 2000). The ability of the body to produce a normal immune response following antigen exposure (immunocompetence) starts developing after birth and continuous during the first years of life (Dietert et al., 2000). This involves the development of the innate system (natural killer cells (NK-cells), eosinophils, basophils, neutrophils, macrophages or dendritic cells) that provides

immediate defense against infection, and the adaptive immune system (antibodies produced by B-cells and cell-mediate response regulated by cytokines released by T cells) that provides long-lasting or protective immunity through humoral response. Disruption of these systems during development by exposure to POPs may result into reduced capacity to fight infections and increased risk to develop allergic manifestations later in life (Bisgaard and Bonnelykke, 2010; Busse et al., 2010; Dietert et al., 2000; Puig et al., 2008).

Although some general reviews are available (Wigle et al., 2008; Winans et al., 2011), none has made a comprehensive and systematic evaluation of available epidemiological evidence on the effects of early-life POP exposure on the developing immune and respiratory systems. Our aim is thus to systematically review the epidemiologic literature on adverse effects of early-life exposure to POPs on respiratory health, allergy and the immune system in infancy, childhood and adolescence.

2. Materials and methods

2.1. Search of studies

A protocol was written based on the PRISMA statement guidelines for reporting systematic reviews and meta-analysis (Moher et al., 2010). The bibliographic search was carried out by two independent reviewers in the MEDLINE engine search (National Library of Medicine) and SCOPUS engine search using the following keywords: *outcome keywords* (“allergic rhinitis” or “allergic conjunctivitis” or asthma or “shortness of breath” or wheeze or wheezing or cough or “lung function” or otitis or bronchiolitis or bronchitis or pneumonia or “ear infection” or atopy or “atopic eczema” or eczema or “atopic dermatitis” or “food allergy” or “sensitization” or “eosinophilic gastroenteritis” or “immune system” or “upper respiratory tract infection” or “lower respiratory tract infection” or “immunoglobulin” or cytokines or lymphocytes or “B-cell” or “T-cell” or Macrophage or “Mast cell” or “NK cell” or interleukin or vaccination) combined with the following *keywords for POPs* (“aldrin” or “chlordane” or “dichlorodiphenyltrichloroethane” or “DDT” or “dichlorodiphenyldichloroethylene” or “DDE” or “dieldrin” or “endrin” or “heptachlor” or “hexachlorobenzene” or “HCB” or “Mirex” or “toxaphene” or “chlordecone” or “α-hexachlorocyclohexane” or

“ α -HCH” or “ β -hexachlorocyclohexane” or “ β -HCH” or “lindane” or “ γ -HCH” or “pentachlorobenzene” or “PeCB” or “polychlorinated biphenyls” or PCBs or “polybrominated biphenyls” or PBBs or “perfluorooctane sulfonic acid” or PFOS or “perfluorooctane sulfonyl fluoride” or “polybrominated diphenyl ether” or “polybromodiphenyl ethers” or PBDEs or “polychlorinated dibenzo-p-dioxins” or “polychlorinated dibenzofurans” or PCDDs or PCDFs or “dioxins” or “persistent organic pollutants” or “POPs”). *Limits:* Human, English, all child 0–18 years. Last search on September 18th 2012. Identification and first screening of the articles were performed using the information available in the title and the abstract. Doubts regarding the inclusion or exclusion of studies were resolved by discussion between the two independent researchers, and if no agreement was reached then a third researcher helped to decide. After the first selection, both reviewers read through the articles to decide whether they were eligible or not.

2.2. Study eligibility criteria

The selection criteria were that the article had to: a) include newborns, children or adolescents as study subjects, b) measure individual exposure to POPs in human tissues or matrixes, or estimate individual exposure during pregnancy (prenatal exposure), around birth (perinatal exposure), or during childhood (postnatal exposure), c) include health outcomes related to respiratory health, allergy and immune function, d) be an original research article: abstracts, case reports, ecological studies and letters to the editor were excluded, e) report on an epidemiologic study with a prospective, cross-sectional or case-control design, and f) be written in the English language.

2.3. Evaluation of evidence

In order to evaluate evidence, we first classified as good quality the studies that had prospective study designs, relatively large study size (> 100 participants), good use of exposure information and multivariate confounder adjustment (Table C, Supplemental material).

We classified strength of evidence for associations between each combination of specific pollutant exposure and specific outcome (separately by pre and postnatal exposure period) based on the levels of evidence used by the International Agency for Research on Cancer (IARC, 2006). Two independent reviewers classified the evidence; in case of disagreement a third reviewer gave the decision. Evidence for causal relationships for each chemical compound – outcome was classified as: *sufficient* – if most of the studies, including good quality studies, report an association, but evidence is not yet conclusive enough to conclude that there is an association or a causal relationship, *limited* – several good quality, independent, studies report an association, but evidence is not yet conclusive enough, *inadequate* – if associations are reported in one or more studies, but insufficient quality, insufficient number of studies, lack of consistency, and/or lack of statistical power preclude a conclusion regarding the presence or absence of an association, *evidence for lack of association* – several good quality studies are consistent in showing no association.

We organized the review by outcome and then by chemical compound, age of the participants (<two years, referred as “younger” and >two years, referred as “older”), and by time of exposure (pre or postnatal).

3. Results

A total of 147 articles were identified in MEDLINE, of which 42 were selected as potentially eligible by both reviewers, who discussed the inclusion of other ten articles; four were finally included (one of them after discussing with a third researcher). In total, 46 articles initially appeared to meet the eligibility criteria, but after reading, seven articles were excluded: four were ecological studies

(Belles-Isles et al., 2002; Lan et al., 1990; Landrigan et al., 1979; Milosevic-Djordjevic et al., 2005), one study used breastfeeding as proxy of exposure to POPs (Karmaus et al., 2003), and two studies were carried out on adults (Daniel et al., 2002; Vine et al., 2001). Finally, one study was also found in MEDLINE but not through the keyword search (Jusko et al., 2012), and another one was found via SCOPUS (Grandjean et al., 2012). All the selection process is detailed in the supplemental material (Figure A). Table A of the supplemental material shows the 41 final selected articles, which are based on 28 separate study populations from 13 countries. It also shows the study design of the articles (mostly longitudinal birth cohorts: N=35), the age of the participants at the time of outcome assessment (ranging from birth up to 19 years old), information on exposure assessment methods, and exposure levels.

3.1. Exposure assessment

Practically all articles (N=35) evaluated PCB and/or dioxin compounds, whereas other POPs were assessed to a lesser extent: seventeen articles assessed DDE, ten assessed HCB and ten assessed a diversity of other POPs such as hexachlorohexane congeners (HCHs), dichlorodiphenyltrichloroethane (DDT), dieldrin, chlordane, perfluorinated chemicals or polybromodiphenyl ethers (PBDEs). Biological matrixes used to measure exposure to these compounds differed between studies; most used maternal blood obtained during pregnancy (N=20), followed by breast milk (N=16), children's serum (N=17) and cord blood (N=11). Three articles used placenta and/or adipose tissue. Articles variously considered breast milk as a marker of pre, peri or postnatal exposure; however, postnatal exposure was often the product of concentrations of POPs measured in breast milk and the number of weeks of breastfeeding or the amount of milk consumed by the child. In one study the intake of dioxins and PCBs during pregnancy was estimated from dietary questionnaires and validated with maternal serum concentrations in a subsample ($r=0.34$ – 0.37 , $p<0.05$) (Stolevik et al., 2011). Units of expression also differed; approximately half of the articles adjusted levels by lipids, whereas the other half did not. When measuring dioxins and/or dl-PCBs, the unit of expression was Toxic Equivalent Factor (TEQ). The specific compounds and congeners used within each study are indicated in Table A of the Supplemental material. It is important to note that in the present review the sum of PCBs can indicate either “unknown congeners” or a mix of non dioxin-like (ndl-) and dioxin-like (dl-) PCBs (ndl-PCBs were predominant in the sum of most of the studies). If only non dioxin-like or dioxin-like PCBs are included in the sum, then it is indicated as ndl-PCBs or dl-PCBs, respectively. When the exposures assessed are PCDDs or PCDFs it is indicated as dioxins, unless specifically indicated in the original study.

3.2. Infections

Overall, sixteen studies evaluated the effects of POPs on infections (Table 1 and Table B.1), mostly lower respiratory tract infections (LRTIs), upper respiratory tract infections (URTIs) and acute otitis media (AOM). Other infections included gastrointestinal infections (GIs), chicken pox, pertussis, measles, and others. Information on infections was most often collected through parental questionnaires asking about doctor-diagnosed infections (Dewailly et al., 2000; Gascon et al., 2012; Karmaus et al., 2001; Miyashita et al., 2011; Okada et al., 2012; Sunyer et al., 2005, 2010; Weisglas-Kuperus et al., 2000, 2004) or from the medical chart (Dallaire et al., 2004, 2006). Three studies asked specific questions on the number of infections but not specifically diagnosed by a doctor (Stolevik et al., 2011; ten Tusscher et al., 2001, 2003), one used open-ended questions (Glynn et al., 2008), and in one study it is not clearly specified how the information was obtained (Yu et al., 1998).

Table 1

Studies on persistent organic pollutants, respiratory and other infections and asthma symptoms and atopy (ordered by age group, year and author).

Author (Year)	Country & study design ^a	N	Child age ^b	Outcomes assessed		Exposure assessment ^d		Statistically significant main findings ^e
				Respiratory & other infections ^c	Asthma symptoms and atopy	Timing	Compound	
<2 years								
Rogan et al. (1987)	USA Cohort (I)	802	3, 6, 12, 18 m & 5 y	LRTIs & URTIs (NS), AOM, GIs	Asthma, reported eczema and allergy symptoms (only prevalences described)	Postnatal	ΣPCBs: DDE:	↓ Prevalence of LRTIs, URTIs & AOM in higher categories of exposure ↓ Prevalence of LRTIs, URTIs & AOM and of having allergy, ↑ prevalence of GIs in higher categories of exposure ↑ Total IgE levels ↑ Total IgE levels
Reichrtova et al. (1999)	Slovakia Cross-sectional	120	At birth (CB)		Total IgE	Prenatal	PCB118: DDE: HCB, other PCBs or POPs:	– – –
Dewailly et al. (2000)	Canada Cohort (I)	65–83	3, 7 & 12 m	AOM		Prenatal	Σ(ndl-)PCBs, Mirex: Dieldrin: HCB, DDE ^f : PCB153 ^{gh} : DDE ^f :	– – ↑ AOM from 4 to 7 m ↑ AOM from 0 to 12 m ↑ LRTIs at 6 m & GIs at 12 m ↑ AOM, URTIs & all infections at 6 m and URTIs & GIs at 12 m
Dallaire et al. (2004)	Canada Cohort (II)	199	6 & 12 m	Bronchitis, bronchiolitis, pneumonia, AOM, diverse URTIs ^g , GIs & all infections together		Prenatal		– – –
Kaneko et al. (2006)	Japan Cohort (II)	281	12 m		Total & specific IgE to HDM, milk egg	Postnatal Perinatal	ΣPCBs, PCB153 ^h , DDE PCDDs, PCDFs & dl-PCBs:	– –
Glynn et al. (2008)	Sweden Cohort (I)	190	3 m	Open general questionnaire on infections		Prenatal	ΣPCBs: PCB153 ^f , ndl-PCBs, dl-PCBs: DDE:	↑ Respiratory infections ↓ Respiratory infections –
						Postnatal	ndl-PCBs, dl-PCBs ^f , DDE ^f : ΣPCBs, PCB153:	↓ Respiratory infections –
Sunyer et al. (2010)	Spanish Cohort (II)	520	6 & 14 m	Bronchitis, bronchiolitis, pneumonia		Prenatal	DDE: ΣPCBs, HCB, β-HCH:	↑ LRTIs at age 6,14 m & recurrent LRTIs –
Jusko et al. (2011)	Slovakia Cohort (I)	350	6 m		Total IgE	Prenatal	ΣPCBs:	–
						Postnatal	Σ(ndl-)PCBs:	–
Miyashita et al. (2011)	Japan Cohort (IV)	364	18 m	AOM	Asthma, reported allergic diseases & eczema	Prenatal	ΣPCDFs: ΣPCDDs: dl-PCBs (non-ortho) ^f : dl-PCBs (mono-ortho) ^f : Total dioxins:	↑ AOM – ↑ AOM, food allergies ↑ Food allergies –
Stolevik et al. (2011)	Norway Cohort (I)	195	12 m	Pneumonia, URTIs (NS), AOM, GIs, urinary infections, chickenpox, exanthema subitum	Asthma, wheeze, reported eczema	Prenatal	ndl-ΣPCBs: Dioxins & dl-ΣPCBs:	↑ URTIs, exanthema subitum & wheeze ↑ URTIs, exanthema subitum & wheeze
Wang et al. (2011)	Taiwan Cohort (II)	244	At birth (CB), 2 y		Doctor diagnosed atopic dermatitis, total IgE	Prenatal	PFOA, PFOS: PFNA, PFHxS:	↑ Total IgE levels in CB –
Gascon et al. (2012)	Spanish Cohort (II extended) population)	1342 (Spanish population)	12–14 m	Bronchitis, bronchiolitis, pneumonia	Wheeze	Prenatal	DDE: ΣPCBs, HCB:	↑ LRTIs (& wheeze ¹) –
Okada et al. (2012) ^j	Japan Cohort (IV)	231–343	18 m	AOM	Wheeze, food allergy, eczema, total IgE	Prenatal	PFOS: PFOA:	– ↓ Total IgE
Tsuji et al. (2012) ^k	Japan Case-control	30	23 m		Specific IgE to egg, milk, wheat and HDM	Postnatal	ΣPCBs: ndl-PCB congeners: dl-PCB congeners:	↑ Milk IgE Not reported Not reported
>2 years								
Yu et al. (1998)	Taiwan Cohort (I)	31	8–16 y	Influenza, AOM, GIs	Asthma, allergic rhinitis	Postnatal	Dioxins:	↑ Influenza frequencies in Yucheng children vs. controls in the previous 6 m
Weisglas-Kuperus et al. (2000)	The NL Cohort (I)	175	42 m	Bronchitis, pneumonia, cough, chest congestion & phlegm, AOM, other diverse infections ¹	Asthma, SOB with wheeze, reported eczema & allergic reaction	Prenatal	ΣPCBs: Dioxins: dl-PCBs (planar & mono-ortho):	↓ SOB with wheeze (only maternal PCB levels) ↑ Cough, chest congestion & phlegm ↑ AOM
						Postnatal	ΣPCBs:	↑ AOM and chicken pox, ↓ allergic reaction

Karmaus et al. (2001)	Germany Cross-sectional (I)	343	7–10 y	Pneumonia, whooping cough (pertussis), AOM	Asthma, total IgE	Postnatal	ΣPCBs, HCB, β-HCH: DDE:	– ↑ Asthma, ↑ total IgE levels, ↓ AOM, ↓ whooping cough
							Combinations → High levels DDE + ΣPCBs: High levels DDE + HCB:	↑ AOM ↑ AOM
Ten Tusscher et al. (2001)	The NL Cohort (II + III)	29	7–12 y	Bronchitis, pneumonia, coughing spells, chest congestion, AOM	Lung function, reported atopy	Prenatal	Dioxins:	↑ Chest congestion, ↓ FEV ₁ /FVC (reduced lung function)
Van Den Heuvel et al. (2002)	Belgium Cross-sectional	200	17–18 y		Asthma, bronchial wheezing, rhinitis, reported atopy, hay fever, total IgE & RAST to HDM, cat, grass pollen	Postnatal	Dioxins: Σ(ndl-)PCBs: dl-PCBs:	↓ FEV ₁ /FVC (reduced lung function) ↑ Reporting ever asthma, hay fever ↓ Total IgE levels, positive RAST to HDM, cat & grass pollen, history of rhinitis
ten Tusscher et al. (2003)	The NL Cohort (III)	27	8 y	Bronchitis, pneumonia, coughing spells, AOM, chickenpox, measles	Asthma, dyspnoea, reported eczema & allergy	Prenatal	Dioxins & furans:	↓ Allergy
Weisglas-Kuperus et al. (2004)	The NL Cohort (I)	167	3–7 y	AOM, chickenpox	SOB with wheeze, reported allergic reaction	Postnatal	Dioxins & furans:	↓ Allergy
						Prenatal	ΣPCBs:	↓ Chicken pox from 3 to 7 years of age, SOB with wheeze
Karmaus et al. (2005)	Germany Cross-sectional (I)	331	7–10 y		Total & specific IgE to aeroallergens	Postnatal	ΣPCBs: Dioxins, ndl-PCBs: DDE	↑ AOM ↑ Total IgE levels
Sunyer et al. (2005)	Spain Cohort (I)	306–405	4 y	Defined as chest infection	Asthma, (persistent) wheeze, specific IgE to cat dander, HDM, grass pollen	Postnatal	ΣPCBs, HCB, γ-HCH:	–
Dallaire et al. (2006)	Canada Cohort (III)	343	5–7 y	Bronchitis, bronchiolitis, pneumonia, AOM, other diverse infections ^m		Prenatal	DDE: PCB153 ^h :	↑ (persistent) wheeze –
Sunyer et al. (2006)	Spain Cohort (I)	402 (pre) 285 (post)	1–6.5 y		Asthma (only at 6.5 y), (persistent) wheeze & skin prick test (only at 6.5 y)	Prenatal	Other OCs: DDE:	↑ LRTIs and AOM. Not presented but similar as for PCB-153 –
						Postnatal	DDT:	–
Grandjean et al. (2010)	Faroe Islands Cohort (II)	464	7 y		Asthma, reported atopic dermatitis, total & specific IgE to grass	Prenatal	DDE, DDT: Σ(ndl-)PCBs:	–
						Postnatal	Σ(ndl-)PCBs:	↓ Atopic dermatitis ↑ Total IgE levels (only 7y PCB levels), ↓ Atopic dermatitis

LRTI = low respiratory tract infection (bronchitis, bronchiolitis, pneumonia); URTI = upper respiratory tract infection (tonsillitis, pharyngitis, laryngitis, sinusitis, acute otitis media (AOM), rhinitis, nasopharyngitis, epiglottitis, laryngotracheitis, tracheitis, common cold); GIs = gastrointestinal infections; NS = the type of LRTI or URTI was not specified; CB = measured in cord blood; SOB = shortness of breath; IgE = immunoglobulin E; RAST = radioallergosorbent; HDM = house dust mite.

^a Different study populations coming from a same country are indicated with (I), (II), (III) or (IV).

^b At the time of outcome assessment (m = months, y = years).

^c Although AOM is an upper respiratory tract infection, it is usually analyzed separately in the studies.

^d Regarding PCB and dioxin exposures, ΣPCBs can indicate either "unknown congeners" or a mix of ndl- and dl-PCBs (ndl-PCBs were predominant in the sum of most of the studies). If only dioxin-like or non dioxin-like PCBs are included in the sum, then it is indicated as dl-PCBs or ndl-PCBs, respectively. When the exposures assessed are PCDDs or PCDFs it is indicated as dioxins, unless specifically indicated.

^e (↑) increasing risk with increasing exposure level, (↓) decreasing risk with decreasing exposure level, and (–) association was not statistically significant.

^f Associations are not significant for the highest tertile/quartile, but are significant among other tertiles/quartiles of exposure, showing a non-linear association.

^g Pharyngitis, tonsillitis, rhinitis, and common cold.

^h Due to the high correlations between compounds ($r = 0.94–0.99$), PCB-153 was used in the models as a surrogate of the ΣPCB exposure [Dallaire et al. (2004)], and as a surrogate of the ΣPCB and DDE exposures [Dallaire et al. (2006)]. These two studies were based on two different populations in Canada.

