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In Utero Exposure to Organic Pollutants and Lung Function in the Offspring

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ABSTRACT

Humans are exposed daily to thousands of chemicals present in many consumer products that can interfere with hormonal signalling systems. The prenatal period is critical because the developing lung is intrinsically subject to hormonal regulation. Alterations at this time may predispose to reduced lung function in later life. In this review, we summarise current knowledge about the role of prenatal exposure to organic pollutants on lung function in the offspring. We divide pollutants into persistent: organochlorine and perfluoroalkyl compounds, and non-persistent: bisphenols, parabens, triclosan, benzophenones, phthalates, and currently used pesticides. Eleven prospective cohort studies, mainly from Europe and the US, have been identified. Overall, the literature is scarce and inconsistent. The observed associations have identified small changes in lung function parameters. Main challenges for future studies include assessment of exposure to non-persistent pollutants and the study of multipollutant effects. In parallel, public health strategies should be implemented to reduce exposure to organic pollutants, particularly in pregnant women.

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INTRODUCTION

Impaired lung development in early life may predispose individuals to reduced lung function in adulthood[1,2]. This can lead to persistent respiratory morbidity and chronic respiratory diseases later in life[3,4]. Chronic respiratory diseases are among the leading causes of mortality and morbidity worldwide and asthma and chronic obstructive pulmonary disease (COPD) are the most common – 358 million people are affected by asthma and 175 million by COPD[5]. There is no curative therapy for either of them. The natural history of both diseases is extensive yet incomplete. It is postulated that they have at least part of their origins in early life when the lung is still undergoing rapid development[6,7]. This fits well with the concept of the Developmental Origins of Health and Disease, which describes how early-life exposures may have a long-term impact on disease in adulthood[8]. Identification of early determinants of lung development is of utmost importance, given their long-term effect on disease throughout life.

The developing lung is extremely susceptible to the effects of environmental exposures[9]. Exposure to an adverse environment during critical periods of pre- and early postnatal life might lead to developmental adaptations resulting in impaired lung growth with smaller airways and lower lung volume, altered immunological responses, and related inflammation. The dramatic increase in childhood asthma prevalence over the last decades[5] has raised concerns about the potential role of environmental pollutants. Exposure to a number of common environmental pollutants, including environmental tobacco smoke[10] and air pollution[11,12] has been associated with childhood respiratory tract illnesses. More recently, concern is growing over the impact of environmental chemicals on childhood lung function.

Environmental chemicals can be classified within organic and inorganic pollutants. Organic pollutants include polychlorinated biphenyls (PCBs), pesticides, perfluoroalkyl substances (PFASs), phenols, and polyaromatic hydrocarbons (PAHs), among others; inorganic pollutants include a variety of heavy metals such as mercury, lead, arsenic, or cadmium. Both organic and inorganic pollutants present in the environment may have the capacity to interfere with the endocrine system and consequently alter many essential body functions such as growth, behaviour, and reproduction[13]. The term "endocrine disrupting chemical" includes a large number of substances (in some lists more than 1,500[14]) whose primary effect is on the endocrine system through interaction with cellular hormone receptors, hormone synthesis or clearance[13]. Endocrine disrupting chemicals can have effects at very low exposure levels, as endogenous hormones do; low doses can have more potent effects than higher doses; and exposure to multiple chemicals can result in synergistic, antagonistic, or cumulative effects[15].

Endocrine disrupting chemicals are produced in large quantities worldwide (millions of tons annually) and consequently, human populations are continuously exposed to them through food, food packaging, cosmetics, dust inhalation, and consumer products. Human biomonitoring studies have shown low but very widespread human exposure[16–18]. Exposure to these chemicals is of special concern

Table 1. Concentrations of organic pollutants in 1,301 pregnant women and children in 6 European population-based cohort studies participating in the HELIX project *(extracted from Haug et al.[18] with permission from the author)*

Pollutant	Maternal samples			Child samples		
	% quantifiable samples	Median (P25-P75)	Max	% quantifiable samples	Median (P25-P75)	Max
Organochlorine compounds – blood (ng/g lipid)						
DDE	99.9	52.3 (25.9, 111)	1903	100	21.8 (11.6, 45.6)	2158
PCB-153	99.6	17.6 (10.4, 30.5)	214	100	11.6 (7.28, 18.6)	217
HCB	99.1	8.16 (5.59, 13.0)	164	99.9	8.19 (6.27, 11.4)	88.1
Perfluoroalkyl substances – blood (μg/L)						
PFOS	100	6.41 (4.12, 9.63)	48.0	99.8	2.03 (1.26, 3.22)	33.8
PFOA	99.7	2.30 (1.38, 3.34)	31.6	100	1.55 (1.19, 1.97)	6.66
Bisphenols – urine (μg/g creatinine)						
Bisphenol A	99.4	2.82 (1.55, 6.60)	107	98.3	4.06 (2.42, 7.17)	362
Parabens, Triclosan, and Benzophenones – urine (μg/g creatinine)						
Methyl-paraben	99.8	167 (39.5, 389)	39,241	99.7	6.50 (3.28, 26.4)	23,963
Ethyl-paraben	97.4	6.26 (1.14, 26.72)	817	99.3	0.67 (0.43, 1.22)	2033
Triclosan	98.5	6.28 (1.50, 79.9)	1653	100	0.61 (0.32, 1.5)	702
Benzophenone-3	99.3	4.90 (1.46, 27.5)	12,837	99.9	2.16 (0.86, 6.96)	7985
Phthalates – urine (μg/g creatinine)						
DEHP metabolite MEHP	99.5	8.73 (4.42, 15.3)	417	96.8	2.88 (1.70, 5.10)	282
MiBP	99.9	38.7 (23.3, 60.7)	705	100	41.8 (25.9, 73.3)	861
Currently used pesticides - urine (μg/g creatinine)						
DAP metabolite DMP	90.8	8.37 (4.13, 16.4)	321	49.3	0.78 (0.29, 4.70)	83.3
DAP metabolite DEP	97.8	3.33 (1.86, 6.44)	198	80.9	1.83 (0.47, 4.52)	665