ⁱ Wheeze was borderline significantly associated to DDE (RR = 1.09, 95% CI = 0.99, 1.21) in the Spanish population. Results for the Latin American population (N = 79) went towards the same direction, but these were not significant for LRTIs (1.14 (0.92, 1.42)) or wheeze (1.20 (0.98, 1.48)).

^j As the association between PFOA/S and IgE was not linear, cubic polynomial regression analyses were performed. After stratification by gender, associations were significant for females (quadratic = $-1.43 (-2.42, -0.42)$, cubic = $-3.08 (-5.43, -0.73)$), but not for males.

^k The study compares exposure levels between children with positive (≥ 0.35 UA IgE/ml) and negative (< 0.35 UA IgE/ml) test for specific IgE.

^l Scarletina, chicken pox, rubella, measles, mumps, pertussis, hepatitis, meningitis or other infectious diseases.

^m Pharyngitis, laryngitis, tonsillitis, sinusitis tracheitis, rhinitis, and common cold.

ⁿ Persistent wheeze was borderline significantly associated to DDE (RR = 1.13, 95% CI = 0.98, 1.30).

3.2.1. Respiratory infections

3.2.1.1. PCBs and dioxins. Overall, seven studies reported a higher risk of respiratory infections, including AOM, at younger (Dallaire et al., 2004; Glynn et al., 2008; Miyashita et al., 2011; Stolevik et al., 2011) and older ages (Dallaire et al., 2006; ten Tusscher et al., 2001; Weisglas-Kuperus et al., 2000) in relation to prenatal exposure to PCBs and/or dioxins. However, these associations were not always for the same congeners (ndl-PCBs, dl-PCBs or dioxins) or consistent across quartiles of exposure (Dallaire et al., 2004; Glynn et al., 2008). Also, in one study increased or decreased risks were found depending on the congeners assessed (Glynn et al., 2008). On the other hand, several other studies reported no association with exposure to PCBs at younger (Dewailly et al., 2000; Gascon et al., 2012; Sunyer et al., 2010) or at older ages (Sunyer et al., 2005; ten Tusscher et al., 2003; Weisglas-Kuperus et al., 2004). Fewer studies assessed the effects of postnatal exposure to PCBs and dioxins; at young ages, one study reported reduced odds of respiratory infections with increasing exposure to only some PCB congeners (Glynn et al., 2008), whereas a Canadian birth cohort study could not find any association (Dallaire et al., 2004). At older ages, two studies assessing the same study population at different ages found increased odds of recurrent AOM in relation to increasing Σ PCB levels (Weisglas-Kuperus et al., 2000, 2004), whereas a cross-sectional study could only find associations with AOM when high Σ PCB levels were combined with high levels of DDE (Karmaus et al., 2001). In a study with Yucheng children of 8–16 years prenatally exposed to dioxins, influenza frequency was increased in this population compared to controls (Yu et al., 1998). Another small birth cohort did not observe an association between dioxins and AOM in children aged 7–12 years (ten Tusscher et al., 2001, 2003).

3.2.1.2. DDE. Higher prenatal DDE levels were associated with an increased risk of developing respiratory infections at young ages in all birth cohort studies evaluated (Dallaire et al., 2004; Dewailly et al., 2000; Gascon et al., 2012; Sunyer et al., 2010), except one (Glynn et al., 2008). However, Dallaire et al. found associations only for URTIs (and not LRTIs) showing a non-linear association (Dallaire et al., 2004). At older ages, Dallaire et al. mentioned that, although not presented, results for prenatal exposure to DDE were similar to those found for prenatal exposure to PCB-153 (increased risk of LRTIs and AOM) (Dallaire et al., 2006). On the other hand, another birth cohort study could not find any association between prenatal exposure to DDE and respiratory infections at a similar age (Sunyer et al., 2005). Postnatal DDE exposure was not associated to respiratory infections in young children of a Canadian study (Dallaire et al., 2004), whereas in a Swedish cohort a reduced risk of infection was found within the second quartile of exposure but not in the third or the fourth (Glynn et al., 2008). At older ages there is only one study available; the odds of developing AOM increased only when high postnatal levels of DDE were combined with high levels of PCBs or HCB, otherwise the odds were reduced (Karmaus et al., 2001).

3.2.1.3. HCB, HCHs and other POPs. There are very few studies assessing the effects of POPs other than PCBs or DDE. In a Canadian cohort, prenatal exposure to Mirex was not associated with any type of respiratory infection, whereas increasing levels of dieldrin increased the risk of AOM between the 4th and 7th month of life and increasing levels of HCB increased the risk of AOM during the first year of life (Dewailly et al., 2000). However, in three larger Spanish studies, where levels of HCB were less highly correlated to levels of other OCs, no association between increasing prenatal HCB exposure and LRTIs was found, either at young (Gascon et al., 2012; Sunyer et al., 2010) or at older ages (Sunyer et al., 2005). Adverse respiratory health effects were found regarding postnatal exposure to high levels of HCB when combined with high levels of DDE (Karmaus et al., 2001). A recent study could not find an association between prenatal perfluorooctanoic

acid (PFOA) and perfluorooctane sulfonate (PFOS) exposure and AOM in children at age 18 months (Okada et al., 2012).

3.2.2. Other infections

Very few studies assessed infections other than respiratory infections (Table 1). Exposure to DDE was found to increase risk of GIs at age 12 months, but only within the second quartile (Dallaire et al., 2004). Overall, five studies assessing exposure to dioxin and/or PCB compounds reported inconsistent results for exanthema subitum and GIs (Dallaire et al., 2004; Stolevik et al., 2011; Weisglas-Kuperus et al., 2000, 2004; Yu et al., 1998) or no associations for chickenpox (Stolevik et al., 2011; ten Tusscher et al., 2003).

On the basis of this, we classified the evidence as limited for an association of prenatal exposure to PCBs and dioxins with the risk of respiratory infections and AOM in childhood. The evidence for an association is also limited for prenatal DDE exposure and respiratory infections but inadequate for AOM. For other exposures, including postnatal PCBs, dioxins and DDE, or infections other than respiratory evidence are inadequate (Table 3).

3.3. Allergic manifestations

We distinguish between asthma symptoms (wheeze, asthma, shortness of breath, lung function (fourteen articles)) and symptoms and markers of atopy (eczema, allergy symptoms and reaction, atopic dermatitis, allergic rhinitis, positive skin prick test (SPT) and total and specific IgE). In the present review IgE was not included as a humoral immune marker but as a marker of atopy because IgE in the mucosal mast cells reflects immediate allergic reactions (Gould et al., 2003). In fact, in most of the studies it was treated specifically as a marker of atopy (nineteen articles included) (Table 1 and Table B.2). Most of studies assessed asthma and wheezing through questionnaires answered by parents, in which most of the questions were based on doctor diagnosed symptoms. One study assessed asthma through direct doctor diagnosis (Grandjean et al., 2010) and another one assessed lung function by spirometry (ten Tusscher et al., 2001). Atopy was assessed by either measuring immunoglobulin E (IgE) levels or by self-reported symptoms (self-reported allergy, eczema, rhinitis) obtained through questionnaire.

3.3.1. Asthma symptoms

3.3.1.1. PCBs and dioxins. At young ages higher prenatal levels of different dl- and ndl-PCB congeners and dioxins were associated with an increased odds of wheeze, but not asthma (Stolevik et al., 2011). Other studies assessing wheeze or asthma at a similar age could not find any association (Gascon et al., 2012; Miyashita et al., 2011). At older ages a small study found lung function at age 7–12 years to be reduced after prenatal and postnatal exposure to dioxins (ten Tusscher et al., 2001); however, no association with asthma symptoms was found (ten Tusscher et al., 2003). Other studies at similar ages could not find any association between asthma symptoms and prenatal exposure to ndl-PCBs or Σ PCBs, respectively (Grandjean et al., 2010; Sunyer et al., 2005). In two studies, lower odds of suffering shortness of breath with wheezing after prenatal exposure to PCBs, but not to dioxins, was reported (Weisglas-Kuperus et al., 2000, 2004). A cross-sectional study including 200 individuals aged 7–18 years found an association between increasing postnatal ndl-PCB levels and risk of ever suffering from asthma, but no associations were found for dl-PCBs (Van Den Heuvel et al., 2002). Other studies including children aged 3 to 8 years did not report an association between postnatal PCB or dioxin exposure and risk of asthma and/or wheeze (Grandjean et al., 2010; Karmaus et al., 2001; ten Tusscher et al., 2003; Weisglas-Kuperus et al., 2000, 2004; Yu et al., 1998).

3.3.1.2. DDE, HCB and other POPs. At young ages only one study assessed the effects of DDE and HCB exposure on allergic manifestations in the respiratory system; no significant associations were found in children at 14 months of age, but increasing prenatal DDE levels were associated with risk of wheezing (Gascon et al., 2012). At older ages, prenatal DDE exposure was associated with a higher risk of wheeze and/or asthma at different ages in a birth cohort study (Sunyer et al., 2005, 2006), whereas a cross-sectional study found that increasing postnatal DDE levels increased the odds of suffering of asthma (Karmaus et al., 2001). These same studies did not find any association of pre or postnatal exposure to HCB and/or β -HCH and risk of wheeze or asthma (Karmaus et al., 2001; Sunyer et al., 2005). Finally, another study on prenatal exposure to PFOA and PFOS could not find associations with wheeze in children aged 18 months (Okada et al., 2012).

3.3.2. Atopy

3.3.2.1. PCBs and dioxins. Among studies evaluating the association between prenatal PCBs and/or dioxins and total or specific IgE levels (Jusko et al., 2011; Kaneko et al., 2006; Reichrtova et al., 1999) or eczema or allergy (Miyashita et al., 2011; Stolevik et al., 2011) in young children, only one study reported a positive correlation between prenatal PCB-118 levels (but not other PCBs) and total IgE levels (Reichrtova et al., 1999). Also, in one of these studies the odds of food allergies was increased for dl-PCBs (Miyashita et al., 2011), although associations were not linear across quartiles. Also, authors could not rule out potential misclassification between food allergies and food intolerance. At older ages, among studies available (Grandjean et al., 2010; Sunyer et al., 2005; ten Tusscher et al., 2001, 2003; Weisglas-Kuperus et al., 2000, 2004; Yu et al., 1998) one small study ($N=27$) found increasing prenatal dioxin levels to be associated with reduced odds of suffering from allergy, but no associations with eczema were found (ten Tusscher et al., 2003), whereas Grandjean et al. reported lower levels of ndl-PCBs among children with atopic dermatitis compared to those with no allergy (Grandjean et al., 2010). Two studies assessed postnatal exposure to PCBs in young children; one found no associations with IgE levels at age 6 months and increasing ndl-PCBs (Jusko et al., 2011). The other study found that increasing Σ PCBs was associated to increasing levels of milk specific IgE at age 23 months (Tsuji et al., 2012). At older ages results are contradictory; a cross-sectional study found no association between Σ PCBs and total or specific IgE levels (Karmaus et al., 2001, 2005). However, another cross-sectional study found increasing dl-PCBs, but not ndl-PCBs, to be associated with a reduced risk of positive radioallergosorbent test (RAST), as well as reduced total IgE levels (Van Den Heuvel et al., 2002). On the other hand, a birth cohort study reported higher concentrations of ndl-PCBs in children with higher total IgE levels, but lower ndl-PCB levels in those with atopic dermatitis compare to those with no allergy symptoms (Grandjean et al., 2010). Van Den Heuvel et al. also found contrasted results regarding atopy symptoms: increased odds of suffering hay fever with increasing ndl-PCB levels, but reduced risk of upper airway disease with increasing dl-PCB exposure (Van Den Heuvel et al., 2002). Two birth cohort studies also found that increasing dioxin or PCB exposure reduced the odds of being atopic (ten Tusscher et al., 2003; Weisglas-Kuperus et al., 2000); however, results of Ten Tusscher et al. are inconsistent, since in a previous study, where practically the same study population was used ($N=27$ vs. $N=29$), no association was found (ten Tusscher et al., 2001). Two other birth cohorts did not observe an association between PCB or dioxin exposure and atopic symptoms (Weisglas-Kuperus et al., 2004; Yu et al., 1998).

3.3.2.2. DDE, HCB and other POPs. Prenatal DDE exposure was positively and correlated to cord blood total IgE levels in a Slovakian birth cohort (Reichrtova et al., 1999), however, in a Spanish cohort with children aged 4 to 6.5 years, no association was found with specific IgE levels or positive SPT (Sunyer et al., 2005, 2006), neither with

postnatal exposure (Sunyer et al., 2006). Postnatal DDE exposure was found to increase the odds of having higher total but not specific IgE levels in a cross-sectional study among children aged 7–10 years (Karmaus et al., 2001, 2005). Effects of pre or postnatal HCB, HCH or other POP exposure on eczema and IgE levels have been evaluated in very few studies, and none of them observed associations (Karmaus et al., 2001, 2005; Reichrtova et al., 1999; Sunyer et al., 2005), except two studies evaluating the effects of prenatal exposure to PFOA and PFOS. One study found total IgE levels measured in cord blood, but not in serum at age 2 years, to be increased in relation to increasing PFOA and PFOS levels (Wang et al., 2011), whereas the other study found total, but not specific IgE levels, to be reduced with PFOA exposure (the association was not linear) (Okada et al., 2012). In the first study, no associations with atopic dermatitis were found (Wang et al., 2011).

In summary, we classified the evidence of an association between prenatal exposure to DDE and risk of asthma-related symptoms as limited, whereas lack of association between postnatal exposure to PCBs, mainly ndl-PCBs, and risk of asthma-related symptoms seems to be evident. For other exposures the evidence is inadequate (Table 3).

3.4. Humoral immune response

Humoral response studies (Table 2 and Table B.3) were subdivided into those studies measuring general antibody concentrations (IgA, IgG and IgM – six articles) and those studies measuring specific antibody concentrations after vaccinations (seven articles).

3.4.1. General antibody concentrations

3.4.1.1. PCBs and dioxins. Studies measuring IgA, IgG and IgM levels in young children reported no association with prenatal exposure (Dewailly et al., 2000; Jusko et al., 2011; Kaneko et al., 2006) or postnatal exposure (Jusko et al., 2011) to PCBs or dioxins. At older ages, only effects of postnatal exposure were assessed; one cross-sectional study reported a negative correlation between postnatal ndl-PCBs and IgG, a positive correlation between dl-PCBs and IgA, and no correlations for IgM (Van Den Heuvel et al., 2002), whereas another study observed, among children in the highest PCB quartile of exposure, higher IgM levels but no associations with IgG or IgA (Karmaus et al., 2005). A small birth cohort study found no correlation between exposure to dioxins and antibody concentrations in children aged 8 to 16 years (Yu et al., 1998).

3.4.1.2. DDE, HCB and other POPs. A Canadian birth cohort study reported no correlation between prenatal exposure to DDE and other OCs and immunoglobulin concentrations measured during the first year of life (Dewailly et al., 2000). However, a cross-sectional German study observed increased IgA concentrations at older ages (7–10 years) in relation to increasing postnatal DDE exposure, reduced IgM concentrations in relation to increasing HCB exposure and no effects of γ -HCH (Karmaus et al., 2005).

3.4.2. Specific antibody counts after vaccination

3.4.2.1. PCBs and dioxins. A birth cohort study reported decreases in diphtheria and/or tetanus Ab concentrations in relation to prenatal dl- and ndl-PCB exposure in children under 2 years of age (Heilmann et al., 2006). However, two other studies, one with a larger study population, did not find any association with exposure to PCBs and/or dioxins (Jusko et al., 2010; Weisglas-Kuperus et al., 1995). At older ages, a Dutch study presenting partial correlations found that increasing prenatal Σ PCB levels were associated with reduced mumps and rubella Ab concentrations at age 42 months (Weisglas-Kuperus et al., 2000). Similar results on tetanus antibodies, but not diphtheria, were obtained by another study with children of 7.5 years of age in the Faroe Islands

Table 2

Studies on persistent organic pollutants, immune cell-mediated response and immune humoral response (ordered by age group, year and author).

Author (Year)	Country & study design ^a	N	Child age ^b	Outcomes assessed		Exposure assessment ^c		Statistically significant main findings ^d
				Cell-mediated response (cell counts and interleukin levels)	Humoral response (general and specific Ab counts)	Timing	Compound	
<2 years								
Weisglas-Kuperus et al. (1995)	The NL Cohort (I)	12– 205	CB, 3 & 18 m	WBC, T-cells, B-cells, NK cells, monocytes, granulocytes (NS)	Ab counts for mumps, measles, rubella (only at 18 m)	Prenatal Postnatal	ΣPCBs: Dioxins & dl-PCBs: Dioxins & dl-PCBs:	↑ T-cells at 18 m (CD3 ⁺ CD8 ⁺) ↑ T-cells in CB (TcRγδ ⁺), ↓ monocytes & granulocytes at 3 m, ↑ T-cells at 18 m (CD3 ⁺ CD8 ⁺ , TcRγβ ⁺) ↓ Monocytes, granulocytes & B-cells at 3 m (CD19 ⁺ CD20 ⁺) ↑ T-cells ratio (CD4 ⁺ /CD8 ⁺ ratio)
Nagayama et al. (1998)	Japan Cohort (I)	36	12 m	T-cells, B-cells		Postnatal	Dioxins & dl-PCBs:	↑ T-cells ratio (CD4 ⁺ /CD8 ⁺ ratio)
Dewailly et al. (2000)	Canada Cohort (I)	94– 109	3, 7 & 12 m	WBC, T-cells, B-cells	IgA, IgG, IgM	Prenatal	Σ(ndl-)PCBs, DDE, HCB, mirex, dieldrin:	–
Bilrha et al. (2003)	Canada Cross-sectional	83	At birth (CB)	T-cells, <i>in vitro</i> cytokine production (IL-10 & TNF-α)		Prenatal	ΣPCBs: DDE: HCB:	↓ TNF-α ↓ TNF-α ↓ TNF-α
Heilmann et al., (2006) ^e	Faroe Islands Cohort (II)	119	18 m		Ab concentrations after tetanus and diphtheria vaccination	Prenatal Postnatal	Σndl-PCBs: dl-PCB (mono-ortho): Σndl-PCBs: dl-PCB (mono-ortho):	↓ Diphtheria Ab concentrations ↓ Diphtheria Ab concentrations ↓ Diphtheria (& tetanus ^f) Ab concentrations ↓ Diphtheria Ab concentrations
Kaneko et al. (2006)	Japan Cohort (II)	281	12 m	T-cells, B-cells, NK cells	IgA, IgG, IgM	Perinatal	PCDDs, PCDFs & dl-PCBs:	–
Noakes et al. (2006)	Australia Cohort (I)	26	At birth (CB)	<i>In vitro</i> cytokine production (IL-13, IL-16, IL-10, INF-γ), lymphoproliferation response		Prenatal Perinatal	DDE, HCB, diel- drin, or others: DDE, HCB, dieldrin:	– –
Brooks et al. (2007)	USA Cross-sectional	19	At birth (CB)	IL-13, IL-4, INF-γ		Prenatal	DDE:	↑ IL-13, IL-4/IFN-γ ratio, IL-13/INF-γ ratio
Nagayama et al. (2007)	Japan Cohort (III)	92	10 m	T-cells, B-cells, NK cells		Perinatal	HCH: HCE: Chlordane: Dioxins & dl-PCBs: ΣPCBs, DDE & DDT: Combinations → Dioxins & dl-PCBs + ΣPCBs: DDE & DDT + ΣPCBs: HCE + Chlordane:	↑ T-cells (HLA-DR ⁺) ↑ T-cells (CD8 ⁺) ↑ T-cells (CD3 ⁺) ↑ T-cells ratio (CD4 ⁺ /CD8 ⁺ ratio) – – ↓ T-cells (CD16 ⁺) ↓ T-cells (CD16 ⁺) ↑ T-cells (CD8 ⁺)
Glynn et al. (2008)	Sweden Cohort (I)	52– 86	3 m	WBC, T-cells, B-cells, NK cells, monocytes, eosino- phils, neutrophils		Prenatal Postnatal	ΣPCBs: DDE: PCB-153, ndl-PCBs, dl-PCBs: PCB-153: ΣPCBs, ndl-PCBs, dl-PCBs, DDE:	↑ Number of WBC, total lymphocytes & monocytes ↓ % eosinophils – ↑ Number & % NK cells (CD56 ⁺) –
Jusko et al. (2010)	Slovakia Cohort (I)	329	6 m		Ab counts for influenza type b, tetanus, diphtheria	Prenatal Postnatal	ΣPCBs: Σ(ndl-)PCBs:	– –
Jusko et al. (2011)	Slovakia Cohort (I)	350	6 m		IgA, IgG, IgM	Prenatal Postnatal	ΣPCBs: Σ(ndl-)PCBs:	– –
Horvathova et al. (2011a) ^g	Slovakia Cohort (I)	313– 362	CB, 6 m, 16 m	T-cells, B-cells, NK-cells		Prenatal	ΣPCBs:	↑ B-cells (CD19, HLADRC19) at all ages, T-cell (CD3) at 16 m, T-cell (CD8) in CB, ↓ NK-cells (CD3CD56/16)
Horvathova et al. (2011b) ^g	Slovakia Cohort (I)	313– 362	CB, 6 m, 16 m	T-cell receptor expression		Prenatal	ΣPCBs:	↓ CD4CD62, CD4CD62 ⁺ CD45RA ⁺ , CD19CD11c ⁺ CD9b ⁺ at all ages, CD4CD45RO [–] CD45RA ⁺ , CD4CD25, CD83CD19 at 6 and 16 m and CD19CD11c [–] CD11b ⁺ at 6 m, ↑ CD4CD62 [–] CD45RA ⁺ at all ages and CD4CD45RO ⁺ CD45RA [–] at 6 and 16 m
Tsuji et al. (2012) ^h	Japan Case-control	30	23 m	IL-8, COX-2		Postnatal	ΣPCBs: ndl-PCB congeners: dl-PCB congeners:	↑ COX-2 ↑ IL-8, COX-2 –
>2 years								
Yu et al. (1998)	Taiwan Cohort (I)	31	8– 16 y	T-cells, B-cells, NK cells, monocytes, eosinophils, basophils, neutrophils	IgA, IgG, IgM	Postnatal	Dioxins:	–