% quantifiable samples: % of the biomarker measurements with concentrations reported.
DAP: dialkyl phosphate; DDE: dichlorodiphenyldichloroethylene; DEHP: di-(2-ethylhexyl) phthalate; DEP: diethyl phosphate
DMP: dimethyl phosphate; HCB: hexachlorobenzene; MEHP: mono-2-ethylhexyl phthalate; MiBP: mono-isobutyl phthalate; P25: 25th percentile; P75: 75th percentile;
PCB-153: polychlorinated biphenyl-153; PFOA: perfluorooctanoate; PFOS: perfluorooctane sulfonate.

in pregnant women and children, with many compounds being detected in more than 90% of samples (Table 1). Foetus and infants are especially sensitive to chemicals that mimic hormones because the protective mechanisms (i.e., detoxification) existing in adulthood are not completely functional in early life. In the EU, the medical cost associated with exposure to endocrine disrupting chemicals has been estimated at €163 billion a year[19]. Nowadays, the reduction of exposure to endocrine disrupting chemicals, and particularly the organic ones, represent a priority for action in the European Commission owing to their high annual production and potential toxicity[20].

In this narrative review, we summarize current knowledge about the role of exposure

to organic pollutants during pregnancy on lung function in the offspring. We have focused the review on the prenatal exposure because is when the lung is more susceptible to the effects of harmful environmental exposures[9]. This summary is mainly based on epidemiological literature published between 2014 and 2020. We have primarily identified relevant literature using the PubMed search engine (National Library of Medicine). Search strategies include keywords for the various combinations of organic pollutants (organochlorine compounds (OCs), PCBs, dichlorodiphenyldichloroethylene (DDE), hexachlorobenzene (HCB), PFASs, bisphenols, parabens, triclosan, benzophenone-3, phthalates, and organophosphate pesticides) and respiratory function (lung function, spirometry, forced expiratory volume in one second [FEV_1], forced vital capacity [FVC], FEV_1/FVC ratio, and forced expiratory flow at 25-75%). We have divided organic pollutants into persistent, characterized as having long biological half-lives in the body (e.g., from months to years), and non-persistent, with short biological half-lives (e.g., from hours to days).

OVERVIEW OF LUNG DEVELOPMENT

The development of the lung starts at the foetal stage and continues after birth until 20 years of age. It consists of five consecutive stages: embryonic, pseudoglandular, canalicular, saccular, and alveolar (Fig. 1). Primary lung buds start to develop at the 4th week of gestation to form the trachea, bronchi, and pulmonary vein and artery. During the second trimester of pregnancy, during the pseudoglandular and canalicular stages, the bronchi continue their segmentation, primitive alveoli are formed, and the synthesis of surfactant starts. This is considered to be the most critical stage for the respiratory system since it is when all conducting airways are formed. The saccular and alveolar are the last prenatal stages. They develop from the third trimester of gestation until the second year after birth. During these stages, the gas exchange region expands. The expansion triggers the production of extracellular matrix, collagen, and elastin. During these phases, there is further growth of the vascular system associated with the respiratory system. After birth and until the second year of age, alveoli continue developing. The gas exchange regions keep expanding through a branching process in concordance to its associated vascular and nervous systems. From two years until adulthood, the process of lung growth and expansion continues by a sustained cellular proliferation[9,21]. Across the lifespan, lung function grows from birth to late adolescence, reaching its maximal levels in early adulthood. This is followed by a plateau period when lung function remains stable for several years before it starts to gradually decline[22].

The developing lung is intrinsically subject to endogenous hormonal regulation[9,23,24]: glucocorticoids, oestrogens, and thyroid hormones promote the structural development of the lung and the production of pulmonary surfactant, while androgens retard surfactant production. Other receptors also play a prominent role on lung development: aryl hydrocarbon receptor (AhR) activation decrease thyroid hormone levels and peroxisome proliferator–activated receptor (PPAR) alter airway cell differentiation and surfactant

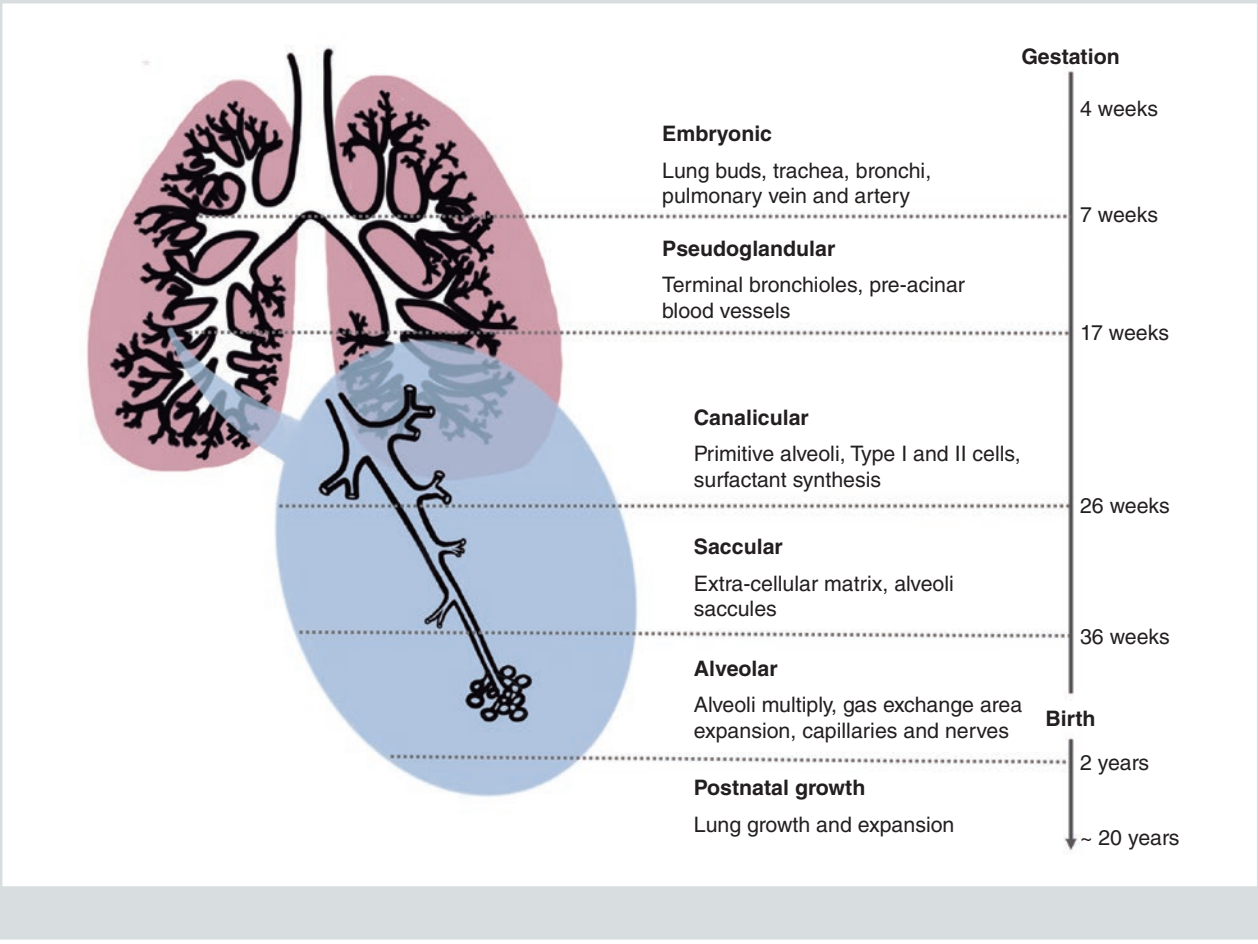

Figure 1. Developmental stages of the lung.

production, among other mechanisms. All these receptors are expressed in the human lung[9]. Of concern, endocrine disrupting chemicals have affinity with glucocorticoids (e.g. pesticides), oestrogens (e.g. bisphenols, pesticides), androgens (e.g. phthalates), and/or thyroid hormones receptors (e.g. bisphenols, metals), to AhR (e.g. pesticides), and/or PPAR (e.g. perfluoroalkyl compounds)[25–28]. Hence, disruption of fundamental biologic processes and associated signalling events due to exposure to endocrine disrupting chemicals may result in significant alterations in lung development.

PERSISTENT ORGANIC POLLUTANTS AND LUNG FUNCTION

Organochlorine compounds

OCs are synthetic persistent organic pollutants mainly used as pesticides or in industrial products such as electrical insulators and flame retardants (Table 2). Their use and production of some of these compounds has been banned for decades[29,30]. For example, the former widely used pesticide dichlorodiphenyl-trichloroethane (DDT) was banned

Table 2. Main sources of exposure to organic pollutants

	Pollutants	Main sources of exposure
Persistent organic pollutants	Organochlorine compounds	Pesticides Electrical insulators Industrial products
	Perfluoroalkyl substances	Surfactants for industrial products coating (i.e., paper packaging, textile, leather) Fire-fighting foams Lubricants Photography industry Non-stick cookware
Non-persistent organic pollutants	Bisphenols	Polycarbonate plastic Canned food Sport bottles Thermal receipt paper Children's toys
	Parabens, Triclosan, Benzophenone-3	Cosmetics Toothpaste Sunscreen Perfumes Pharmaceutical products Detergents Soaps Plastic packaging Textiles
	Phthalates	Polyvinyl chloride (PVC) plastics Vinyl building products Adhesives Fragrances Medical equipment Detergents
	Currently used pesticides	Agriculture Residential settings

Source[101].

in the European Union in the early 80s[30]. Due to the strong evidence of the adverse health effects of other OCs, these compounds were internationally banned at the Stockholm Convention in 2001[31]. However, they can bioaccumulate and persist in the environment for long periods. They have long biological half-lives that can range from several years to decades in some compounds[32]. Currently, the main source of exposure to OCs is diet. Biomonitoring studies show that current populations are exposed to these substances finding detectable levels in blood samples[18] (Table 1).