Table 2 (continued)

Author (Year)	Country & study design ^a	N	Child age ^b	Outcomes assessed		Exposure assessment ^c		Statistically significant main findings ^d
				Cell-mediated response (cell counts and interleukin levels)	Humoral response (general and specific Ab counts)	Timing	Compound	
Weisglas-Kuperus et al. (2000)	The NL Cohort (I)	85– 150	42 m	T-cells, B-cells, NK cells, monocytes, granulocytes (NS)	Ab counts for mumps, measles, rubella	Prenatal	ΣPCBs: Dioxins, dl-PCBs (planar & mono-ortho):	↑ T-cells (CD3 ⁺ , CD3 ⁺ CD8 ⁺ , CD4 ⁺ CD45RO ⁺ , CD3 ⁺ HLA-DR ⁺) ¹ & lymphocyte counts, ↓ Mumps and rubella Ab counts. –
Van Den Heuvel et al. (2002)	Belgium Cross-sectional	200	17– 18 y	WBC, T-cells, B-cells, NK cells, eosinophils	IgA, IgG, IgM	Postnatal	ΣPCBs: Σ(ndl-)PCBs: dl-PCBs:	– ↓ IgG levels ↓ Eosinophils & NK cells (CD16 ⁺ CD56 ⁺), ↑ IgA levels
ten Tusscher et al. (2003)	The NL Cohort (III)	27	8 y	T-cells, B-cells, NK cells		Prenatal	Dioxins & furans:	–
Karmaus et al. (2005)	Germany Cross-sectional (I)	331	7– 10 y	WBC, T-cells, B-cells, NK cells, eosinophils (granula content), basophils (IgE count)	IgA, IgG, IgM	Postnatal	Dioxins & furans: ΣPCBs: DDE: HCB: γ-HCH:	↑ T-cells (CD4 ⁺ , CD45RA ⁺) ↑ WBC ² , IgM ↑ WBC ² , IgG, IgA & IgE count in basophils ² , ↓ Eosinophilic granula ² ↓ IgA, IgM Associated to NK-cells (CD16 ⁺ CD56 ⁺ , CD16 ⁺ CD56 ⁺ CD57 ⁺), but unclear dose–response (use of quartiles)
Sunyer et al. (2005)	Spain Cohort (I)	306	4 y	WBC, T-cells, B-cells, NK cells, eosinophils		Prenatal	ΣPCBs, DDE, HCB:	–
Heilmann et al., (2006) ^e	Faroe Islands Cohort (I)	129	7.5 y		Ab concentrations after tetanus and diphtheria vaccination	Prenatal	Σndl-PCBs: dl-PCBs (mono-ortho):	↓ Tetanus Ab concentrations –
						Postnatal	Σndl-PCBs: dl-PCBs (mono-ortho):	– –
Leijds et al. (2009)	The NL Cohort (IV)	18– 33	14– 19 y	WBC, lymphocytes (NS), monocytes, eosinophils, basophils, (polymorphic) neutrophils		Prenatal	Dioxins:	↓ Polymorphic neutrophils
						Postnatal	dl-ΣPCBs: PBDEs: Dioxins:	↓ Polymorphic neutrophils ↓ Lymphocytes
Heilmann et al. (2010)	Faroe Islands Cohort (II)	106– 587	5 & 7 y		Ab concentrations for tetanus and diphtheria	Prenatal	Σndl-PCBs:	–
						Postnatal ^k	Σndl-PCBs:	↓ Diphtheria Ab concentrations at age 5 y, ↓ Diphtheria & tetanus Ab concentrations at age 7 y, ↑ risk of an Ab concentration below a clinically protective level at age 5 y ↓ Diphtheria prebooster Ab at 5 y
Grandjean et al., (2012)	Faroe Islands Cohort (II)	380– 510	5 & 7 y		Ab concentrations for tetanus and diphtheria	Prenatal	PFOS: PFOA: PFDA: PFHxS, PFNA:	↓ Diphtheria at 7 y ↓ Diphtheria pre and postbooster at 5 y
						Postnatal	PFOS, PFOA ¹ : PFNA: PFHxS ¹ , PFNA:	↓ Diphtheria at 7 y ↓ Diphtheria prebooster Ab at 5y –

WBC = white blood cell counts (total leukocytes), which include lymphocytes (T-cells, B-cells and Natural Killer (NK) cells), monocytes (derive into macrophages and dendritic cells) and granulocytes (basophils, eosinophils and neutrophils); IL = interleukin; TNF-α = tumor necrosis factor-α; INF-γ = interferon-γ; NS = subtypes of leukocytes are not specified in the text of the paper; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M, IgG = immunoglobulin G; Ab = antibody; COX-2 = cyclooxygenase-2.

^a Different study populations coming from a same country are indicated with (I), (II), (III) or (IV).

^b At the time of outcome assessment (m = months, y = years).

^c Regarding PCB and dioxin exposures, ΣPCBs can indicate either “unknown congeners” or a mix of ndl- and dl-PCBs (ndl-PCBs were predominant in the sum of most of the studies). If only dioxin-like or non dioxin-like PCBs are included in the sum, then it is indicated as dl-PCBs or ndl-PCBs, respectively. When the exposures assessed are PCDDs or PCDFs it is indicated as dioxins, unless specifically indicated.

^d (↑) Increasing risk with increasing exposure level, (↓) decreasing risk with decreasing exposure level, and (–) association was not statistically significant.

^e This is a same article including two different birth cohorts of different ages each.

^f Significant associations only when performing structural equation models.

^g Exposure is not introduced in the models as continuous PCB levels measured in maternal serum but as a dichotomous variable (highly exposed children (polluted area of Michalovce) vs. less exposed children (area of Svidnik/Stropkov)). In the original papers results are also shown for blood measurements at age 6 m, but in the present tables these are not shown (results were similar to those obtained in both CB and at age 16 m).

^h The estimations for those congeners for which no significant results were found (all dl-PCBs and some ndl-PCBs) are not shown in the manuscript. In the present table and the supplementary tables we only show the results for the sum of PCBs, but not the results for the different congeners for which significant associations were found; they are available in the original manuscript.

ⁱ Only significant among non breastfeeding children and for PCBs measured in maternal and cord blood.

^j In the highest quartile of PCB exposure the WBC is significantly reduced compared to the lowest quartile, but the reduction is not linear across quartiles. There is a similar situation with the increase of WBC or IgE BC within the 4th and 3rd quartiles of DDE exposure, respectively. Although the F-test is not significant, eosinophilic granula levels within the highest quartile were significantly lower than in the lowest quartile of DDE exposure (T-test). For γ-HCH, there are significant differences between quartiles of exposure, however, in some quartiles NK cell levels are increased and in others these are decreased.

^k In all cases, the associations found between Ab counts and postnatal exposure measured at age 18 months were only significant after imputation of 88.5% of the 18 m serum samples (based on maternal blood and breast milk, serum at age 5 and 7 y levels).

^l The association between postnatal PFOA and PFHxS and tetanus and diphtheria Ab counts at age 7 years was significant when models were adjusted for Ab counts at age 5 y.

in relation to ndl-PCB exposure (Heilmann et al., 2006). However, in another birth cohort in the same study area, no association was observed between prenatal exposure to ndl-PCBs and Ab concentrations at a similar age (Heilmann et al., 2010). Regarding postnatal exposure, at young ages Heilmann et al. found a decrease of diphtheria Ab concentrations in relation to both dl- and ndl-PCBs (Heilmann et al., 2006), however other two studies could not find an association (Jusko et al., 2010; Weisglas-Kuperus et al., 1995). At older ages, postnatal ndl-PCB exposure reduced tetanus and/or diphtheria Ab concentrations in children aged 5 and 7, mainly when exposure was measured at age 18 months rather than at older ages (5 to 7 years) (Heilmann et al., 2010). It is important to note that associations were mainly found for ndl-PCBs, whereas only one study found associations with dl-PCBs (Heilmann et al., 2006).

3.4.2.2. PFCs (perfluorinated compounds). In a birth cohort study in the Faroe Islands the effects of different PFC congeners (PFOA, PFOS, PFNA (perfluorononanoic acid), PFHxS (perfluorohexane sulfonic acid) and PFDA (perfluorodecanoate)) on antibody concentrations were also assessed at age 5 and 7 years (Grandjean et al., 2012). Associations were found between prenatal exposure to PFOS, PFOA and PFDA and diphtheria concentrations measured at age 5 and 7 years. Associations, though, were not always found for all congeners and Ab measurements. The effects of different PFC congeners (PFOS, PFOA, PFHxS and PFDA) on Ab concentrations were stronger for postnatal exposure (Grandjean et al., 2012).

The evidence for an association between postnatal exposure to PCBs, mainly ndl-PCBs, and specific antibody counts is limited, whereas for prenatal exposure to PCBs and pre or postnatal exposure to other POPs the evidence is inadequate (Table 3).

3.5. Cell-mediated immune response and immune cell counts

There are four studies evaluating the effects of POPs on cell-mediated response (cytokines) and sixteen measuring immune cell counts such as lymphocyte (T-cells, B-cells, NK-cells) and monocytes or granulocytes (Table 2 and Table B.4). Many of these studies have small study populations ($N \approx 30$) (Brooks et al., 2007; Leijds et al., 2009; Noakes et al., 2006; ten Tusscher et al., 2003; Tsuji et al., 2012; Yu et al., 1998) or do not adjust for potential confounders (Bilrha et al., 2003; Dewailly et al., 2000; Glynn et al., 2008; Kaneko et al., 2006; Leijds et al., 2009; Nagayama et al., 1998, 2007; Noakes et al., 2006; Tsuji et al., 2012; Van Den Heuvel et al., 2002; Weisglas-Kuperus et al., 1995, 2000; Yu et al., 1998). The largest studies ($N = 362$) available and adjusting for potential confounders compared cell counts between a highly polluted area and a less polluted area, but did not introduce measured PCB exposure in the model (Horvathova et al., 2011a,b). Also, the multiple subtypes of T-cells (i.e. HLA-DR⁺, CD8⁺, CD3⁺ or CD16⁺) or cytokines measured differ between studies, making comparisons difficult.

3.5.1. Cell-mediated response

Three studies measured levels of various cytokines in cord blood at birth; in one study TNF- α was negatively correlated to prenatal Σ PCBs, DDE and HCB concentrations (Bilrha et al., 2003). In the other two studies one found interleukin levels and ratios to be positively correlated to DDE levels (Brooks et al., 2007), but the other study did not find any correlation (Noakes et al., 2006). Finally, one study measuring postnatal levels of PCBs found that increasing Σ PCB and ndl-PCB levels were associated with increasing levels of COX-2 (cyclooxygenase-2) and/or IL-8. No associations were found for dl-PCBs (Tsuji et al., 2012).

3.5.2. Cell counts

3.5.2.1. PCBs and dioxins. Most of the studies did not find an association between prenatal (Bilrha et al., 2003; Dewailly et al., 2000; Kaneko et

al., 2006; Leijds et al., 2009; Sunyer et al., 2005; ten Tusscher et al., 2003) or postnatal (Leijds et al., 2009; Weisglas-Kuperus et al., 2000; Yu et al., 1998) exposure to PCBs or dioxins and different lymphocyte counts at different ages. Some studies observed increased white blood-cell counts (WBC) and/or different T-cell counts (not B or NK-cell counts) in relation to prenatal exposure to PCBs and/or dioxins (Glynn et al., 2008; Nagayama et al., 2007; Weisglas-Kuperus et al., 1995, 2000). A recent study which measured cell levels at different time points (cord blood, 6 and 16 months of life) also reported increased T-cell and B-cell, but reduced NK-cell levels, in children from a highly polluted area with Σ PCBs compared to children from a less polluted area in Slovakia (Horvathova et al., 2011a). In this same study population, different T-cell and dendritic cell receptors were found to be reduced, and other T-cell receptors increased, among children from the highly polluted area (Horvathova et al., 2011b). Regarding postnatal exposure to PCBs and/or dioxins, some studies found increased and others found decreased levels of different lymphocyte types (Glynn et al., 2008; Karmaus et al., 2005; Nagayama et al., 1998; ten Tusscher et al., 2003; Van Den Heuvel et al., 2002; Weisglas-Kuperus et al., 1995). Fewer studies evaluated the effects of prenatal and postnatal exposure on granulocyte and monocyte counts and results were inconsistent between studies (Glynn et al., 2008; Karmaus et al., 2005; Leijds et al., 2009; Sunyer et al., 2005; Van Den Heuvel et al., 2002; Weisglas-Kuperus et al., 1995, 2000; Yu et al., 1998).

3.5.2.2. DDE, HCB and other POPs. Pre or perinatal DDE or DDT exposure was not associated with cell counts in any of the available studies (Bilrha et al., 2003; Dewailly et al., 2000; Nagayama et al., 2007; Sunyer et al., 2005), only one found a decrease in the percentage, but not the number, of eosinophil counts (Glynn et al., 2008). Karmaus et al. found postnatal exposure to DDE to increase WBC counts in children aged 7 to 10 years when comparing the highest quartile of exposure with the lowest (Karmaus et al., 2005), but another study could not detect any association at younger ages (Glynn et al., 2008).

No associations between prenatal HCB, Mirex or dieldrin exposure and cell counts were found in most of the studies (Bilrha et al., 2003; Dewailly et al., 2000; Sunyer et al., 2005). Increasing perinatal HCH and HCE (heptachlor epoxide) exposures increased counts of different T-cell subtypes in Japanese children aged 10 months (Nagayama et al., 2007). No, or at least not consistent, effects of postnatal exposure to HCB (Karmaus et al., 2005; Sunyer et al., 2005) or γ -HCH (Karmaus et al., 2005; Leijds et al., 2009) were described, only PBDE levels were negatively correlated to lymphocyte counts in adolescents aged 14 to 19 years (Leijds et al., 2009).

We summarize the evidence for an association between immune response and any pre or postnatal exposure to POPs as inadequate (Table 3).

3.6. Other outcomes

A Slovakian study including 982 newborns found that the size of the thymus, the organ where T-cells are 'educated', was reduced at birth due to prenatal exposure to PCBs (β (SE, pval) = -0.036 (0.018, $p = 0.047$)), even after selecting those children ($N = 187$) assessed by the most experienced radiologist (-0.102 (0.047, $p = 0.033$)). No associations were found for DDT or DDE (Park et al., 2008). In the same study population no associations were found between prenatal exposure to ndl-PCBs and the size of the thymus at age 6 (change in thymus index SD (95%CI) = -0.09 ($-0.29, -0.11$)) or 16 months (-0.02 ($-0.21, 0.17$)). However, results showed an association between postnatal exposure to ndl-PCBs measured at 6 months of age and the size of thymus at the same age (-0.40 ($-0.76, -0.04$)), whereas no associations between ndl-PCBs measured at age 16 months and the thymus size at that time were found (0.17 ($-0.04, 0.38$)) (Jusko et al., 2012).

Table 3
Summary of the evidence.

	PCBs and ndl-PCBs		Dioxins and dl-PCBs		DDE/DDT		HCB		Other POPs (HCHs, mirex, dieldrin, chlordane, PBDEs, PFCs)	
	Prenatal ^a	Postnatal	Prenatal	Postnatal	Prenatal	Postnatal	Prenatal	Postnatal	Prenatal	Postnatal
<i>Infections</i>										
Acute otitis media (AOM)	Limited	Inadequate	Limited	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate
Respiratory tract infections	Limited	Inadequate	Limited	Inadequate	Limited	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate
Other infections	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate
<i>Allergic manifestations</i>										
Asthma symptoms	Inadequate	Evidence of lack of association	Inadequate	Inadequate	Limited	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate
Atopy	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate
<i>Immune humoral response</i>										
General antibody concentrations	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate
Specific antibody counts after vaccination	Inadequate	Limited	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate
<i>Immune cell-mediated response & cell counts</i>										
Cell-mediated response	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate
Cell counts	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate	Inadequate
<i>Other outcomes</i>										
Thymus size	Inadequate	Inadequate	–	–	Inadequate	–	–	–	–	–

Sufficient – if most of the studies, including good quality studies, report an association, but evidence is not yet conclusive enough to conclude that there is an association or a causal relationship, *limited* – several good quality, independent, studies report an association, but evidence is not yet conclusive enough, *inadequate* – if associations are reported in one or more studies, but insufficient quality, insufficient number of studies, lack of consistency, and/or lack of statistical power preclude a conclusion regarding the presence or absence of an association, *evidence for lack of association* – several good quality studies are consistent in showing no association.

^a Prenatal exposure can also include perinatal.