OCs may interfere in the lung morphogenesis as well as play a role in inflammation processes both pre- and postnatally. These compounds are endocrine disruptors with estrogenic and anti-androgenic properties[33]. Therefore, they may interact with oestrogenic and androgenic receptors and alter the related signalling pathways, including the activation of the AhR pathway, which has been shown to delay lung development in animal studies[34]. Furthermore, exposure to OCs has also been related to inflammation, observing increased interleukins and immunoglobulins in children exposed to them[35–37].

Table 3. Studies on persistent organic pollutants and lung function by year of publication

Pollutant	Author (year)	Country, study design (cohort name)	N	Year of recruitment	Outcome age	Exposure assessment	Statistically significant main findings
Organochlorine compounds	Hansen et al. (2016)[38]	Denmark, birth cohort (Danish Fetal Origins Birth Cohort)	414	1988-1989	20y	Blood (pregnancy)	OCs - Airway obstruction: PCBs OR = 2.96 (1.14 to 7.70)[a] HCB OR = 2.63 (1.07 to 6.46)[a] DDE OR = 2.87 (1.09 to 7.57)[a]
	Abellan et al. (2019)[39]	Spain, birth cohort (INMA)	1308	2004-2008	4y and 7y	Blood (pregnancy/ birth)	DDE - FEV_1 4y: β = –53.61 (–89.87 to –17.35)[b]; FEV_1 7y: β = –36.07 (–65.21 to –6.92)[c]; FVC 7y β = –39.45 mL (–71.23 to –7.66)[c] HCB - FVC 7y: β = –56.68 (–89.87 to –23.49)[c]
	Agier et al. (2019)[41]	6 EU countries, birth cohort (HELIX)	1033	2003-2009	6-12y	Blood (pregnancy)	None
Perfluoroalkyl substances	Impinen et al. (2018)[49]	Norway, birth cohort (ECA)	641	1992-1993	Birth	Blood (birth)	None
	Agier et al. (2019)[41]	6 EU countries, birth cohort (HELIX)	1033	2003-2009	6-12y	Blood (pregnancy)	PFOA - FEV_1: β = –1.4 (–2.7 to –0.1)[d] PFNA - FEV_1: β = –1.4 (–2.7 to –0.1)[d]
	Manzano-Salgado et al. (2019)[50]	Spain, birth cohort (INMA)	992	2003-2008	4y and 7y	Plasma (pregnancy)	PFOA - FVC 4y: β = –0.17 (–0.34 to –0.01)[e]

[a]Coefficient estimates are Odds Ratios of airway obstruction (FEV_1/FVC < 75%) given on the third versus the first (lowest) quartile of exposure. [b]Coefficient estimates are given for a change in FEV_1 (ml) on the third versus the first (lowest) quartile of exposure. [c]Coefficient estimates are given for a change in FEV_1 or FVC (ml) on the second versus the first (lowest) quartile of exposure. [d]Coefficient estimates are given for a change in mean FEV_1% for an interquartile range change in PFASs concentration. [e]Coefficient estimates are given for a change in FVC z-score for each doubling of PFASs concentration.
DDE: dichlorodiphenyldichloroethylene; ECA: The Environment and Childhood Asthma; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; HCB: hexachlorobenzene; HELIX: Human Early-Life Exposome; INMA: *INfancia y Medio Ambiente* (Environment and Childhood); OCs: organochlorine compounds; PCBs: polychlorinated biphenyl; PFASs: perfluoroalkyl substances; PFNA: perfluorononanoate; PFOA: perfluorooctanoate; y: years.

Current evidence suggests that prenatal exposure to OCs is associated with reduced lung function in the offspring (Table 3). Prenatal exposure to very high levels of DDE, HCB, and PCBs was associated with increased risk of airway obstruction at 20 years of age in a Danish birth cohort established in the 80s[38]. In a recent study from a Spanish birth cohort, prenatal exposure to DDE was associated with lower lung function at 4 and 7 years of age, even at low exposure levels. In this study they also observed reduced forced vital capacity (FVC) at certain exposure levels of HCB and found inconsistent results with PCBs[39]. Recently, in a study assessing the effects of the "exposome" - the totality of environmental exposures from conception onwards[40]- on lung function, DDT and DDE tended to be associated with reduced FEV_1 in school-age children, but results did not reach statistical significance[41].

Perfluoroalkyl substances

PFASs are synthetic fluorinated organic compounds produced in large quantities since the

1950s. PFASs have been widely used as surfactants in industrial and commercial products including paper, textile, and leather coatings, fire-fighting foams, lubricants, and photography industry[28] (Table 2). Perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) are the most common PFASs and are widely detected in the environment (i.e. water)[42] and in human blood[17] (Table 1). Although they are not stored in the adipose tissue, they are classified as persistent organic pollutants because they form chemical adducts with liver and serum proteins (e.g. albumin) and have long biological half-lives in humans (3-5 years)[43]. PFASs can also cross the placental barrier[44].

Studies assessing the levels of PFASs in different organs in mice and humans, observed the highest levels in lungs[45,46], suggesting the lung to be a target of PFASs toxicity. Indeed, new-born rats prenatally exposed to PFASs had retarded lung maturation, namely diminished alveolar airspace and increased alveolar thickness[47]. PFASs are synthetic surfactant molecules and therefore, have the potential to interfere with the integrity of the surface-active interfacial films formed by natural surfactant in the alveolar space. A recent in vitro study showed that PFASs can inhibit lung surfactant function and also induce a pro-inflammatory response in human bronchial epithelial cells[48].