4. Discussion

This review finds limited evidence for prenatal DDE, PCB and dioxin exposures to increase the risk of respiratory infections (with the exception of DDE and AOM, for which evidence is inadequate) and for postnatal exposure to PCBs, specifically ndl-PCBs, to reduce immune response after vaccination in childhood. Results of available studies also indicate lack of association between postnatal exposure to PCBs/ndl-PCBs and risk of asthma-related symptoms. For the other combinations of exposures and outcome evidence is inadequate, mainly due to the reduced number of studies available within each combination. Heterogeneity between studies in exposure and outcome assessment, as well as the small number of studies for any given exposure–outcome relationship, currently make the combination of studies for meta-analysis impossible, but this review raises important issues that may guide both the design and presentation of future studies.

4.1. Exposure assessment

In the reviewed studies, chemical compounds were measured in different matrixes, reported in different units, and postnatal estimates were sometimes derived by multiplying breast milk concentrations and breastfeeding duration. These differences make it difficult to compare exposure levels or results, let alone perform meta-analyses. However, a recent European study on POPs and birth weight has shown that it is possible to perform a meta-analysis of cohort studies that measured POPs in different matrices by going back to the original data and using conversion factors to compare between matrices (Govarts et al., 2012). For the estimation of postnatal levels physiologically based pharmacokinetic (PBPK) models are now being developed for studies on environmental health effects in children (Verner et al., 2010, 2012). These may provide improved estimates of postnatal exposure as they take into account information on exposure determinants such as time of breastfeeding, maternal age or pre-pregnancy weight. These models could also help researchers in identifying critical windows of

susceptibility, a field poorly explored so far (Dietert et al., 2000; Verner et al., 2010, 2012).

Different PCB and dioxin congeners have been measured in different studies and the sums of congeners calculated are thus not always based on the same congeners. This may affect risk estimation since congeners may interact differently with elements of the immune system; for instance, some PCB congeners interact more strongly with the Ah receptor than others (Holladay and Smialowicz, 2000). Also, correlations between different POP exposures, including different congeners, can be very high in some populations (Dallaire et al., 2004; Karmaus et al., 2001); in this sense, effects seen for one compound (i.e. PCB) could be explained by another highly correlated (i.e. DDE). Synergistic effects of mixtures of POPs, together with other pollutants like heavy metals, for instance, is another important issue that coming studies should address (Carpenter et al., 1998); some in-vitro and animal models have shown that different POPs can enhance their immunotoxic effects when cells or animals are coexposed to them (Ferrante et al., 2011; Mori et al., 2008). Some of the reviewed studies applied multipollutant models to detangle the effects of multiple exposures. This approach may sometimes be helpful, as shown, for example, by Sunyer et al. (2010) who found that the association between prenatal DDE and LRTIs was not modified by exposure to other POPs (Sunyer et al., 2010). However, most of the epidemiological studies currently available generally have little power to study complex interactions between multiple exposures and multiple effects because of the small study populations included. On the other hand, more sophisticated statistical tools, such as the use of latent class analysis, to identify clusters of exposures (Sánchez et al., 2012), combined with the use of structural equation models (SEM) (Budtz-Jørgensen et al., 2002; Davis, 2012; Sánchez et al., 2005) and/or Bayesian profile regression techniques (Molitor et al., 2010), may help to study increasingly complex exposure–outcome associations (Davis, 2012; Sánchez et al., 2005; Sohn et al., 2004). In fact, SEMs have already been applied in a couple of studies of the present review, with the aim to disentangle the effects of pre and postnatal exposure to PCBs or to determine the joint effects of different PFCs (Grandjean et al., 2012; Heilmann et al., 2006).

Finally, animal and in vitro models have shown potential immunotoxic capacity of PBDEs (Gill et al., 2004) and PFCs (Dewitt et al., 2012), relatively new POPs. However, as also shown in the present review, there is still very scarce information on their effects on humans (Grandjean et al., 2012; Leijds et al., 2009; Okada et al., 2012; Wang et al., 2011). There is also concern on other non-persistent compounds, such as phthalates, for which studies seem to indicate that they increase the risk of allergy and asthma in children (Jurewicz and Hanke 2011; Winans et al., 2011), and bisphenol A (BPA), for which data on animal models suggests its capacity to modulate the developing immune system (Winans et al., 2011). Further epidemiological studies on such compounds suspected of being immunotoxic are also required.

4.2. Outcome assessment

Most studies assessed respiratory and allergy symptoms by standardized questionnaires and definitions (i.e. The ISAAC questionnaire (Beasley, 1998)), thus resulting in fairly comparable outcome assessment for these outcomes. However, an important difference between the reviewed studies is age of the children at outcome assessment: this may be particularly important for respiratory infections and allergy manifestations since the behavior of these diseases differs by age (Nair et al., 2010; Rudan et al., 2004; Stein and Martinez, 2004). In order to take this factor into account, in the present review we described results according to the age of the children among younger (<two years) and older ages (>two years). Conclusions were similar when considering these age groups separately; we therefore presented our summary table (Table 3) for all ages together.

Previous studies have reported early life respiratory infections, basically LRTIs, to be one of the major risk factors to develop asthma later in life (Bisgaard and Bonnelykke, 2010; Busse et al., 2010). However, very few of the reviewed longitudinal studies have made continued assessments of respiratory and asthma symptoms at different ages (Karmaus et al., 2005; Sunyer et al., 2005, 2006; Weisglas-Kuperus et al., 2000). More studies should use continued assessments of children (from birth up to adolescence) in order to identify critical stages of the effects of POPs and to see if the effects seen at early ages (i.e. increased respiratory infections due to prenatal exposure to DDE) persist later in life. Additionally, recent studies focusing on other risk factors have tried to identify groups of individuals with similar patterns of related respiratory and allergic symptoms using latent class analysis techniques (Hepworth et al., 2010; Siroux et al., 2011), rather than analyzing each symptom as a separate outcome. Employing such methods in the field of immunotoxicants would facilitate our understanding on how such exposures may affect interrelated symptoms.

Regarding immune response, a very large variety of cell subtypes, cell-markers and cytokine was investigated, covering many aspects of the innate and adaptive immune responses. There was little correspondence between studies in the indicators used making comparisons difficult. Also, an explanation of why specific markers were chosen instead of others, and of the exact meaning of increases or decreases in the biomarker levels, is often lacking for some of these biomarkers.

In a novel and big European project, MeDALL (Mechanisms of the Development of ALLergy), current aims are to generate novel knowledge on the mechanisms of initiation of allergy and to propose early diagnosis, prevention, and targets for therapy (Bousquet et al., 2011). Within this project harmonized questionnaires and clinical examinations are being developed. Also, new biomarkers, such as cytokines and inflammation markers, are being evaluated and implemented. Such tools and methods could serve as a basis for harmonizing outcome assessment in future studies.

4.3. Risk of bias

As seen in the Supplementary tables B.1–B.4, in a great number of studies when no association was found between a compound and an

outcome, results were not reported, and if so, only a brief comment was sometimes given stating “no association (data not shown)”. This leads to reporting bias which makes impossible to evaluate with more exactitude the evidence of an association. Also, the possibility of publication bias cannot be discarded, since probably many studies with no significant results have not been published. This is certainly a limitation of the present systematic review. On the contrary, the possibility of recall and differential information bias is minor or inexistent in most of the studies, given their prospective nature (cohort studies, except a few cross-sectional studies) and because participants were blind to exposure levels to POPs.

4.4. Mechanisms

The biological mechanisms by which POPs may be immunotoxic are not fully understood; animal and in vitro studies have reported immunotoxicity of POPs and have found that these compounds reduce cell proliferation (Misumi et al., 2005; Mori et al., 2008; Rehana and Rao, 1992; Sormo et al., 2009), increase inflammatory biomarkers, such as TNF- α and NO (Dewitt et al., 2012; Dutta et al., 2008; Ezendam et al., 2004, 2005), and induce oxidative stress (Perez-Maldonado et al., 2005) which increases apoptosis and necrosis of leukocyte cells (Dutta et al., 2008; Misumi et al., 2005; Perez-Maldonado et al., 2006). However, results between animal studies can differ, in part due to differences in the species or strains used, leading to difficulties to interpret the results (Dewitt et al., 2012; Grandjean et al., 2010). In epidemiological studies cell counts can serve as a general indicator of the immune status, but cytokine assays can provide a more mechanistic examination of the effect of exposure (Duramad et al., 2007). In the present review only four studies assessed cytokine response, three of them in cord blood, where cytokine response has been shown to be very low (Holt and Jones, 2000; Krampera et al., 2000). Some other studies assessed humoral cell response, but very few assessed specific antibody counts. Improvements in the state of the art can thus be made by larger studies that include mechanistic markers of specific antibody responses (i.e. T-cell-dependent IgM antibody responses (TDAR)), markers of specific cell-receptor expression (i.e. peroxisome proliferator-activated receptor (PPAR α)) and markers of inflammation (i.e. TNF α and IL-6) and patterns of cytokine alterations, including alterations in the Th₁/Th₂ cytokine profile, which if shifted toward one subset over another, the risk of immune dysfunction increases (Dewitt et al., 2012; Dietert and Piepenbrink, 2006). Measurement of key components of the immune system, such as collectins, important in the innate immunity, or serum lysozyme, which is an indicator of antibacterial responses of the innate immune system, might be another interesting new field to explore (Dewitt et al., 2012; Dietert and Piepenbrink, 2006). Additionally, animal and human studies have shown differences in immunotoxicity according to sex (Dewitt et al., 2012; Dietert and Piepenbrink, 2006); thus, future studies should assess effects by performing stratified analyses according to sex.

4.5. Limitations of the classification

In the present review, the IARC classification for evidence of an association was used as a guide. However, such classifications can be subject to a degree of subjectivity. In the present review, in order to avoid subjectivity, two independent reviewers classified the evidence; in the case of disagreement a third reviewer gave the decision. Only in the case of the evidence for prenatal dioxins and dl-PCB exposure and respiratory infections, including AOM, the first two reviewers did not agree.

5. Conclusions and recommendations

The present review suggests that POP compounds can adversely influence immune and respiratory system development. However, the scientific evidence for many of the exposure–outcome associations

evaluated in this review is inadequate, mainly due to the reduced number of studies and heterogeneity between studies in exposure and outcome assessment. Also, mechanisms remain largely unexplored. Recommendations for significantly improving our understanding of how POPs may affect the developing human respiratory and immune systems thus include:

Congeners, mixtures of chemicals and exposures of emerging concern: application of conversion factors of levels measured in different matrices would facilitate the performance of meta-analysis including different birth cohort studies. PBPK models should also be applied when possible in order to explore critical windows of exposure. Potential immunotoxicity effects of the mixtures of chemicals and exposures of emerging concern should be assessed, as should the effects of co-exposures.

Related outcomes and persistent effects: studies should focus on long-term assessment of respiratory infections and asthma-related symptoms in order to identify critical stages and persistency of effects. Also, further understanding is needed on how exposures may affect interrelated respiratory and allergic symptoms by applying latent class analysis techniques. The methods and tools under development as part of MeDALL and other asthma and allergy projects could serve as a basis for outcome harmonization in future studies.

Mechanisms: improved knowledge on the potential mechanisms of immunotoxic action of POPs is needed; this may be achieved by the integration of the measurement of specific immunoglobulin and cytokine response, as well as specific cell-receptor expression and other important components of the immune system. Sex differences should also be considered.

Larger studies and meta-analyses: this review reveals that there are many small-sized studies with often inconsistent results. Larger studies are needed to improve statistical power and causal inference. Combining data from different ongoing birth cohorts may be a promising way to improve statistical power (Govarts et al., 2012; Vrijheid et al., 2012); for the study of respiratory and immune system outcomes this would require a substantial effort on both exposure and outcome harmonization.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.envint.2012.11.005>.

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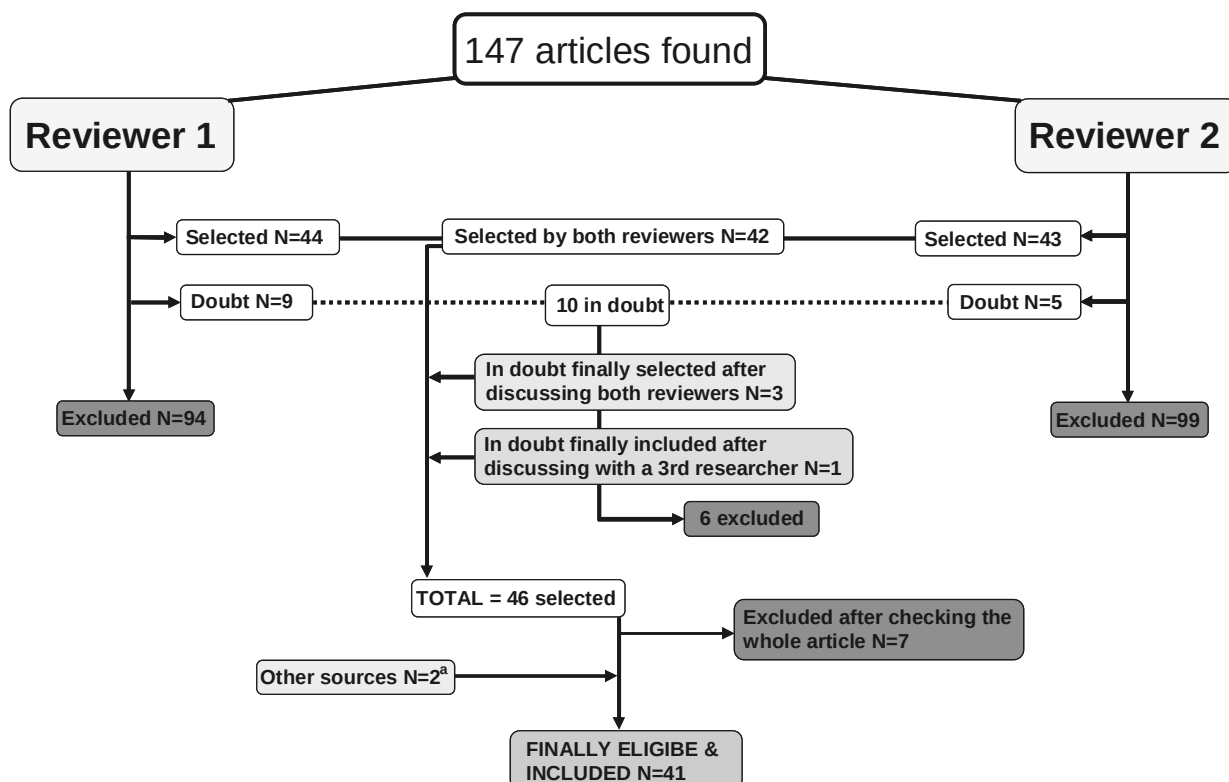
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APPENDIXES

“Effects of persistent organic pollutants on the developing respiratory and immune systems: a systematic review”

Figure A. Articles selection process.



^aAfter checking references there were 5 possible new articles found by reviewer 1, but after discussing with reviewer 2, the articles were not finally included. One study was also found through MEDLINE but not through the standard search, and the other one was found through the second search engine, SCOPUS.

Table A. Study design and exposure assessment of eligible studies (ordered by year and then alphabetically).

Author (Year)	Country & Study design ^a	Exposure			
		Biological Matrix	Prenatal, Postnatal, Perinatal	Compound ^b	Levels of exposure
Rogan (1987)	USA Cohort (I)	Breastmilk x Breastfeeding ^c	Postnatal	(unknown) Σ PCBs DDE	Min-Max: 0.31 – 23.8 ppm 0.49 – 15.80 ppm
Weisglas-Kuperus (1995)	The NL Cohort (I)	Maternal blood	Prenatal	(1dl- & 3 ndl-) Σ PCBs	Mean (SD): 2.25 (0.98) μ g/L
		Breastmilk ^c	Prenatal	(unkwon) Dioxins & 6 dl-PCBs	66.59 (24.35) pg/g fat total TEQ
		Breastmilk x breastfeeding ^c	Postnatal	(unkwon) Dioxins & 6 dl-PCBs	Levels not provided
Nagayama (1998)	Japan Cohort (I)	Breastmilk x breastfeeding ^c	Postnatal	(unkwon) Dioxins & dl-PCBs	Mean (Min-Max): 34 (6-84) ng/kg body weight total TEQ intake
Yu (1998)	Taiwan Cohort (I)	Serum at 8-16y	Postnatal	(unkwon) PCB/PCDFs	Levels not provided
Reichertová (1999)	Slovakia Cross-sectional	Placenta	Prenatal	PCB-118	Median (Min-Max) (two regions): Industrial: 0.1 (0-23.5)
				DDE	Rural: ND (0-0.4) μ g/kg Industrial: 0.1 (0-2.2) μ g/kg
				HCB	Rural: 0.1 (0-2.0) μ g/kg Industrial: 0.6 (0-72.0) μ g/kg
				Other POPs	Rural: 0.4 (0-2.0) μ g/kg HCH, PeCB, DDT and other PCBs
Dewailly (2000)	Canada Cohort (I)	Breastmilk ^c	Prenatal	(3 ndl-) Σ PCBs	GM (95%CI): 621 (530 – 727) μ g/kg
				DDE	962 (835 – 1108) μ g/kg
				HCB	107 (92 – 125) μ g/kg
				Dieldrin	30 (26 – 35) μ g/kg
				Mirex	14 (12-16) μ g/kg
				Others	Chlordane, Endrin, HCE
Weisglas-Kuperus (2000)	The NL Cohort (I)	Maternal blood	Prenatal	(1dl- & 3 ndl-) Σ PCBs	Median (Min-Max): 2.07 (0.59 – 7.35) μ g/L
		Cord blood	Prenatal	(1dl- & 3 ndl-) Σ PCBs	0.40 (0.08 – 2.08) μ g/L
		Breastmilk ^c	Prenatal	(unkwon) dl-PCBs (Planar)	14.9 (4.4 – 45.7) pg TEQ/g milk fat
				(unkwon) dl-PCBs (Mono-ortho)	14.0 (3.2-44.4) pg TEQ/g milk fat
				(unkwon) Dioxins	35.8 (10.2 – 87.2) pg TEQ/g milk fat
		Plasma at 42m	Postnatal	(1dl- & 3 ndl-) Σ PCBs	0.39 (0.08 – 5.90) μ g/L
Karmaus (2001)	Germany Cross-sectional (I)	Plasma at 7-10y	Postnatal	(1dl- & 6 ndl-) Σ PCBs	GM (Max): 0.49 (4.48) μ g/L
				DDE	0.32 (4.02) μ g/L
				HCB	0.22 (2.49) μ g/L
				β -HCH	0.06 (4.48) μ g/L
Ten Tusscher (2001)	The NL Cohort (II + III)	Breastmilk ^c	Prenatal	(unkwon) Dioxins	Mean (Min-Max): 34.6 (8.74 – 88.8) ng TEQ/kg fat
		Breastmilk x breastfeeding ^c	Postnatal	(unkwon) Dioxins	75.4 (4.34 – 384.5) ng TEQ/kg fat

Table A (cont.)