Up to now, three prospective studies in humans have evaluated whether prenatal exposure to PFASs impairs lung function in the offspring (Table 3). Impinen et al. (2018)[49] did not find any association between exposure to PFASs during pregnancy and lung function at birth. In the first exposome study, *in utero* exposure to PFOA and perfluorononanoate (PFNA) was associated with reduced FEV_1 in children aged 6–12 years[41]. In a recent study in the Environment and Childhood - *INfancia y Medio Ambiente* (INMA) cohort, although authors observed a reduction in FVC at 4 years associated with prenatal exposure to PFOA, this association disappeared after applying a more stringent reproducibility criterion for the spirometry test[50].

NON-PERSISTENT ORGANIC POLLUTANTS AND LUNG FUNCTION

Bisphenols

Bisphenols are widely present in daily life products such as plastic packaging, children's toys, thermal paper, and canned food (Table 2). The general population is continuously exposed to them through dermal contact, inhalation or ingestion. Bisphenol A (BPA) is the most produced bisphenol and has been found in > 90% of urine samples in general population[51,52] (Table 1). It has been related to adverse health effects (e.g., metabolic and reproductive disorders, behavioural problems) and in 2017 it was considered a "substance of very high concern" by the European Chemical Agency[53]. Its production and use have been prohibited in some products and in some countries, giving rise to the production of substitute products of similar structure such as bisphenol S (BPS) and bisphenol F (BPF)[54]. After exposure, bisphenols are rapidly excreted from the body (half-life of less than 6 hours).

Bisphenols might interfere in the developing lung thanks to their capacity to cross the placental barrier and the ubiquitous daily

exposure after birth. A study in mice observed that exposure to BPA during gestation severely retarded foetal lung maturation[55]. This immaturity was characterized by diminished alveolar airspace and thickened septa and by a diminished number of type I pneumocytes[55]. Bisphenols can also induce oxidative stress, endocrine disruption and mitochondrial dysfunction[56–58]. These chemicals can alter inflammatory responses through different signalling pathways. They can activate the reactive oxygen species (ROS) pathway and the mitogen-activated protein kinase (MAPK) signalling pathways that lead to DNA damage and cellular death. Bisphenols might also alter immune responses by the stimulation of pro-inflammatory cytokines and the inhibition of anti-inflammatory cytokines production[59].

Current evidence suggests that BPA exposure increases the risk of respiratory symptoms (reviewed by Vrijheid et al, 2016[60]) but there is limited evidence on the effects of BPA and their substitutes on lung function (Table 4). A study observed that increasing maternal urinary BPA levels were associated with 14.2% (95% CI: -24.5, -3.9) decrease in the % predicted FEV_1 at 4 years of age but did not see such association at 5 years[61]. In the Étude des déterminants pré et postnatals du développement de la santé de l'enfant (EDEN) birth cohort study, no association was observed between prenatal BPA levels and predicted FEV_1 at 5 years[62]. No association was observed in the Human Early-Life Exposome (HELIX) cohorts between prenatal BPA levels and lung function in school-age children in the first exposome study[41]. Recently, Berger et al. (2020)[63] assessed the effects of prenatal exposure to 20 endocrine disruptors at the same time, including BPA, on lung function at 7 years. By using the Bayesian Kernel Machine Regression (BKMR), a statistical tool that allows the identification of the most relevant group and pollutant within the group associated with a specific outcome, the authors did not observe any association between BPA and lung function[63]. These findings were previously observed in the same cohort in a study assessing BPA and eight phthalates[73]. We should consider that all previous studies have used one or two spot urines, which, due to the high temporal variability of bisphenols and their short half-lives, might have led to exposure misclassification that biases the associations towards the null.

Parabens, Triclosan, and Benzophenones

Parabens, triclosan, and benzophenones belong to the chemical group of phenols. Parabens have bactericide and fungicide properties, and they are used in the cosmetic and pharmaceutical industry (Table 2). Triclosan is an antibacterial agent and preservative in detergents and personal care products. Benzophenones act as filters for ultraviolet radiation and are present in sunscreens, perfumes, soaps, and plastic packaging. Human exposure to these chemicals is widespread[18] (Table 1). The most common parabens used are methyl-, ethyl-, propyl-, and butyl-paraben whereas benzophenone-3 (BP-3) is the most used benzophenone.

Experimental studies suggest that parabens, triclosan, and BP-3 lead to reduced lung function through their capacity to link to estrogenic receptor and PPAR[64]. For

Table 4. Studies on non-persistent organic pollutants and lung function by year of publication

Pollutant	Author, Year	Country, study design (cohort name)	N	Year of recruitment	Outcome age	Exposure assessment	Statistically significant main findings
Bisphenols	Spanier et al. (2014)[61]	US, birth cohort (HOME)	208	2003-2006	4-5y	2 urines (pregnancy)	BPA - FEV_1 4y: β = –14.2 (–24.5 to –3.90)[a]
	Vernet et al. (2017)[62]	France, birth cohort (EDEN)	228	2002-2006	5y	1 urine (pregnancy)	None
	Berger et al. (2019)[69,b]	US, birth cohort (CHAMACOS)	260	1999-2000	7y	2 urines (pregnancy)	None
	Agier et al. (2019)[41]	6 EU countries, birth cohort (HELIX)	1,033	2003-2009	6-12y	1 urine (pregnancy and childhood)	None
	Berger et al. (2020)[63,b]	US, birth cohort (CHAMACOS)	282	1999-2000	7y	2 urines (pregnancy)	None
Parabens, Triclosan, Benzophenones	Vernet et al. (2017)[62]	France, birth cohort (EDEN)	228	2002-2006	5y	1 urine (pregnancy)	None
	Berger et al. (2018)[69,b]	US, birth cohort (CHAMACOS)	296	1999-2000	7y	2 urine (pregnancy)	None
	Agier et al. (2019)[41]	6 EU countries, birth cohort (HELIX)	1,033	2003-2009	6-12y	1 urine (pregnancy and childhood)	None
	Berger et al. (2020)[63,b]	US, birth cohort (CHAMACOS)	282	1999-2000	7y	2 urines (pregnancy)	None
Phthalates	Vernet et al. (2017)[62]	France, birth cohort (EDEN)	228	2002-2006	5y	1 urine (pregnancy)	None
	Berger et al. (2018)[69,b]	US, birth cohort (CHAMACOS)	296	1999-2000	7y	2 urines (pregnancy)	MEP - FEF_{25-75}: β = –3.22 (–6.02 to –0.34)[c]
	Berger et al. (2019)[74,b]	US, birth cohort (CHAMACOS)	260	1999-2000	7y	2 urines (pregnancy)	MCOP - FEV_1: β = –0.09 (–0.15 to –0.03)[c]; FEF_{25-75}: β = –7.06 (–11.04 to –2.90)[c]
	Agier et al. (2019)[41]	6 EU countries, birth cohort (HELIX)	1,033	2003-2009	6-12y	1 urine (pregnancy and childhood)	None
	Berger et al. (2020)[63,b]	US, birth cohort (CHAMACOS)	282	1999-2000	7y	2 urines (pregnancy)	MCOP - FEV_1: PIP = –0.07 (0.05)[d]
Currently used pesticides	Raanan et al. (2017)[81]	US, birth cohort (CHAMACOS)	279	1999-2000	7y	2 urines (pregnancy), 5 urines (childhood)	None
	Agier et al. (2019)[41]	6 EU countries, birth cohort (HELIX)	1,033	2003-2009	6-12y	1 urine (pregnancy and childhood)	None

[a]Coefficient estimates are given for a change in FEV_1% for every 10-fold increase in the mean BPA concentration. [b]In Berger et al.[69] three phthalates were assessed together with three parabens and four phenols; in Berger et al.[74] eight phthalates were assessed together with BPA; in Berger et al.[63] eleven phthalates were assessed together with four parabens and five phenols. [c]Coefficient estimates are given for a change in L/s of FEF_{25-75} percent difference or L of FEV_1 for each doubling of phthalates concentration. [d]Predicted probability and standard deviation obtained in the Bayesian Kernel Regression Model for an interquartile range change in phthalates concentration.
BPA: bisphenol A; DAPs: dialkyl phosphate metabolites; DEHP: di-(2-ethylhexyl) phthalate; Développement et de la Santé de l'Enfant; EDEN: Étude des déterminants pré et postnatals du développement de la santé de l'enfant; FEF_{25-75}: forced expiratory flow at 25–75% of FVC; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; HELIX: Human Early-Life Exposome; HOME: Health Outcomes and Measures of the Environment; MCOP: monocarboxyisooctyl phthalate; MEP: monoethyl phthalate; PIP: posterior inclusion probability; y: years.

example, studies in rats show that prenatal exposure to BP-3 can impair the expression of estrogenic receptor -α and -β[65,66]. Estrogenic receptor-β is abundantly expressed and biologically active in the lungs and regulates alveolar formation and surfactant homeostasis[9]. BP-3 may also disrupt the levels of PPARγ receptor, down-regulating surfactant protein expression in alveolar type II cells[9], essential for lung maturation. Triclosan was shown to decrease the viability, growth and morphology of lung epithelial cells[67]. Parabens, triclosan, and BP-3 can also increase biomarkers of oxidative stress and inflammation[68].

Four studies in humans have evaluated whether prenatal exposure to parabens, triclosan, and BP-3 can affect lung function in the offspring (Table 4). The French cohort EDEN evaluated exposure to parabens, triclosan, and BP-3 in 228 pregnant women and their male's offspring and observed that exposure to ethyl-paraben was associated with reduced FEV_1 at 5 years; however, this association did not reach statistical significance. No association was observed for the other phenols[62]. In 392 pregnant women and their children of the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) cohort, an agricultural community in California, US, Berger et al. (2018)[69] assessed the association between prenatal exposure to parabens, triclosan, and BP-3 and lung function but did not observe any association. These null results have recently been confirmed in another study in the same cohort evaluating the combined effect of 20 endocrine disruptors on lung function at 7 years[63]. Parabens and BP-3 showed a low contribution in the overall model including eleven phthalates, five phenols, and four parabens; for triclosan, they observed a positive association but in the BKMR model, its importance was low. Finally, in the HELIX cohort, Agier et al. (2019)[41] did not observe any association between prenatal exposure to ethyl-paraben and lung function at 6-12 years. Prenatal exposure to the other phenols was also not associated with lung function at school age.

Phthalates

Phthalates are phthalic acid diester compounds commonly used as plasticizers to increase flexibility and transparency of hard polyvinyl chloride (PVC) plastics. Phthalates are divided into long- and short-chain phthalates. The long-chain are the ones used in PVC plastics whereas the short-chain are used in non-PVC products including adhesives and personal care products[28] (Table 2). Both groups of phthalates are produced in large quantities worldwide and humans are continuously exposed to them through food, cosmetics products, and indoor air[28]. After exposure, they are metabolized and excreted from the body in hours or days. In order to avoid external contamination (e.g., phthalates present in lab plastic material), the metabolites and not their parent compounds are detected in biological samples, preferably in urine.