Author (Year)	Country & Study design ^a	Exposure			
		Biological Matrix	Prenatal, Postnatal, Perinatal	Compound ^b	Levels of exposure
Van Den Heuvel (2002)	Belgium Cross-sectional	Serum at 17-18y	Postnatal	(3 ndl-) Σ PCBs (unkwon) dl-PCBs:	GM (95%CI): Girls: 189.7 (172.2-208.5) pmol/g fat Boys: 359.8 (326.6-397.2) pmol/g fat Girls: 28.6 (24.9-32.8) pg TEQ/g fat Boys: 34.9 (28.7-42.5) pg TEQ/g fat
Bilrha (2003)	Canada Cross-sectional	Cord blood	Prenatal	(4 dl- & 10 ndl-) Σ PCBs DDE HCB	GM (95%CI): Fishing group: 197 (155-250) μ g/kg lipids Reference group: 80 (75-86) μ g/kg lipids Fishing group: 144 (114-182) μ g/kg lipids Reference group: 84 (73-96) μ g/kg lipids Fishing group: 14 (12-16) μ g/kg lipids Reference group: 9 (8-10) μ g/kg lipids
Ten Tusscher (2003)	The NL Cohort (III)	Breastmilk ^c Breastmilk x breastfeeding ^c	Prenatal Postnatal	(unkwon) Dioxins & furans (unkwon) Dioxins & furans	Mean (Min-Max): 27.8 (8.74 – 46.6) ng TEQ/kg fat 43.4 (4.34 – 123.7) ng TEQ/kg fat
Dallaire (2004)	Canada Cohort (II)	Maternal blood Serum at 7m	Prenatal Postnatal	(4 dl- & 10 ndl-) Σ PCBs PCB-153 ^d DDE (4 dl- & 10 ndl-) Σ PCBs PCB-153 ^d DDE	GM (95%CI): 308 (279-340) μ g/kg lipid 102 (91.4-113) μ g/kg lipid 294 (267-324) μ g/kg lipid 259 (218-307) μ g/kg lipid 76.1 (62.4-92.9) μ g/kg lipid 256 (214-307) μ g/kg lipid
Weisglas-Kuperus (2004)	The NL Cohort (I)	Maternal blood Cord blood Breastmilk x breastfeeding ^c	Prenatal Prenatal Postnatal	(1 dl- & 3 ndl-) Σ PCBs (1 dl- & 3 ndl-) Σ PCBs (1 dl- & 3 ndl-) Σ PCBs (20) ndl- Σ PCBs (17) Dioxins & (6 dl-) PCBs	Median (Min-Max): 2.06 (0.73 – 5.08) μ g/L 0.41 (0.08 – 1.99) μ g/L 0.39 (0.17-0.80) μ g/g milk fat 0.44 (0.20 – 0.89) μ g/g milk fat 67.1 (27.7 – 135.2) pg/g milk fat total TEQ
Karmaus (2005)	Germany Cross-sectional (I)	Blood at 7-10y	Postnatal	(1 dl- & 6 ndl-) Σ PCBs DDE HCB γ -HCH	GM (95% Confidence Interval): Girls:0.43 (0.16-1.39) Boys:0.54 (0.19-1.66) μ g/L Girls:0.32 (0.13-1.07) Boys:0.31 (0.13-0.96) μ g/L Girls:0.21 (0.11-0.48) Boys:0.23 (0.11-0.54) μ g/L Girls:0.02 (0.01-0.06) Boys:0.02 (0.01-0.04) μ g/L
Sunyer (2005)	Spain Cohort (I)	Cord blood	Prenatal	(1 dl- & 6 ndl-) Σ PCBs DDE HCB	Median (25 th -75 th): 0.69 (0.50-0.98) ng/mL 1.03 (0.57-1.94) ng/mL 0.68 (0.46-1.02) ng/mL
Dallaire (2006)	Canada Cohort (III)	Cord blood	Prenatal	(4 dl- & 10 ndl-) Σ PCBs PCB-153 ^d Other OCs	Mean (Min-Max): 323.5 μ g/kg (not provided) 93.6 (12.3-653.6) μ g/kg DDE, HCB, aldrin, chlordane, mirex

Table A (cont.)

Author (Year)	Country & Study design ^a	Exposure			
		Biological Matrix	Prenatal, Postnatal, Perinatal	Compound ^b	Levels of exposure
Heilmann (2006)	Faroe Islands Cohort (I) ^e	Maternal blood	Prenatal	(3 ndl-) ΣPCBs	GM (IQR): 1.22 (0.70-2.10) µg/L
		Breastmilk	Postnatal	(3 ndl-) ΣPCBs	1.60 (0.87-2.78) µg/L
		Serum at 7.5y	Postnatal	(3 ndl-) ΣPCBs	1.29 (0.45-1.54) µg/L
		All samples	Pre/Postnatal	(3) dl-PCBs (mono-ortho):	TEQ calculated but not provided
	Faroe Islands Cohort (II) ^e	Maternal blood	Prenatal	(3) ndl-ΣPCBs	1.28 (0.83-2.15) µg/L
		Breastmilk	Postnatal	(3) ndl-ΣPCBs	1.35 (0.84-2.48) µg/L
		Serum at 18m	Postnatal	(3) ndl-ΣPCBs	1.16 (0.66-2.07) µg/L
		All samples	Pre/Postnatal	(3) dl-PCBs (mono-ortho):	TEQ calculated but not provided
Kaneko (2006)	Japan Cohort (II)	Breastmilk ^c	Perinatal	(14) PCDDs, (15) PCDFs, (12) dl-PCBs	Mean (SD): 14.8 (6.1) pg TFQ/g fat (Total dioxins)
Noakes (2006)	Australia Cohort (I)	Maternal blood and cord blood	Prenatal	DDE, HCB, dieldrin, or others	Median (IQR): Very few samples over the DL, all had values of 0.0005 (0.0005-0.0005) mg/L
			Prenatal	DDE	0.07 (0.05-0.12) mg/kg fat
		Breastmilk	Perinatal	HCB & dieldrin	Very few samples over the DL
				DDE	0.003 (0.001-0.009) mg/L
				HCB & dieldrin	Very few samples over the DL
Sunyer (2006)	Spain Cohort (I)	Cord blood	Prenatal	DDE	Median (25 th -75 th): 1.03 (0.57-1.94) ng/mL
				DDT	0.08 (0.04-0.20) ng/mL
		Serum at 4y	Postnatal	DDE	0.81 (0.44-1.77) ng/mL
				DDT	0.05 (0.02-0.11) ng/mL
Brooks (2007)	USA Cross-sectional	Placenta	Prenatal	DDE	Median (95%CI): 58.3 (40.2-388.4) pg/g
Nagayama (2007)	Japan Cohort (III)	Breastmilk	Perinatal	(unknown) ΣPCBs	Median (Min-75 th): 110 (20-162) ng/g lipid
				(20) Dioxins & dl-PCBs	23 (3.4-29) pg TEQ/g lipid
				DDE & DDT	286 (52-428) ng/g lipid
				HCH	334 (39-609) ng/g lipid
				HCE	3.0 (ND-7.0) ng/g lipid
				Chlordane	68 (10-98) ng/g lipid
Glynn (2008)	Sweden Cohort (I)	Maternal blood	Prenatal	(1 dl- & 2 ndl-) ΣPCBs	Median (Min-Max): 4 (3-427) ng/g lipid
				PCB-153	60 (23-179) ng/g lipid
				(3) ndl-PCBs	131 (44-362) ng/g lipid
				(4) dl-PCBs	4 (1-20) pg TEQ/g lipid
				DDE	88 (21-622) ng/g lipid
		Breastmilk	Postnatal	(1 dl- & 2 ndl-) ΣPCBs	8 (0-155) ng/g fresh weight*days of nursing
				PCB-153	187 (0-853) ng/g fresh weight*days of nursing
				(3) ndl-PCBs	364 (0-1666) ng/g fresh weight*days of nursing
				(4) dl-PCBs	11 (0-54) pg TEQ/g fresh weight*days of nursing
				DDE	311 (0-2199) ng/g fresh weight*days of nursing

Table A (cont.)

Author (Year)	Country & Study design ^a	Exposure			
		Biological Matrix	Prenatal, Postnatal, Perinatal	Compound ^b	Levels of exposure
Park (2008)	Slovakia Cohort (I)	Maternal blood	Prenatal	(2 dl- & 4 ndl-) Σ PCBs DDE & DDT	Median (10 th -90 th): 440 (190-1170) ng/g lipid Levels not indicated
Leijs (2009)	The NL Cohort (IV)	Breastmilk	Prenatal	Dioxins (7 PCDDs & 12 PCDFs)	Mean (Min-Max): 32.6 (8.7-88.8) pg TEQ/g lipid
		Breastmilk x breastfeeding	Postnatal	Dioxins (7 PCDDs & 12 PCDFs)	66.9 (4.34-279) ng TEQ
		Serum at 15y	Postnatal	Dioxins (7 PCDDs & 12 PCDFs)	2.2 (0.4-6.1) pg TEQ/g lipid
				(3) dl- Σ PCBs (8) PBDEs	2.2 (0.04-7.8) pg TEQ/g lipid 13.9 (4.9-73.6) ng/g lipid
Grandjean (2010)	Faroe Islands Cohort (II)	Maternal blood	Prenatal	(3 ndl-) Σ PCBs	GM (IQR): 1.25 (0.83-1.90) μ g/g lipid
		Breastmilk	Postnatal	(3 ndl-) Σ PCBs	1.34 (0.85-2.13) μ g/g lipid
		Serum at 5y	Postnatal	(3 ndl-) Σ PCBs	1.14 (0.70-1.93) μ g/g lipid
		Serum at 7y			0.75 (0.43-1.38) μ g/g lipid
Heilmann (2010)	Faroe Islands Cohort (II)	Maternal blood	Prenatal	(3) ndl- Σ PCBs	GM (IQR): 1.25 (0.83-1.90) μ g/g lipid
		Breastmilk	Postnatal	(3) ndl- Σ PCBs	1.34 (0.85-2.13) μ g/g lipid
		Serum at 18m	Postnatal	(3) ndl- Σ PCBs	1.17 (0.65-2.11) μ g/g lipid
		Serum at 5y			1.14 (0.70-1.93) μ g/g lipid
		Serum at 7y			0.75 (0.43-1.38) μ g/g lipid
		All samples	Pre/Postnatal	(3) dl-PCBs (mono-ortho):	TEQ calculated but not provided
Jusko (2010)	Slovakia Cohort (I)	Maternal blood	Prenatal	(2 dl- & 4 ndl-) Σ PCBs	Median (25 th -75 th): 455.0 (334.5-719.9) ng/g lipid
		Cord blood	Prenatal	(4 ndl-) Σ PCBs	343.1 (224.3-534.8) ng/g lipid
		Serum at 6m	Postnatal	(4 ndl-) Σ PCBs	360.7 (93.7-786.7) ng/g lipid
Sunyer (2010)	Spain Cohort (II)	Maternal blood	Prenatal	(1 dl- & 3 ndl-) Σ PCBs	Median (25 th -75 th): 84.7 (62.2-119.3) ng/g lipid
				DDE	112.3 (70.1-169.0) ng/g lipid
				HCB	43.7 (27.3-69.8) ng/g lipid
				β -HCH	34.6 (23.6-49.1) ng/g lipid
Horváthová (2011a)	Slovakia Cohort (I)	Maternal blood	Prenatal	(2 dl- & 4 ndl-) Σ PCBs	Median: Polluted area: 531.3 ng/g lipid Cleaner area: 269.5 ng/g lipid
				(1 dl- & 8 ndl-) Σ OH-PCBs	Polluted area: 0.55 ng/g lipid Cleaner area: 0.32 ng/g lipid
Horváthová (2011b)	Slovakia Cohort (I)	Maternal blood	Prenatal	(2 dl- & 4 ndl-) Σ PCBs	Mean: Polluted area: 718.5 ng/g lipid Cleaner area: 373.7 ng/g lipid Median (25 th -75 th)
		Cord blood			Total population: 343 (224-535) ng/g lipid
		Serum at 6m	Postnatal		Total population: 361 (94-787) ng/g lipid

Table A (cont.)

Author (Year)	Country & Study design ^a	Exposure			
		Biological Matrix	Prenatal, Postnatal, Perinatal	Compound ^b	Levels of exposure
Jusko (2011)	Slovakia Cohort (I)	Maternal blood	Prenatal	(2 dl- & 4 ndl-) ΣPCBs	Median (25 th -75 th): 455 (335-720) ng/g lipid
		Cord blood	Prenatal	(4 ndl-) ΣPCBs	343 (224-535) ng/g lipid
		Serum at 6m	Postnatal	(4 ndl-) ΣPCBs	361 (94-787) ng/g lipid
Miyashita (2011)	Japan Cohort (IV)	Maternal blood	Prenatal	(7) ΣPCDDs	Median (25 th -75 th): 460.9 (365.5-609.0) pg/g lipid
				(10) ΣPCDFs	18.0 (14.4-22.6) pg/g lipid
				(4) dl-ΣPCBs (non-ortho)	76.0 (53.4-99.5) pg/g lipid
				(8) dl-ΣPCBs (mono-ortho)	11471.7 (7747.1-15641.8) pg/g lipid
				Total Dioxins	11968.1 (8149.7-16432.2) pg/g lipid
				Total Dioxins TEQ	13.9 (10.14-18.35) pg TEQ/g lipid
Stolevik (2011)	Norway Cohort (I)	Estimated intake during pregnancy ^f	Prenatal	(6) ndl-ΣPCBs (17) Dioxins & (12) dl-ΣPCBs	Median (IQR): 2.59 (1.80-4.09) ng/kg body weight/day 0.58 (0.45-0.81) ng/kg body weight/day
Wang (2011)	Taiwan Cohort (II)	Cord blood	Prenatal	PFOA	Median (range): 1.71 (0.75-17.40) ng/mL
				PFOS	5.50 (0.11-48.36) ng/mL
				PFNA	2.30 (0.38-63.87) ng/mL
				PFHxS	0.035 (0.035-0.42) ng/mL
Gascon (2012)	Spain Cohort (II extended)	Maternal blood	Prenatal	(1 dl- & 3 ndl-) ΣPCBs	Median (25 th -75 th): Spanish: 113.7 (79.4-158.6) ng/g lipid Latin-American: 27.9 (23.4-45.2) ng/ g lipid
				DDE	Spanish: 116.3 (72.6-191.7) ng/g lipid Latin-American: 385.0 (146.2-953.8) ng/g lipid
				HCB	Spanish: 46.4 (26.4-79.0) ng/g lipid Latin-American: 6.9 (5.8-18.8) ng/g lipid
Grandjean (2012)	Faroe Islands Cohort (II)	Maternal blood	Prenatal	PFOS	GM (IQR): 27.3 (23.2-33.1) ng/mL
				PFOA	3.20 (2.56-4.01) ng/mL
				PFHxS	4.41 (2.24-8.43) ng/mL
				PFNA	0.60 (0.46-0.79) ng/mL
				PFDA	0.28 (0.22-0.38) ng/mL
		Serum at age 5y	Postnatal	PFOS	16.7 (13.5-21.1) ng/mL
				PFOA	4.06 (3.33-4.96) ng/mL
				PFHxS	0.63 (0.45-0.88) ng/mL
				PFNA	1.00 (0.76-1.24) ng/mL
				PFDA	0.28 (0.21-0.38) ng/mL
Jusko (2012)	Slovakia Cohort (I)	Maternal blood	Prenatal	(4 ndl-) ΣPCBs	Median (25 th – 75 th): 415 (267-660) ng/g lipid
				PCB-153	143 (91-220) ng/g lipid
		Serum at 6m	Postnatal	(4 ndl-) ΣPCBs	278 (87-726) ng/g lipid
				PCB-153	98 (33-264) ng/g lipid
		Serum at 16m	Postnatal	(4 ndl-) ΣPCBs	292 (100-707) ng/ g lipid
				PCB-153	106 (37-254) ng/g lipid
Okada (2012)	Japan Cohort (IV)	Maternal blood	Prenatal	PFOS	Median (25 th – 75 th): 5.2 (3.4-7.2) ng/mL
				PFOA	1.3 (0.8-1.7) ng/mL

Table A (cont.)

Author (Year)	Country & Study design ^a	Exposure			
		Biological Matrix	Prenatal, Postnatal, Perinatal	Compound ^b	Levels of exposure
Tsuji (2012) ^d	Japan Case-control	Serum at 23m	Postnatal	(3-dl & 13-ndl) ΣPCBs	Median (95%CI): Low tertile: 3.4 (2.3-4.2) pg/g wet Medium tertile: 8.2 (5.9-8.7) pg/g wet High tertile: 12.5 (11.0-16.7) pg/g wet

"x breastfeeding"= by weeks of breastfeeding or amount of milk consumed by the infant; **DL**=detection limit; **GM**=Geometric mean; (Σ-sum, dl-dioxin like, ndl-non dioxin like)-**PCBs** (polychlorinated biphenyls); **DDE** (dichlorodiphenyldichloroethylene); **DDT** (dichlorodiphenyltrichloroethane); **HCB** (hexachlorobenzene); **HCH** (hexachlorohexane); **HCE** (heptachlor epoxide); **PCDD** (polychlorinated dibenzodioxins); **PCDFs** (polychlorinated dibenzofurans); **PFOA** (perfluorooctanoic acid); **PFOS** (perfluorooctane sulfonate); **PFNA** (perfluorononanoic acid); **PFHxS** (perfluorohexane sulfonic acid); **PFDA** (perfluorodecanoate).

^aDifferent study populations coming from a same country are indicated with (I), (II), (III) or (IV).

^bExposure assessed is indicated in the tables as it is used in the original study. However, in order to indicate the congeners included in the sums, mainly PCBs, we have indicated the number of congeners (N) and the type of congeners included in the sum (N-dl and N-ndl).

^cMeasured only in breastfeeding mothers.

^dDue to the high correlations between compounds ($r=0.94-0.99$), PCB-153 was used in the models as a surrogate of the sum of PCBs exposure (Dallaire et al. 2004), and as a surrogate of the ΣPCBs and DDE exposure (Dallaire et al. 2006). These two studies were based on two different populations in Canada.

^eTwo different study populations in one paper.

^fCorrelated to blood concentrations of a subsample ($r=0.34-0.37$, $p<0.05$).

^gLevels of the different PCB congeners analyzed are not provided in the manuscript, nor the final congeners included in the final sum.

Table B.1 Studies on persistent organic pollutants and respiratory and other infections (ordered by age group, year and author).