In vivo studies have shown that exposure to phthalates during gestation can lead to delayed lung maturation in newborn rats. Offspring of rats exposed to the long-chain di-(2-ethylhexyl) phthalate (DEHP) during gestation had increased lung interstitial tissue proportion and diminished number of

airspace units leading to a reduction of the gas-exchange surface[70–72]. A significant increase in the number and dimension of type-II pneumocytes, responsible for secretion of pulmonary surfactant and implicated in the epithelial repair, was observed[71]. Moreover, an *in vitro* study showed that exposure to DEHP altered the structure and migration of A549 cells, cell lines used as prototypes of type-II pneumocytes, and the production of pulmonary surfactant[73].

A total of five studies, three of them from the same cohort, have evaluated this association (Table 4). In the French cohort EDEN, the high molecular weight phthalate monocarboxyisooctyl phthalate (MCOP) and the low molecular weight phthalate mono-isobutyl phthalate (MiBP) tended to be associated with reduced FEV_1% at 5 years, but associations did not reach statistical significance[62]. A total of three studies have been conducted within the CHAMACOS cohort in the US[63,69,74]. These three studies differ in the number of phthalate metabolites included and the statistical tools used to assess the combined effect. The most consistent finding of these studies was the reduction of FEV_1 at 7 years associated with exposure to MCOP, even after accounting for other pollutants. Indeed, the most recent study included three pollutant groups (i.e. phthalates, parabens, and other phenols), and the BKMR model identified the phthalate group, and particularly MCOP, as the most important associated with impaired lung function[63]. Finally, in the HELIX study including a large number of pollutants and other environmental factors, exposure to DEHP metabolites during pregnancy was not associated with lung function at 6-12 years of age[41].

Currently used pesticides

Restriction on the use of persistent pesticides such as DDT has led to the use of non-persistent alternatives such as organophosphate pesticides, carbamates, and pyrethroids. They are widely produced and used worldwide for controlling pests in both agricultural and residential settings (Table 2). In 2018, around 400,000 tonnes of pesticides were sold in Europe with the majority used in agriculture[75]. Organophosphate pesticides (e.g., chlorpyrifos, malathion) are the most widely used active substances, followed by pyrethroids and carbamates. Exposure to pesticides is ubiquitous in humans (Table 1), primarily through their diet. However, the detection frequencies in biospecimens are usually low due to the intermittent exposure and their rapid elimination from the body[76–78].

Organophosphate pesticides can affect lung function by inhibition of the acetylcholinesterase (AChE) enzyme, preventing the metabolism of acetylcholine and consequently increasing bronchoconstriction and mucus secretion. It is also postulated that organophosphate pesticides can produce bronchoconstriction at levels below those needed to inhibit AChE via direct effect on muscarinic receptors; receptors responsible of controlling muscle tone, mucus secretion, vasodilatation, and inflammation[79,80].

We have identified two studies that evaluated the lung function effects of prenatal exposure to currently used pesticides (Table 4); the two were focused on organophosphate pesticides[41,81]. The first study was conducted in the CHAMACOS cohort. Organophosphate pesticides, particularly six dialkyl phosphate

Table 5. Summary of the effects of in utero exposure to organic pollutants on lung function

Pollutants	Number of studies	Effects observed	Evidence[a]
Persistent organic pollutants			
Organochlorine compounds	3	3 ↓ lung function	Insufficient
Perfluoroalkyl substances	3	2 ↓ lung function / 1 no effects	Insufficient
Non-persistent organic pollutants			
Bisphenols	5	1 ↓ lung function / 4 no effects	Insufficient
Parabens, Triclosan, Benzophenones	4	4 no effects	Insufficient
Phthalates	5	3 ↓ lung function / 2 no effects	Insufficient
Currently used pesticides	2	2 no effects	Insufficient

[a]Good evidence: for an association based on consistent results from multiple studies and meta-analyses; Moderate evidence: of an association based on multiple studies, but with some inconsistencies; Insufficient evidence: evidence for an association based on only a few studies, or with substantial inconsistencies; 0: no or very few studies[102].

metabolites (DAPs), were measured twice during pregnancy[81]. Prenatal exposure to DAPs was not associated with FEV_1 or FVC at 7 years. In the HELIX cohorts, DAPs were also measured during pregnancy but no association was found with lung function at school-age[41].

DISCUSSION

In this review, we provide a broad summary of the current evidence of the effects of prenatal exposure to organic pollutants on lung function in the offspring. Overall, evidence is insufficient for all organic pollutants, with few studies and inconsistent results across them (Table 5). Few studies have found associations and the effects observed (i.e. changes in lung function parameters) are small (e.g., 50 mL reduction in FEV_1 for DDE exposure[39]). Inconsistencies across studies may reflect differences in sociodemographic characteristics of the populations, different use of consumer products between countries, measurement error associated with the assessment of the outcome and the exposure, and the statistical approaches used to assess the lung function effects of organic pollutants. Hereby we discuss different possibilities that may explain the inconsistent results across studies.