Author (year)	Child age ^a	Outcome	Statistic	Prenatal exposure ^b					Postnatal exposure ^b				
				PCBs and ndl-PCBs	Dioxins and dl-PCBs	DDE (DDT)	HCB	Other POPs	PCBs and ndl-PCBs	Dioxins and dl-PCBs	DDE (DDT)	HCB	Other POPs
AOM													
<2 years													
Dewailly (2000)	3,7,12m ^c	At least one episode	RR (95%CI)	dl-PCBs: T3 1.28 (0.92,1.77)		T3 1.52 (1.05,2.22)	T3 1.49 (1.10,2.03)	Mirex: T3 1.36 (0.99,1.86) Dieldrin: T3 1.26 (0.93,1.71)					
		Three or more episodes		T3 1.65 (0.49,5.57)		T3 3.48 (0.86,14.11) ^d	T3 3.71 (1.10,12.56)	Mirex: T3 1.03 (0.31,3.43) Dieldrin: T3 3.50 (0.95,12.97)					
Dallaire (2004)	6m	Ever	RR (95%CI)	PCB153 ^e : Q4 1.39 (0.82,2.35)		Q4 1.55 (0.90,2.68) ^d			NS ^e		NS ^e		
	12m	Ever		Q4 0.97 (0.73,1.28)		Q4 1.02 (0.76,1.35)							
Miyashita (2011) ^f	18m	Ever	OR (95%CI)		Total Dioxins: Q4 1.69 (0.70,4.07) PCDFs: Q4 2.50 (1.07,5.88) dl-PCBs (non-ortho): Q4 1.51 (0.62,3.63) ^d								
Stolevik (2011)	12m	Ever	OR (95%CI)	ndl-PCBs (>=80th vs <80th percentile): 1.85 (0.67,5.17)	Dioxins and dl-PCBs (>=80th vs <80th percentile): 2.41 (0.90,6.51)								
Okada (2012)	18m	Ever	OR (95%CI)					PFOS: 1.40 (0.33,6.00) PFOA: 1.51 (0.45,5.12)					
>2 years													
Yu 1998	8-16y	Episodes last 6 months	T-test *p<0.05							Dioxins: no differences between exposed and controls			
Weisglas-Kuperus (2000) ^g	42m	One or more episodes Six or more episodes	OR (95%CI)	PCBs: 0.89 (0.65,1.23) 1.37 (0.87,2.17)	Dioxins and dl-PCBs (planar and mono-ortho): NR dl-PCBs (planar): 1.10 (1.00,1.20) dl-PCBs (mono-ortho): 1.17 (1.04,1.32) Dioxins: NR				PCBs: 1.27 (0.61,2.64) 3.06 (1.17,7.98)				

Author (year)	Child age ^a	Outcome	Statistic	Prenatal exposure ^b					Postnatal exposure ^b				
				PCBs and ndl-PCBs	Dioxins and dl-PCBs	DDE (DDT)	HCB	Other POPs	PCBs and ndl-PCBs	Dioxins and dl-PCBs	DDE (DDT)	HCB	Other POPs
Karmaus (2001)	7-10y	Ever	OR (95%CI)						PCBs: high DDE + high vs low PCBs: 3.70 (1.64,8.34) ^h		0.5 (0.31,0.79)	High DDE + high vs low HCB: 2.38 (1.08,5.25) ^h	β-HCH: NR
Ten Tusscher (2001)	7-12y	Ever	OR (95%CI)		Dioxins: NS					Dioxins: NS			
Ten Tusscher (2003)	8y	Ever	OR (95%CI)		Dioxins and furans: 1.01 (0.92,1.11)					Dioxins and furans: 1.00 (0.97,1.03)			
Weisglas-Kuperus (2004)	3-7y	Recurrent	OR (95%CI)	PCBs: 0.98 (0.53, 1.80)					PCBs: 1.19 (1.01,1.41)	Dioxins and dl-PCBs: NS			
Dallaire (2006)	5-7y	Ever	RR (95%CI)	PCB153 ^e : 1.12 (1.05,1.20)		NS ^e	NR	NR					
Respiratory infections <2 years													
Dallaire (2004)	6m	LRTIs	RR (95%CI)	PCB153 ^e : Q4 1.18 (0.68,2.04) ^d		Q4 0.96 (0.55,1.66)			NS ^e		NS ^e		
		URTIs		Q4 1.32 (0.87,2.00)		Q4 1.40 (0.90,2.16) ^d							
	12m	LRTIs		Q4 1.03 (0.72,1.48)		Q4 1.00 (0.69,1.45)							
		URTIs		Q4 1.23 (0.92,1.65)		Q4 1.30 (0.96,1.78) ^d							
Glynn (2008)	3m	General infections	OR (95%CI)	PCBs: T3 3.4 (1.4,7.8)	dl-PBCs: Q4 0.23 (0.06,0.91)	Q4 0.74 (0.25,2.20)			PCBs: Q4 1.4 (0.53,3.8)	dl-PBCs: Q4 0.33 (0.10,1.1) ^d	Q4 0.52 (0.17,1.50) ^d		
				PCB153: Q4 0.42 (0.12,1.4) ^d ndl-PCBs: Q4 0.29 (0.08,1.00)					PCB153: Q4 0.20 (0.06,1.73) ndl-PCBs: Q4 0.14 (0.04,0.50)				
Sunyer (2010)	6, 14m	Recurrent LRTIs	RR (95%CI)	PCBs: 0.84 (0.49,1.47) ⁱ		1.43 (1.09,1.88)	NS	NS					
Stolevik (2011)	12m	URTIs	β coef (95%CI)	ndl-PCBs (>=80 th vs <80 th percentile): 1.16 (0.16,2.16)	Dioxins and dl-PCBs (continuous): 1.31 (0.40,2.22)								
		Pneumonia		NS	NS								
Gascon (2012) ^j	14m	LRTIs	RR (95%CI)	PCBs: 1.00 (0.86,1.18)		1.11 (1.00, 1.22)	1.06 (0.95, 1.17)						

Table B.1 (cont.)														
Author (year)	Child age ^a	Outcome	Statistic	Prenatal exposure ^b					Postnatal exposure ^b					
				PCBs and ndl-PCBs	Dioxins and dl-PCBs	DDE (DDT)	HCB	Other POPs	PCBs and ndl-PCBs	Dioxins and dl-PCBs	DDE (DDT)	HCB	Other POPs	
>2 years														
Yu 1998	8-16y	Influenza episodes last 6 months	T-test *p<0.05								Dioxins: higher* frequency of influenza in exposed vs controls			
Weisglas-Kuperus (2000) ^g	42m	Coughing, chest infection and phlegm Pneumonia	OR (95%CI)	PCBs: 1.08 (0.75,1.54)	Dioxins: 1.06 (1.00,1.11) dl-PCBs (planar and mono-ortho): NR				PCBs: 1.12 (0.58,2.16)					
Karmaus (2001)	7-10y	Pneumonia	OR (95%CI)	0.41 (0.10,1.63)					0.01 (0.01,29.68) PCBs: high DDE + high vs low PCBs: 0.68 (0.26,1.76) ^h		0.79 (0.45,1.40)	High DDE + high vs low HCB: 1.64 (0.56,4.81) ^h	β-HCH: NR	
		Whooping cough							High DDE + high vs low PCBs: 2.48 (0.94,6.57) ^h		0.61 (0.38,0.99)	High DDE + high vs low HCB: 1.69 (0.68,4.20) ^h		
Ten Tusscher (2001)	7-12y	LRTIs, coughing spells Chest infection	OR (95%CI) (cont pval given)		Dioxins: NS						Dioxins: NS			
					Increased chest infection with increasing exposure (p=0.02)									
Ten Tusscher (2003)	8y	LRTIs, coughing spells	OR (95%CI)		Dioxins and furans: NS						Dioxins and furans: NS			
Sunyer (2005)	4y	Chest infection	RR (95%CI)	PCBs: NR		NS	NR							
Dallaire (2006)	5-7y	LRTIs	RR (95%CI)	PCB153 ^e : 1.14 (1.04,1.24)		NS ^e	NR	NR						
		URTIs		0.99 (0.93,1.06)										
Other infections <2 years														
Dallaire (2004)	6m	Gis	RR (95%CI)	PCB153 ^e : Q4 1.54 (0.66,3.60)		Q4 1.35 (0.54,3.42)			NS ^e		NS ^e			
	12m			Q4 1.26 (0.78,2.04) ^d		Q4 1.43 (0.87,2.34) ^d								

Table B.1 (cont.)

Author (year)	Child age ^a	Outcome	Statistic	Prenatal exposure ^b					Postnatal exposure ^b				
				PCBs and ndl-PCBs	Dioxins and dl-PCBs	DDE (DDT)	HCB	Other POPs	PCBs and ndl-PCBs	Dioxins and dl-PCBs	DDE (DDT)	HCB	Other POPs
Stolevik (2011)	12m	Exanthema subitum Gis, urinary infections, chickenpox	OR (95%CI)	(Continuous): 1.10 (1.02,1.20) ndl-PCBs: NS	(Continuous): 2.38 (1.11,5.13) Dioxins and dl-PCBs: NS								
>2 years													
Yu 1998	8-16y	GI episodes last 6 months	T-test *p<0.05										Dioxins: no differences between exposed and controls
Weisglas-Kuperus (2000) ^g	42m	Chickenpox	OR (95%CI)	PCBs: 1.43 (0.92,2.24)	Dioxins and dl-PCBs (planar and mono-ortho): NR				PCBs: 7.63 (1.21,48.54)				
Ten Tusscher (2003)	8y	Chickenpox, measles	OR (95%CI)		Dioxins and furans: NS								Dioxins and furans: NS
Weisglas-Kuperus (2004)	3-7y	Chickenpox	OR (95%CI)	PCBs: 0.53 (0.30,0.94)					PCBs: 0.94 (0.80,1.10)				Dioxins and dl-PCBs: NS

An empty cell indicates that the compound has not been assessed in the study, **NR**=results not reported, presumably because not significant associations were found; **NS**=results not shown but it is mentioned there is no association; **T3**=3rd tertile; **Q4**=4th quartile; **LRTI**=low respiratory tract infection (bronchitis, bronchiolitis, pneumonia); **URTI**=upper respiratory tract infection (tonsillitis, pharyngitis, laryngitis, sinusitis, acute otitis media (**AOM**), rhinitis, nasopharyngitis, epiglottitis, laryngotracheitis, tracheitis, common cold); **GIs**=gastrointestinal infections.

^aAt the time of outcome assessment (m=months, y=years).

^bIn order to simply the summary table, results for DDE (DDT) are in general referred to DDE, otherwise it will be indicated as "DDT". Regarding PCB and dioxin exposure, PCBs can indicate either "unknown congeners" or a mix of ndl- and dl-PCBs included in the final sum (ndl-PCBs were predominant in the sum of most of the studies). If only dioxin-like or non dioxin-like PCBs are included in the sum, then it is indicated as dl-PCBs or ndl-PCBs, respectively. When the exposures assessed are PCDDs or PCDFs it is indicated as dioxins, unless specifically indicated.

^cOutcome assessment in three periods: 0-3m, 4-7m, 8-12m, but results provided in the present table are for all three periods together. For example, within the 4-7m period, significant results were obtained in the 3rd tertile of dieldrin exposure (RR=1.75, 95%CI=1.05,2.91).

^dAssociations are not significant for the highest tertile/quartile, but are significant among other tertiles/quartiles of exposure, showing a non-linear association.

^eDue to the high correlations between compounds (r=0.94-0.99), PCB-153 was used in the models as a surrogate of PCB exposure [Dallaire (2004)], and as a surrogate of PCB and DDE exposure [Dallaire (2006)]. These two studies were based on two different populations in Canada.

^fOther compounds such as PCDDs, non-ortho and mono-ortho PCBs were analyzed; no significant associations were found.

^gResults are presented for maternal PCBs and breastmilk levels (dioxins and dl-PCBs), however, results for cord blood levels (PCBs), not shown in the original paper, were similar to those of the maternal levels, although not significant. For other infections only results on chickenpox are presented in this table, other infections, including scarlatina were not associated to PCBs.

^hIn this paper two categories of DDE exposure using the median as cut-off were created to run the analyses. Categories of DDE were combined with categories of PCBs and HCB exposure to perform the analysis: only when combining high levels of DDE with high levels of PCBs or HCB associations were found with AOM, however, low levels of DDE with high levels of PCBs and HCB did not result into an association with any of the outcomes assessed.

ⁱPCB results are only available after adjusting for DDE exposure.

^jOnly results for the Spanish population (N=1342) presented in this table; the original paper reports similar results for the Latin-American population (N=79).

Table B.2. Studies on persistent organic pollutants and asthma symptoms and atopy (ordered by age group, year and author).

Table 2.12: Studies on persistent organic pollutants and asthma symptoms and atopy (ordered by age group, year and author).														
Author (year)	Child age ^a	Outcome	Statistic	Prenatal exposure ^b					Postnatal exposure ^b					
				PCBs and ndl-PCBs	Dioxins and dl-PCBs	DDE (DDT)	HCB	Other POPs	PCBs and ndl-PCBs	Dioxins and dl-PCBs	DDE (DDT)	HCB	Other POPs	
Asthma symptoms <2 years														
Miyashita (2011) ^c	18m	Asthma	OR (95%CI)		Total Dioxins: Q4 1.32 (0.38,4.59)									
Stolevik (2011)	12m	Asthma	OR (95%CI)	ndl-PCBs: NS	Dioxins and dl-PCBs: NS									
		Wheeze		(>=80th vs <80th percentile): 2.79 (1.20, 6.49)	(>=80th vs <80th percentile): 3.35 (1.45,7.74)									
Gascon (2012) ^d	14m	Wheeze	RR (95%CI)	PCBs: 0.94 (0.81, 1.09)		1.09 (0.99, 1.21)	1.02 (0.93, 1.12)							
Okada (2012)	18m	Wheeze	OR (95%CI)					PFOS: 2.68 (0.39,18.30) PFOA: 1.27 (0.27,6.05)						
>2 years														
Yu 1998	8-16y	Asthma episodes last 6 months	T-test *p<0.05							Dioxins: no differences between exposed and controls				
Weisglas-Kuperus (2000) ^e	42m	SOB with wheeze	OR (95%CI)	PCBs: 0.44 (0.18,0.99)	dl-PCB (planar and mono-ortho): NR				PCBs: 0.34 (0.02,4.49)					
		Asthma or bronchitis		0.87 (0.55,1.40)	NR				0.38 (0.06,2.57)					
Karmaus (2001)	7-10y	Asthma	OR (95%CI)						PCBs: high DDE + high vs low PCBs: 0.56 (0.13,2.52) ^f		3.71 (1.10,12.56)	High DDE + high vs low HCB: 0.53 (0.13,2.16) ^f	β-HCH: NR	
Ten Tusscher (2001)	7-12y	Lung function	OR (95%CI) (only pval given)		Dioxins: reduced lung function with increasing exposure (p=0.045)					Dioxins: reduced lung function with increasing exposure (p=0.0002)				
Van den Heuvel (2002)	17-18y	Ever asthma	OR (95%CI)						ndl-PCBs: 2.12 (1.01, 4.46)	dl-PCBs: 0.75 (0.49,1,15)				
		Bronchial wheezing							1.18 (0.69,2.04)	0.72 (0.51, 1.03)				

Table B.2 (cont.)

Author (year)	Child age ^a	Outcome	Statistic	Prenatal exposure ^b					Postnatal exposure ^b				
				PCBs and ndl-PCBs	Dioxins and dl-PCBs	DDE (DDT)	HCB	Other POPs	PCBs and ndl-PCBs	Dioxins and dl-PCBs	DDE (DDT)	HCB	Other POPs
Ten Tusscher (2003)	8y	Asthma	OR (95%CI)		Dioxins and furans: 0.96 (0.88, 1.06)					Dioxins and furans: 1.00 (0.98,1.04)			
Weisglas-Kuperus (2004)	3-7y	SOB with wheeze	OR (95%CI)	PCBs: 0.59 (0.36,0.97)					PCBs: 0.93 (0.80,1.08)	Dioxins and dl-PCBs: NS			
Sunyer (2005)	4y	Asthma	RR (95%CI)	PCBs: NR		1.46 (0.92,2.32)	NR						
		Wheeze		0.99 (0.81,1.21)		1.32 (1.13,1.54)	0.96 (0.69,1.30)						
		Persistent wheeze		NR		1.26 (1.04,1.54)	NR						
Sunyer (2006)	6.5y	Asthma	OR (95%CI)			1.18 (1.01,1.39)					DDE, DDT: NS		
	1	Wheeze				0.92 (0.80,1.07)							
	2					1.02 (0.92,1.13)							
	3					1.07 (0.96,1.19)							
	4					1.14 (1.02,1.28)							
	6,5					0.99 (0.82,1.19)							
	1-6.5y	Persistent wheeze				1.13 (0.98,1.30)					DDE: NS		
	All	All				DDT: NS					DDT: NS		
Grandjean (2010) ^g	7y	Asthma	Average (IQR) pval	ndl-PCBs: no allergy=1.24 (0.83,2.0), asthma=1.46 (0.80,2.60) p=0.17					ndl-PCBs (7y); no allergy=0.77 (0.44,1.39), asthma=0.89 (0.49,1.70) p=0.33				
Atopy <2 years													
Reichertová (1999)	CB	Total IgE	Correlation *p<0.05	PCB118: 0.35*		0.33*	NR	HCH congeners: NR					
				Other PCB congeners: NR		DDT: NR							
Kaneko (2006)	12m	Total & specific IgE	Correlation *p<0.05		PCDDs, PCDFs and dl-PCBs: NS								
Jusko (2011)	6m	Total IgE	% change per IQR (95%CI)	PCBs: 7.4 (-8.7,26.5)					PCBs: 2.3 (-23.0,25.9)				

Table B.2 (cont.)

Author (year)	Child age ^a	Outcome	Statistic	Prenatal exposure ^b					Postnatal exposure ^b				
				PCBs and ndl-PCBs	Dioxins and dl-PCBs	DDE (DDT)	HCB	Other POPs	PCBs and ndl-PCBs	Dioxins and dl-PCBs	DDE (DDT)	HCB	Other POPs
Miyashita (2011) ^d	18m	Eczema Food allergy	OR (95%CI)		Total Dioxins: Q4 (0.82 (0.28,2.37) Q4 (1.18 (0.45,3.08) dl-PCBs (non-ortho): Q4 1.09 (0.40,3.00) ^d dl-PCBs (mono-ortho): Q4 1.34 (0.49,3.70) ^d								
Stolevik (2011)	12m	Eczema	OR (95%CI)	ndl-PCBs: NS	Dioxins and dl-PCBs: NS								
Wang (2011)	CB	Total IgE	β coef (SE) *p<0.05					PFOA: 0.13 (0.12)* PFOS: 0.16 (0.15)* PFNA: 0.02 (0.15) PFOA: 0.03 (0.24) PFOS: 0.25 (0.18) PFNA: 0.04 (0.47) PFOA: Q4 0.58 (0.22,1.58) PFOS: Q4 2.19 (0.78,6.17) PFNA: Q4 0.72 (0.23,2.21) PFHxS: NR					
	2y												
	CB	Atopic dermatitis	OR (95%CI)										
Okada (2012)	All	All											
	18m	Food allergy	OR (95%CI)					PFOS: 3.72 (0.81,17.10) PFOA: 1.67 (0.52,5.37) PFOS: 0.87 (0.15,5.08) PFOA: 0.96 (0.23,4.02)					
		Eczema											

Table B.2 (cont.)

Author (year)	Child age ^a	Outcome	Statistic	Prenatal exposure ^b					Postnatal exposure ^b				
				PCBs and ndl-PCBs	Dioxins and dl-PCBs	DDE (DDT)	HCB	Other POPs	PCBs and ndl-PCBs	Dioxins and dl-PCBs	DDE (DDT)	HCB	Other POPs
Okada (2012, cont.)	18m	Total IgE ^h	β coef (95%CI)					PFOS: linear -0.24 (-0.89,0.41), quadratic 0.15 (-1.15,1.44), cubic 0.85 (-3.73,5.43) PFOA: linear 0.28 (-0.23,0.79), quadratic -1.00 (-1.92,-0.10), cubic -1.43 (-3.38,0.52)					
Tsuji (2012)	23m	Specific IgE	Median levels test (pg/g wet)						PCBs ⁱ : Milk IgE positive=836 (492,1155), negative=435 (291,592) p=0.03	Results not shown			
>2 years													
Yu 1998	8-16y	Allergi rhinitis episodes last 6 months	T-test *p<0.05							Dioxins: no differences between exposed and controls			
Weisglas- Kuperus (2000) ^e	42m	Allergic reaction Eczema	OR (95%CI)	PCBs: 0.62 (0.29,1.32) 1.18 (0.82,1.71)	dl-PCB (planar and mono-ortho): NR NR				PCBs: 0.01 (0.01,0.37) 0.92 (0.41,2.08)				
Karmaus (2001)	7-10y	Total IgE (>=200uK/l)	OR (95%CI)						PCBs: high DDE + high vs low PCBs: 0.82 (0.32,2.08) ⁱ		2.28 (1.20,4.31)	High DDE + high vs low HCB: 0.49 (0.19,1.23) ^f	β-HCH: NR
Ten Tusscher (2001)	7-12y	Atopy	OR (95%CI)		Dioxins: NS					Dioxins: NS			
Van den Heuvel (2002)	17- 18y	Upper airway disease Hay fever Positive RAST (overall) Total IgE	OR (95%CI) β coef (SE) *p<0.05						ndl-PCBs: 1.18 (0.62,2.25) 1.63 (1.02,2.61) 1.03 (0.64,1.66)	dl-PCBs: 0.66 (0.47, 0.93) 0.97 (0.71,1.33) 0.77 (0.58, 1.01) ^j			
									-0.015 (0.03)	-1.08 (0.46)*			

Table B.2 (cont.)

Author (year)	Child age ^a	Outcome	Statistic	Prenatal exposure ^b					Postnatal exposure ^b				
				PCBs and ndl-PCBs	Dioxins and dl-PCBs	DDE (DDT)	HCB	Other POPs	PCBs and ndl-PCBs	Dioxins and dl-PCBs	DDE (DDT)	HCB	Other POPs
Ten Tusscher (2003)	8y	Allergy	OR (95%CI)		Dioxins and furans: 0.87 (0.77,0.98)					Dioxins and furans: 0.94 (0.89,0.99)			
		Eczema			0.90 (0.76,1.02)					0.97 (0.92,1.02)			
Weisglas-Kuperus (2004)	3-7y	Allergic reaction	OR (95%CI)	PCBs: 0.95 (0.59, 1.52)					PCBs: 1.09 (0.97,1.22)	Dioxins and dl-PCBs: NS			
Karmaus (2005)	7-10y	Specific IgE against aeroallergens	F-test (pval)						PCBs: p=0.84		Increased IgE levels with increasing quartile of exposure (p=0.02)	p=0.95	γ-HCH: p=0.59
Sunyer (2005)	4y	Specific IgE (cat, HDM, grass pollen)	RR (95%CI)	PCBs: NR		0.92 (0.73, 1.17)	NR						
Sunyer (2006)	1-6.5y	SPT	RR (95%CI)			DDE and DDT: NS					DDE and DDT: NS		
Grandjean (2010) ^g	7y	Atopic dermatitis (AD)	Average (IQR) pval	ndl-PCBs: no allergy=1.24 (0.83,2.0), AD=0.70 (0.55,1.58) p=0.01					ndl-PCBs (7y): no allergy=0.77 (0.44,1.39), AD=0.60 (0.29,1.19) p=0.04				
		Total IgE (and specific IgE to grass)		low IgE=1.16 (0.73,1.79), medium IgE=1.17 (0.76,1.97), high IgE=1.29 (0.83,2.3) p=0.30					low IgE=0.66 (0.35,1.30), medium IgE=0.74 (0.46,1.26), high IgE=0.88 (0.56,1.47) p=0.005				

An empty cell indicates that the compound has not been assessed in the study, **NR**=results not reported, presumably because not significant associations were found; **NS**=results not shown but it is mentioned there is no association; **Q4**=4th quartile; **SOB**=shortness of breath; **IgE**=immunoglobulin E; **RAST**=radioallergosorbent; **HDM**=house dust mite.

^aAt the time of outcome assessment (m=months, y=years).

^bIn order to simplify the summary table, results for DDE (DDT) are in general referred to DDE, otherwise it will be indicated as "DDT". Regarding PCB and dioxin exposure, PCBs can indicate either "unknown congeners" or a mix of ndl- and dl-PCBs included in the final sum (ndl-PCBs were predominant in the sum of most of the studies). If only dioxin-like or non dioxin-like PCBs are included in the sum, then it is indicated as dl-PCBs or ndl-PCBs, respectively. When the exposures assessed are PCDDs or PCDFs it is indicated as dioxins, unless specifically indicated.

^cOther compounds, such as PCDDs, non-*ortho* and mono-*ortho* PCBs were analyzed; if not presented in the table, no significant associations were found.

^dOnly results for the Spanish population (N=1342) presented in this table; the original paper reports similar results for the Latin-American population (N=79).

^eResults are presented for maternal PCBs and breastmilk levels (dioxins and dl-PCBs), however, results for cord blood levels (PCBs), not shown in the original paper, were similar to those of the maternal levels, although not significant.

^fIn this paper two categories of DDE exposure using the median as cut-off were created to run the analyses. Categories of DDE were combined with categories of PCBs and HCB exposure to perform the analysis. When combining low levels of DDE with high levels of PCBs or HCB no associations were found with any of the outcomes assessed.

^gChildren with asthma were compared with those with no allergy symptoms as reference group. For total IgE levels children with high (>47.7 kUA/l) and medium (13.6-47.7 kUA/l) IgE levels were compared with children with low levels (<13.6kUA/l). Results for specific grass IgE not shown in this table (they were never significant). Results for postnatal exposure measured at age 5 years were similar to those for postnatal exposure measured at age 7 years.

^hAs the association between PFOA/S and IgE was not linear, cubic polynomial regression analyses were performed. After stratification by gender, associations were significant for females (quadratic=-1.43 (-2.42,-0.42), cubic=-3.08 (-5.43,-0.73)), but not for males.

ⁱThe study compares exposure levels between children with positive (≥0.35 UA IgE/ml) and negative (<0.35 UA IgE/ml) test for specific IgE..Only significant results are provided (Milk IgE results), however, other specific IgE were measured: egg, wheat, house dust mite.

^jResults for specific allergens showed significant negative associations between dl-PCBs and HDM, cat and pollen, but not with birch.

Table B.3 Studies on persistent organic pollutants and immune humoral response (ordered by age group, year and author).

Author (year)	Child age ^a	Outcome	Statistic	Prenatal exposure ^b					Postnatal exposure ^b				
				PCBs and ndl-PCBs	Dioxins and dl-PCBs	DDE (DDT)	HCB	Other POPs	PCBs and ndl-PCBs	Dioxins and dl-PCBs	DDE (DDT)	HCB	Other POPs
General Ab counts													
<2 years													
Dewailly (2000)	3,7,12m	IgA, IgG, IgM	Correlation *p<0.05	ndl-PCBs: NS		NS	NS	Mirex and dieldrin: NS					
Kaneko (2006)	12m	IgA, IgG, IgM	Correlation *p<0.05		PCDDs, PCDFs and dl-PCBs: NS								
Jusko (2011) ^c	6m	IgA	Change % (95%CI)	PCBs: -2.0 (-9.9, 6.5)					ndl-PCBs: -2.4 (-14.4, 11.3)				
		IgG		-1.2 (-4.2, 7.0)				6.4 (-1.5, 14.9)					
		IgM		0.1 (-6.1, 6.6)				-6.1 (-13.0, 1.3)					
>2 years													
Yu (1998)	8-16y	IgA, IgG, IgM	T-test *p<0.05							Dioxins: no differences between exposed and controls			
Van den Heuvel (2002)	17-18y	IgA	β coef (SE) *p<0.05						ndl-PCBs: 0.005 (0.007)	dl-PCBs: 0.20 (0.1)*			
		IgG							-0.009 (0.004)*	0.03 (0.05)			
		IgM							0.0002 (0.007)	-0.02 (0.1)			
Karmaus (2005)	7-10y	IgA	F-test (pval)						PCBs: p=0.34		DDE: increased IgA levels with increasing quartile of exposure (p=0.05)	p=0.08 ^d	γ -HCH: p=0.71
		IgG							p=0.78		p=0.14 ^d	p=0.29	p=0.84
		IgM							Increased IgM levels with increasing quartile of exposure (p<0.01) ^d		p=0.92	Decreased IgM levels with increasing quartile of exposure (p<0.01,not linear across quartiles) ^d	p=0.42

Table B.3 (cont.)

Author (year)	Child age ^a	Outcome	Statistic	Prenatal exposure ^b					Postnatal exposure ^b				
				PCBs and ndl-PCBs	Dioxins and dl-PCBs	DDE (DDT)	HCB	Other POPs	PCBs and ndl- PCBs	Dioxins and dl- PCBs	DDE (DDT)	HCB	Other POPs
Specific Ab counts													
<2 years													
Weisglass- Kuperus (1995)	18m	[Ab] for mumps, measles, rubella	Correlation *p<0.05	PCBs: NR	Dioxins and dl-PCBs: NR					Dioxins and dl- PCBs: NR			
Heilmann (2006) ^e	18m	[Ab] after tetanus vaccination	Change % (pval)	ndl-PCBs: -2.73 (0.83)	dl-PCB: -4.07 (0.76)				ndl-PCBs in milk: - 7.05 (0.53) ^e	dl-PCB (mono- ortho): -7.02 (0.51) ^e			
		[Ab] after diphtheria vaccination		-20.6 (0.04)	-22.6 (0.03)				Serum 18m: -13.8 (0.13)	-5.83 (0.59)			
									Milk: -19.0 (0.04)	-20.7 (0.02)			
									Serum 18m: -20.3 (0.01)	-17.3 (0.06)			
Jusko (2010) ^c	6m	[Ab] after influenza type b vaccination	Change % (95%CI)	PCBs: -6.8 (- 23.4, 13.3)					ndl-PCBs: -6.4 (-30.0, 25.1)				
		[Ab] after tetanus vaccination		-1.7 (-19.5, 20.1)					5.4 (-18.8, 36.9)				
		[Ab] after diphtheria vaccination		-4.5 (-18.9, 12.5)					-16.6 (-35.9, 8.7)				
>2 years													
Weisglas- Kuperus (2000)	42m	[Ab] for mumps, measles, rubella	Correlation *p<0.05	PCBs maternal serum: -0.17* for mumps [Ab] Cord: -0.19* for rubella [Ab] Other [Ab]: NS	Dioxins and dl-PCBs: NS				PCBs at 42m: NS				
Heilmann (2006) ^e	7.5y	[Ab] after tetanus vaccination	Change % (pval)	ndl-PCBs: - 16.5 (0.03)	dl-PCBs (mono-ortho): -1.72 (0.80)				ndl-PCBs: -13.8 (0.08)	dl-PCBs (mono- ortho): -13.8 (0.10)			
		[Ab] after diphtheria vaccination		-3.30 (0.76)	2.05 (0.83)				-5.47 (0.65)	-4.24 (0.74)			

Table B.3 (cont.)

Author (year)	Child age ^a	Outcome	Statistic	Prenatal exposure ^b					Postnatal exposure ^b				
				PCBs and ndl-PCBs	Dioxins and dl-PCBs	DDE (DDT)	HCB	Other POPs	PCBs and ndl-PCBs	Dioxins and dl-PCBs	DDE (DDT)	HCB	Other POPs
Heilmann (2010) ^f	5y	[Ab] after tetanus vaccination	Change % (95%CI)	ndl-PCBs: -0.67 (-14.4, 15.3)					ndl-PCBs in milk: -0.89 (-11.6, 11.1)				
		[Ab] after diphteria vaccination		-12.9 (-26.0, 2.6)					Serum 18m: -6.0 (-16.5, 5.7)				
	7y	[Ab] after tetanus vaccination		8.0 (-8.9, 28.0)					Serum 5y: 0.6 (-8.7, 10.8).				
									Milk: -13.9 (-24.2, -2.4)				
		[Ab] after diphteria vaccination		1.3 (-13.3, 18.5)					Serum 18m: -15.4 (-25.8, -3.5)				
									Serum 5y: -6.4 (-15.9, 4.2)				
Grandejan (2012) ^g	5y (prebooster)	[Ab] after tetanus vaccination	Change % (95%CI)						Milk: -3.6 (-15.4, 9.9)				
									Serum 18m: -21.7 (-33.1, -8.2)				
	5y (postbooster)								Serum 7y: -1.3 (-11.0, 9.4)				
									Milk: -2.0 (-13.6, 11.0)				
	7y								Serum 18m: -18.3 (-31.9, -2.1)				
									Serum 7y: 1.4 (-7.8, 11.5)				
	5y (prebooster)	[Ab] after diphteria vaccination							PFOS: -10.1 (-31.9, 18.7)				PFOS: -11.9 (-30.0, 10.9)
									PFOA: -10.5 (-28.2, 11.7)				
	5y (postbooster)								PFOS: -2.3 (-28.6, 33.6)				PFOS: -28.5 (-45.5, -6.1)
									PFOA: 14.5 (-10.4, 46.7)				
	7y								PFOS: 35.3 (-3.9, 90.6)				PFOS: -23.8 (-44.3, 4.2)
									PFOA: 7.4 (-17.1, 39.0)				
	5y (prebooster)								PFOS: -38.6 (-54.7, -16.9)				PFOS: -16.0 (-34.9, 8.3)
									PFOA: -16.2 (-34.2, 6.7)				
	5y (postbooster)								PFOS: -20.6 (-37.5, 0.9)				PFOS: -15.5 (-31.5, 4.3)
									PFOA: -6.2 (-22.4, 13.3)				
													PFOA: -6.1 (-23.6, 15.5)

Table B.3 (cont.)

Author (year)	Child age ^a	Outcome	Statistic	Prenatal exposure ^b					Postnatal exposure ^b				
				PCBs and ndl-PCBs	Dioxins and dl-PCBs	DDE (DDT)	HCB	Other POPs	PCBs and ndl-PCBs	Dioxins and dl-PCBs	DDE (DDT)	HCB	Other POPs
Grandejan (2012, cont.) ^g	7y							PFOS: -19.7 (-41.8,10.7) PFOA: -22.8 (-39.4,-1.7)					PFOS: -27.6 (-45.8,-3.3) PFOA: -25.2 (-42.9,-2.0)

An empty cell indicates that the compound has not been assessed in the study, **NR**=results not reported, presumably because not significant associations were found; **NS**=results not shown but it is mentioned there is no association; **IgA**=immunoglobulin A; **IgG**=immunoglobulin G; **IgM**=immunoglobulin M, **IgG**=immunoglobulin G; **[Ab]**=antibody concentrations.

^aAt the time of outcome assessment (m=months, y=years).

^bIn order to simply the summary table, results for DDE (DDT) are in general referred to DDE, otherwise it will be indicated as "DDT". Regarding PCB and dioxin exposure, PCBs can indicate either "unknown congeners" or a mix of ndl- and dl-PCBs included in the final sum (ndl-PCBs were predominant in the sum of most of the studies). If only dioxin-like or non dioxin-like PCBs are included in the sum, then it is indicated as dl-PCBs or ndl-PCBs, respectively. When the exposures assessed are PCDDs or PCDFs it is indicated as dioxins, unless specifically indicated.

^cIn Jusko 2010 and Jusko 2011, analyses were also performed by using PCBs levels measured in cord blood (CB), but in this review only those results for maternal exposure (very similar) are presented.

^dIn this study F-test were performed to study differences of biomarker levels among categories of exposure, however, T-test were performed to compare biomarker levels between the highest and the lowest quartile of exposure; in this case, some associations were significant (those indicated with letter ^d, p<0.05).

^eIn this study equation models combining pre and postnatal exposures were also performed, in this case, postnatal exposure to all kinds of PCBs showed significant associations (change%=-18.9, p=0.04). For other results see original paper.

^fDue to high correlations between compounds, only the sum of PCBs was analyzed. In all cases, the associations found between [Ab] and postnatal exposure measured at age 18 months was only significant after imputation of 88.5% of the 18m serum samples (based on maternal blood, breastmilk, serum at age 5 and 7 year levels).

^gIn the original paper results are also presented for other congeners present in lower levels (PFHxS, PFNA, PFDA) than PFOA or PFOS. Results also showed associations with [Ab] at age 7y after adjusting for [Ab] at age 5y, but results did not materially vary.

Table B.4 Studies on persistent organic pollutants and immune cell-mediated response (ordered by age group, year and author).

Table 2-4 Studies on persistent organic pollutants and immune cell-mediated response (ordered by age group, year and author).													
Author (year)	Child age ^a	Outcome	Statistic	Prenatal exposure ^b					Postnatal exposure ^b				
				PCBs and ndl-PCBs	Dioxins and dl-PCBs	DDE (DDT)	HCB	Other POPs	PCBs and ndl-PCBs	Dioxins and dl-PCBs	DDE (DDT)	HCB	Other POPs
Cell mediated response													
<2 years													
Bilrha (2003)	CB	In vitro TNF- α production	Correlation *p<0.05	PCBs: -0.26*		-0.29*	-0.28*						
		In vitro IL-10 production		-0.14	-0.16		-0.17						
Noakes (2006)	CB	In vitro IL10,13,16, INF- γ production	Correlation *p<0.05			IL10: -0.20 IL13: 0.11 INF- γ : -0.14	NS	Dieldrin and others: NS					
		Lymphoproliferation response		NS	NS	NS							
Brooks (2007)	CB	IL4, 13, INF- γ	β coef (SE) *p<0.05			IL4: 0.002 (0.003), IL13: 0.007 (0.003)*, INF- γ : -0.010 (0.006), IL4/INF- γ ratio: 0.033 (0.010)*, IL13/INF- γ ratio: 0.017 (0.006)*							
Tsuji (2012) ^c	23m	IL8, COX-2	β coef (SE) *p<0.05						PCBs: IL8 0.13 (0.07), COX-2 0.15 (0.07)*		no significant results (not shown)		
>2 years													
No studies available													
Cell counts													
<2 years													
Weisglass-Kuperus (1995)	CB	Monocytes, granulocytes, lymphocytes, T-cells (CD3,4,8, TcR $\alpha\beta$,TcR $\gamma\delta$, HLA-DR), B-cells (CD19/20), NK-cells (CD16,56)	Correlation *p<0.05 ^d	PCBs: no significant correlations	Dioxin and dl-PCBs: TcR $\gamma\delta$ 0.50*								
	3m	no significant correlations		Monocytes -0.64*, granulocytes -0.47*	dl-PCBs: monocytes -0.49*, granulocytes -0.55*, CD19/20 -0.45*								
	18m	CD3CD8 0.38*		CD3CD8 0.65*, TcR $\alpha\beta$ 0.57*	no significant correlations								

Table B.4 (cont.)

Author (year)	Child age ^a	Outcome	Statistic	Prenatal exposure ^b					Postnatal exposure ^b				
				PCBs and ndl-PCBs	Dioxins and dl-PCBs	DDE (DDT)	HCb	Other POPs	PCBs and ndl-PCBs	Dioxins and dl-PCBs	DDE (DDT)	HCb	Other POPs
Nagayama (1998)	12m	T-cells (CD3, 4,8, HLA-DR)	Correlation *p<0.05 (only p-value reported)							Dioxins and dl-PCBs: increased CD4/CD8*, CD4, CD8, HLA-DR: NR			
Dewailly (2000)	3,7,12m	WBC, T-cells (CD3,4,8), B-cells (CD20)	Correlation *p<0.05	ndl-PCBs: NS		NS	NS	Mirex and dieldrin: NS					
Bilrha (2003)	CB	T-cells (CD3,4,8)	Correlation *p<0.05	PCBs: NS		NS	NS						
Kaneko (2006)	12m	T-cells (CD3,4,8), B-cells (CD19,20,86), NK cells	Correlation *p<0.05	PCDDs, PCDFs, dl-PCBs: NS									
Nagayama (2007) ^e	10m	T-cells (CD3)	OR *p<0.1	PCBs: NS	Dioxins: NS	DDT+DDE: 0.51		HCE: 1.59, HCH: NS, chlordanes: 1.70*					
		T-cells (CD4)		NS	1.48	1.56		HCE, HCH, chlordanes: NS					
		T-cells (CD8)		NS	NS	NS		HCE: 2.34*, HCH: NS, chlordanes: 1.44					
		T-cells (HLA-DR)		NS	NS	NS		HCH: 0.33*, HCE and chlordanes: NS					
		T-cell ratio (CD4/CD8)		NS	1.71*	NS		HCE, HCH, chlordanes: NS					
		B-cells (CD20)		NS	NS	1.52		HCE: 0.57, HCH and chlordanes: NS					
		NK cells (CD16)		0.64	0.55	0.52		HCE, HCH, chlordanes: NS					

Table B.4 (cont.)

Author (year)	Child age ^a	Outcome	Statistic	Prenatal exposure ^b					Postnatal exposure ^b				
				PCBs and ndl-PCBs	Dioxins and dl-PCBs	DDE (DDT)	HCB	Other POPs	PCBs and ndl-PCBs	Dioxins and dl-PCBs	DDE (DDT)	HCB	Other POPs
Glynn (2008) ^f	3m	WBC	β coef (SE) *p<0.01	PCB153: see footnote, PCBs: increased*	dl-PCBs (mono-ortho): 0.31 (0.45)	0.46 (0.36)			PCB153: T3 0.07 (0.01)* for NK cells (CD56), for other PCBs see footnote	see footnote	DDE: see footnote		
				ndl-PCBs: 0.04 (0.54)									
		Neutrophils		PCBs: see footnote ndl-PCBs: 0.05 (0.18)	0.08 (0.15)	-0.03 (0.12)							
		Eosinophils		PCBs: see footnote ndl-PCBs: 0.001 (0.04)	0.01 (0.03)	-0.06 (0.03) ^e							
		Lymphocytes		PCBs: increased* ndl-PCBs: -0.01 (0.43)	0.17 (0.35)	0.48 (0.28)							
		Monocytes		PCBs: increased* ndl-PCBs: 0.01 (0.05)	-0.01 (0.04)	0.04 (0.03)							
		Lymphocyte subsets (CD3,4,19,56, CD4CD8)		see footnote	see footnote	see footnote							
Horváthová (2011a) ^g	CB, 6m, 16m	T-cells (CD3)	β coef (SE) *p<0.05	PCBs: 2.03 (2.09) in CB, 3.86 (1.31)* at 16m									
		T-cells (CD4)		-0.36 (1.84) in CB, 1.03 (0.45) at 16m									
		T-cells (CD8)		2.82 (0.89)* in CB, 1.40 (0.91) at 16m									
		B-cells (CD19)		2.49 (1.02)* in CB, 3.97 (1.23)* at 16m									
		B-cells (HLADRCD19)		2.49 (1.02)* in CB, 3.80 (1.20)* at 16m									
		NK cells (CD3CD16/56)		-5.73 (1.58)* in CB, -6.40 (0.99)* at 16m									

Table B.4 (cont.)

Author (year)	Child age ^a	Outcome	Statistic	Prenatal exposure ^b					Postnatal exposure ^b							
				PCBs and ndl-PCBs	Dioxins and dl-PCBs	DDE (DDT)	HCB	Other POPs	PCBs and ndl-PCBs	Dioxins and dl-PCBs	DDE (DDT)	HCB	Other POPs			
Horváthová (2011b) ^g	CB, 6m, 16m	T-cell CD4CD45RO ⁺ CD45RA ⁺	β coef (SE) *p<0.05	PCBs: 0.29 (1.78) in CB, -9.12 (1.68)* at 16m												
		T-cell CD4CD45RO ⁺ CD45RA ⁻		0.06 (0.97) in CB, 6.03 (1.07)* at 16m												
		T-cell CD4CD62 ⁻ CD45RA ⁺		9.48 (3.13)* in CB, 4.95 (1.83)* at 16m												
		T-cell CD4CD62 ⁺ CD45RA ⁺		-8.39 (3.17)* in CB, -12.82 (1.41)* at 16m												
		T-cell CD4CD62		-13.78 (3.75)* in CB, -15.07 (1.58)* at 16m												
		T-cell CD4CD25		0.09 (0.42) in CB, -0.54 (0.24)* at 16m												
		Dendritic cell CD19CD11c ⁺ CD11b ⁺		-8.45 (2.07)* in CB, -8.07 (1.62)* at 16m												
		Dendritic-cell CD19CD11c ⁺ CD11b ⁻		1.34 (2.11) in CB, 3.61 (2.59) at 16m												
		Macrophage-like cell CD19CD11c ⁻ CD11b ⁺		-0.53 (0.58) in CB, -0.48 (0.36) at 16m												
		Dendritic-like cell CD83CD19		-0.14 (0.09) in CB, -0.33 (0.07)* at 16m												
>2 years																
Yu (1998)	8-16y	Monocytes, granulocytes, lymphocytes	T-test						Dioxins: no differences between exposed and controls							
Weisglas- Kuperus (2000) ^h	42m	Lymphocytes	Correlation *p<0.05	PCBs: 0.25*	Dioxins and dl-PCBs: NS NS		PCBs at 42m: NS									
		T-cells (CD3,4,8,HLA- DR,45)		CD3 0.25*, CD3CD8 0.27*, CD4CD45RO 0.25*, CD3HLA- DR 0.26*			NS									
		B-cells (CD19,20)		0.12			NS									
		NK cells (CD16,56)		0.13	NS											
		Monocytes		0.04	NS											
		Granulocytes (NS)		0.14	NS											

Table B.4 (cont.)

Author (year)	Child age ^a	Outcome	Statistic	Prenatal exposure ^b					Postnatal exposure ^b				
				PCBs and ndl-PCBs	Dioxins and dl-PCBs	DDE (DDT)	HCB	Other POPs	PCBs and ndl-PCBs	Dioxins and dl-PCBs	DDE (DDT)	HCB	Other POPs
Van den Heuvel (2002) ⁱ	17-18y	WBC, lymphocytes (different types), monocytes, eosinophils	β coef (SE) *p<0.05						ndl-PCBs: eosinophils -0.41 (0.15)*, CD16CD56 -0.20 (0.1)*	dl-PCBs: no significant associations			
Ten Tusscher (2003)	8y	T-cells (CD3,8,45), B-cells (CD19), NK cells (CD16,56)	β (95%CI)		Dioxins and furans: NS					Dioxins and furans: CD4 0.08 (0.03,0.14), CD45 0.08 (0.01,0.14), results for other cell types NS			
Karmaus (2005)	7-10y	T-cells (CD3,4,8,45), B-cells (CD19), NK cells (CD16,56), WBC, eosinophils (granula), IgE basophils count (BC)	F-test (pval)						PCBs ⁱ : ↓ WBC (p=0.02 ^h)		DDE: ↑ WBC and IgE (p=0.09 and 0.67, respectively) ^j ↓ eosinophilic granula (p=0.22 ^h)	no significant associations	γ-HCH ⁱ : NK cells (p<0.03, unclear dose-response ^h)
Sunyer (2005)	4y	WBC, eosinophils	Not specified	PCBs: NR		NS	NR						
Leijs (2009)	14-19y	WBC, lymphocytes, monocytes, eosinophils, basophils, (polymorphic) neutrophils	Correlation (pval)		Dioxins: negative correlation with polymorphic neutrophils (numbers not provided)					Dioxins: NR dl-PCBs: negative correlation with polymorphic neutrophils (p=0.02)			PBDEs: negative correlation with lymphocytes (p=0.02)

An empty cell indicates that the compound has not been assessed in the study, NR=results not reported, presumably because not significant associations were found; **NS**=results not shown but it is mentioned there is no association; **CB**=cord blood; **WBC**=White blood cell counts (total leukocytes), which include lymphocytes (T-cells, B-cells and Natural Killer (NK) cells), monocytes (derive into macrophages and dendritic cells) and granulocytes (basophils, eosinophils and neutrophils); **IL**=interleukin; **TNF-α**=tumor necrosis factor-α; **INF-γ**=interferon-γ; **COX-2**=cyclooxygenase-2.

^aAt the time of outcome assessment (m=months, y=years).

^bIn order to simplify the summary table, results for DDE (DDT) are in general referred to DDE, otherwise it will be indicated as "DDT". Regarding PCB and dioxin exposure, PCBs can indicate either "unknown congeners" or a mix of ndl- and dl-PCBs included in the final sum (ndl-PCBs were predominant in the sum of most of the studies). If only dioxin-like or non dioxin-like PCBs are included in the sum, then it is indicated as dl-PCBs or ndl-PCBs, respectively. When the exposures assessed are PCDDs or PCDFs it is indicated as dioxins, unless specifically indicated.

^cEstimations for those congeners for which no significant results were found (all dl-PCBs and some ndl-PCBs) are not shown in the original manuscript. In the present table we only show the results for the sum of PCBs, but not the results for the different congeners for which significant associations were found; they are available in the original manuscript.

^dOnly significant correlations shown.

^eIn the original paper all significant associations, and only some of the non-significant, are shown. In the study, results of the combinations of cells types or combinations of compound types are also shown, but are not presented in the present table.

^fLevels of PCBs included in the sum (28,52,101) were below the LOD in 40% of samples (maternal serum), thus, 3 categories of exposure were created (<LOD and 2 categories above LOD). Regarding prenatal exposure, in the present table results for the sum of PCBs are only indicated if significant. Results are presented for the number of cells, not the % (also shown in the original paper); results were in general similar as those found for the number of cells, but in the case of eosinophils de % was significantly decreased with increasing DDE levels (b coef (SE)=-1.06 (0.38), pval<0.01). Results for lymphocyte subsets and/or PCB153 are not shown, but in all cases these were not significant (p>0.01), except in the case of CD4CD8 subset (significantly reduced with PCB153, ndl-PCBs and dl-PCBs exposure). Results for postnatal exposure (expressed as mean (SE) by tertile of exposure and available in additional files) are not shown in this table, but none of the results were significant, except the association shown in the table.

^gExposure is not introduced in the models as continous PCB levels measured in maternal serum but as a dichotomous variable (highly exposed children (polluted area of Michalovce) vs less exposed children (area of Svidnik/Stropkov)). In the original papers results are also shown for blood measurements at age 6m, but in the present tables these are not shown (results were similar to those obtained in both CB and at age 16m).

^hOnly results for maternal exposure are shown, but in the original paper correlations with cord blood PCBs are also presented (similar results). For T-cell subtypes only significant results are shown in the present table.

ⁱFor other cell types no significant associations found.

^jIn the highest quartile of PCBs exposure the WBC are significantly reduced compared to the lowest quartile, but the reduction is not linear across quartiles. There is a similar situation with the increase of WBC or IgE on basophils within the 4th and the 3rd quartiles of DDE exposure, respectively. Although the F-test is not significant, eosinophilic granula levels within the highest quartile were significantly lower than in the lowest quartile of DDE exposure (T-test). For γ-HCH, there are significant differences between quartiles of exposure, however, in some quartiles NK cells levels are increased and in others these are decreased.

Table C. Quality assessment of the different studies^a.

Author (year)	Study design	N	Statistical methods ^b	Co-variables assessed ^c	Adjustment for other POPs	Good quality study
Rogan (1987)	Cohort	802	Prevalences	No	No	
Weisglas-Kuperus (1995)	Cohort	12-205	(Partial) correlation ^d	Sex, nutritional status, birth weight, gestational age, sex, maternal smoking and alcohol drinking during pregnancy, maternal education, parental occupation, Bfeed	No	
Nagayama (1998)	Cohort	36	Correlation	No	No	
Yu (1998)	Cohort	31	Correlation T-test (exposed vs non-exposed) ^e	No	No	
Reichertová (1999)	Cross-sectional	120	Correlation	No	No	
Dewailly (2000)	Cohort	65-109	Partial correlation Logistic regression	Bfeed, maternal age, age and past Bfeed episodes	No	
Weisglas-Kuperus (2000)	Cohort	175	Partial correlation Logistic regression	Sex, breastfeeding or not, Bfeed, parity, maternal education, parental occupation, smoking at home, family history of atopy, day care attendance	No	Yes ^f
Karmaus (2001)	Cross-sectional	343	Logistic regression	Sex, age, breastfeeding, ETS	Combination of categories of different POPs	
Ten Tusscher (2001)	Cohort	29	Linear and logistic regression	Respiratory history of parents and child, sex and age of the child, child and maternal smoking, medication related respiratory diseases, atopy	No	
Van Den Heuvel (2002)	Cross-sectional	200	Partial correlations Linear and logistic regression	Sex, child smoking and drinking alcohol, history of allergic or infectious disease, familiar history of asthma or hay fever, maternal smoking during pregnancy, breastfeeding, body mass index, social class of the parents, oral contraceptive use, O ₃ concentrations and temperature during the week before sampling	No	
Bilrha (2003)	Cross-sectional	83	Correlation and multiple regression analyses	Ethnicity, smoking during pregnancy, maternal weight and n-3 PUFAs	No	
Ten Tusscher (2003)	Cohort	27	Linear and logistic regression	Maternal smoking during pregnancy and at the time of the testing	No	
Dallaire (2004)	Cohort	199	Poisson regression	Maternal age at delivery, season of birth, year of birth, Bfeed, sex, socioeconomic status of the caregiver, smoking during pregnancy, number of children, village of residence, day care attendance, n-3 PUFAs, number of smokers in the house, birth weight, gestational age, reviewer of the medical chart	No	Yes
Weisglas-Kuperus (2004)	Cohort	167	Logistic regression	Sex, breastfeeding or not, Bfeed, parity, maternal education, parental occupation, smoking at home, family history of atopy, day care attendance	No	Yes
Karmaus (2005)	Cross-sectional	331	Student's t-test and F-test	Age, gender, ETS in child's home in the last 12m	Combination of DDE and lead categories	
Sunyer (2005)	Cohort	306-405	Poisson regression	Maternal age at delivery, maternal asthma and atopy, smoking during pregnancy, parity, education, social class, fish consumption during pregnancy, sex, gestational age, birth weight, Brfeed, place of residence	No	Yes
Dallaire (2006)	Cohort	343	Poisson regression	Maternal age, parity, smoking during pregnancy, sex, reviewer of the medical chart, gestational age	No	Yes
Heilmann (2006)	Cohort	119-129	Regression analyses and structural equation models	Sex, age, birth weight, maternal smoking during pregnancy, time for last vaccination	No	Yes
Kaneko (2006)	Cohort	281	Correlation	No	No	
Noakes (2006)	Cohort	26	Correlation	No	No	

Table C (cont.)

Author (year)	Study design	N	Statistical methods ^b	Co-variables assessed ^c	Adjustment for other POPs	Good quality study
Sunyer (2006)	Cohort	285-402	Logistic regression	Maternal age, smoking, asthma, atopy, BMI and education. Child age, birth weight, gestational age, BMI at age 6 and parity	No	Yes
Brooks (2007)	Cross-sectional	19	Linear regression	Maternal age, atopic status, ETS	No	
Nagayama (2007)	Cohort	92	Logistic regression	No	Combination of different compounds	
Glynn (2008)	Cohort	52-86	Linear regression	Maternal age, smoking & alcohol consumption during pregnancy, education, vaccination status of the child, nursing of the infant, age of the infant, infant's past history of respiratory infections during the study period	No	
Park (2008)	Cohort	982	Linear regression	Sex, socioeconomic status, smoking, alcohol consumption, ethnicity, maternal medical history	No	Yes
Leijs (2009)	Cohort	18-33	Correlation	No	No	
Grandjean (2010)	Cohort	464	Linear and logistic regression	Sex, age, season of birth, preterm birth, maternal age, parity, maternal fish intake and smoking during pregnancy, parental smoking at home, daycare attendance, child's BMI	No	Yes
Heilmann (2010)	Cohort	106-587	Linear and logistic regression	Sex, age, birth weight, maternal smoking during pregnancy, Bfeed	No	Yes
Jusko (2010)	Cohort	329	Linear regression	Ethnicity, maternal smoking before & during pregnancy and 6m after birth, maternal age at birth, sex, age of the child at age 6m visit, number of vaccines, time since last vaccine, birth weight	No	Yes
Sunyer (2010)	Cohort	520	Poisson regression	Maternal age, social class, education, smoking during pregnancy and the postnatal period, parity, allergy, asthma, total IgE, weight, sex, birth weight, predominant breastfeeding	Yes	Yes
Horváthová (2011a) ^h	Cohort	313-362	Linear regression analyses	Sex, parity, maternal age, smoking and education, season of birth, breastfeeding, birth weight	No	
Horváthová (2011b) ^h	Cohort	313-362	Linear regression analyses	Sex, parity, maternal age, season of birth, breastfeeding, birth weight	No	
Jusko (2011)	Cohort	350	Linear regression	ethnicity, smoking pregnancy, and age at child's birth, smoking at 6m, infant sex, and infant age at the time of 6m blood draw	No	Yes
Miyashita (2011)	Cohort	364	Logistic regression	maternal age, pre-pregnancy BMI, maternal education level, parity, parental allergic history, infant gender, duration of breast-feeding, environmental tobacco exposure, day care attendance and sampling period, maternal education level	No	Yes
Stolevik (2011) ⁱ	Cohort	195	Logistic regression	Birth weight, gestational age, mother's previous breast-feeding, parity, maternal history of atopy, maternal age, maternal smoking, maternal passive smoking, maternal education, maternal BMI, child's gender, birth season, type of delivery, breast-feeding of the child at six months, Apgar score after 1 min, and day-care attendance at 12 months	No	Yes
Wang (2011)	Cohort	244	Linear and logistic regression	Gender, gestational age, parity, maternal age, and pre-natal ETS exposure, maternal history of atopy and duration of breast feeding	No	Yes
Gascon (2012)	Cohort	1342 (+79) ^g	Poisson regression	Study regions, sex of the child, age and pre-pregnancy weight of the mother, allergic or asthmatic mother, parity, social class, predominant breastfeeding, maternal smoking status, day-care attendance	Yes	Yes
Grandjean (2012)	Cohort	380-510	Regression analyses and structural equation models	Age, sex, time since vaccination, booster type, child's specific antibody concentration at age 5y, PCB exposure, birth weight, maternal smoking during pregnancy, and duration of breastfeeding	Yes	Yes

Table C (cont.)

Author (year)	Study design	N	Statistical methods ^b	Co-variables assessed ^c	Adjustment for other POPs	Good quality study
Jusko (2012)	Cohort	210-966	Mixed and linear regression analyses	Age, sex, ethnicity, district of residence, infant weight, duration of exclusive breastfeeding	No	Yes
Okada (2012)	Cohort	231-343	Cubic polynomial and logistic regression	maternal age, maternal education, pre-pregnancy BMI, parity, parental allergic history, infant gender, duration of breast-feeding, environmental tobacco exposure, day care attendance and sampling period, maternal education level, birth season, distance from home to highway, sampling period, daycare attendance	No	Yes
Tsuji (2012)	Case-control	30	Univariate regression models and Mann-Whitney U test	No	No	

^a**Sufficient** - if most of the studies, including good quality studies, report an association, but evidence is not yet conclusive enough to conclude that there is an association or a causal relationship, **limited** - several good quality, independent, studies report an association, but evidence is not yet conclusive enough, **inadequate** - if associations are reported in one or more studies, but insufficient quality, insufficient number of studies, lack of consistency, and/or lack of statistical power preclude a conclusion regarding the presence or absence of an association, **evidence for lack of association** - several good quality studies are consistent in showing no association.

^bIn some studies different statistical methods are applied depending on the outcome assessed.

^cThese are confounders assessed or that have been considered, but not all of them are finally included in the adjusted models.

^dIn this study it is not indicated whether the final results provided are adjusted or not and for which variables.

^eExposed children are children born from Yucheng mothers, highly exposed to PCBs/PCDFs. Controls are not clearly defined.

^fThe models including infections and allergy symptoms were adjusted for potential confounders, whereas those models including immunologic markers were not adjusted.

^gIn this study the main study population were 1342 children born from Spanish mothers, however, there were 79 children born from Latin-American mothers who were analyzed separately.

^hIn this study exposure was not entered as a continuous variable but as a dichotomous variables (children from a highly exposed area vs children from a less polluted area).

Exposure is an estimation of PCBs and dioxin intake through diet during pregnancy (correlated to blood concentrations of a subsample ($r=0.34-0.37$, $p<0.05$)).