Outcome measurement: The evidence on the effects of organic pollutants on respiratory health is larger and more consistent in relation to respiratory symptoms (i.e. respiratory tract infections, wheezing, asthma) (reviewed by Vrijheid et al., 2016[60]). More studies have been conducted in this regard because information on respiratory symptoms can be easily obtained from questionnaires administered to the parents. On the contrary, spirometry is not easily conducted in young untrained children participating in population-based studies and needs to be performed by a pulmonologist or trained nurse; however, spirometry offers an objective measurement of lung function less subject to bias than parental administered questionnaires. All the studies included in this review performed spirometry from 4 to 20 years of age except Impinen et al. (2018)[49] where children performed tidal breathing shortly after birth. Spirometry is a good

method to measure pulmonary function and the most commonly performed[82]. However, there are other techniques that can be performed to complement or improve the outcome measurement. The reliability of spirometry performance in very young children has been argued. Techniques such as body plethysmography and interrupter resistance technique (R_{int}) can be a good complement or alternative to spirometry testing in younger children, being the latter the most suitable for young children due to its minimal difficulty to be performed[83-85]. In very young children (less than 4 years of age), pulmonary function can be measured with non-invasive techniques that do not require sedation such as multiple-breath washout test, tidal breathing (as did Impinen et al., 2018[49]), and forced oscillation technique[3,86,87]. These techniques are simple to perform, require little cooperation, and provide information on lung development, including its volume and ventilation inhomogeneity (multiple-breath washout), airway size (tidal breathing and forced oscillation), mechanical properties (forced oscillation), respiratory control (tidal breathing), and small airway function (multiple-breath washout and forced oscillation). With these techniques, researchers have been able to detect changes in lung function in relation to prenatal exposure to air pollution[86]. In older children and adults, the reversibility test can be performed to measure airflow limitation. This technique measures lung function performing spirometry before and after the administration of a bronchodilator such as salbutamol. A positive result is given when there is a significant improvement in lung function after the administration of the bronchodilator (change in $FEV_1 \geq 12\%$ or ≥ 200ml). It is considered consistent with the diagnosis of asthma and COPD[88,89], although in population studies a positive result cannot discern between asthma and COPD[90]. The reversibility test is easy to conduct and does not require medical assistance.

Exposure assessment: We have restricted ourselves to articles assessing the levels of organic pollutants in human biospecimens. Studies where exposure to organic pollutants (e.g. pesticides) was estimated by means of residential proximity to a contaminated area (e.g. crops) have not been included (e.g. Raanan et al., 2017[91]). Biomonitoring is the most extensive strategy for the assessment of environmental influences on health because samples are easy to collect, multiple exposures can be measured in the same biospecimen, and levels provide information of exposure for those pollutants found in many sources, as the case of organic pollutants[92]. However, biomarker levels could be subject to physiological distortion (e.g., renal clearance in the case of PFASs), could not reflect the internal dose (more directly related with the health outcome), and in the case of non-persistent pollutants, a single spot urine sample only reflects exposure for a short period of time (leading to exposure misclassification and attenuation of the results). We should consider all these limitations when interpreting the results. Alternatively, physiological conditions can be considered such as the glomerular filtration rate[93], internal dose can be estimated by using physiologically based pharmacokinetic modelling (PBPK)[94], and multiple samples per subject can be collected to obtain information on long-term exposure[76,95].

Statistical approach: The majority of studies included in this review assessed one pollutant

at each time. However, humans are exposed to multiple organic pollutants at the same time. In the last decade, the exposome approach has been proposed as a new to paradigm to encompass the totality of human environmental (meaning all non-genetic) exposures from conception onwards, complementing the genome[96]. Some of the studies included in this review have already developed multipollutant models with the aim to identify the most relevant pollutant associated with lung function[41,63,69,74]. Novel statistical tools are being developed to study chemical mixtures[15]. For the study of the health effects of endocrine disrupting chemicals, these methods should consider non-linear exposure-outcome relationships (lower doses can have more harmful effects than higher doses[39]) and potential interactions and confounding between pollutants, as the BKMR method used by Berger et al. (2020)[63] offers.

External validity: Particularly for non-persistent organic pollutants, we should consider that these pollutants have been studied among the same few population-based cohort studies (i.e., in the US: CHAMACOS; and in Europe: HELIX, EDEN, INMA), thus, limiting the generalization of the results in other population settings with different use of chemicals (and in consequence different exposure levels) and sociodemographic characteristics.

Public health implications: Although the changes in lung function associated with exposure to organic pollutants may not be clinically relevant (e.g. 50 mL reduction in FEV_1 for DDE exposure[39], as mentioned before), they can be important from an etiological perspective and at a population level. A good example to illustrate the societal impact of small effects associated with exposure to environmental pollutants is the case of lead exposure in children and the reduction of intelligence quotient (IQ) of 6 points[97,98]. It is estimated that an average drop of 6 points in IQ across the population would nearly double the number of people with an IQ below 70[99]. Therefore, when there is absence of consistent evidence about the health effects of a given exposure, such as the association of organic pollutants with lung function, the precautionary principle should prevail and apply policy measures to reduce its exposure.

CONCLUSION

In conclusion, although in the last decade the number of studies assessing the lung function effects of prenatal exposure to organic pollutants have increased, the evidence is still limited and inconsistent. Many studies did not find any association; this can reflect a real null effect or methodological limitations such as exposure misclassification, an important challenge of the study of the health effects of non-persistent pollutants, or measurement error of lung function parameters performed at young age. Further studies, with larger sample size to study susceptible groups, conducted in different population settings, with a thoughtful sampling design, and considering multiple pollutants, are needed. In parallel, public health strategies, such as the one that the Federation of Gynecology and Obstetrics, the University of California, and the Health and Environment Alliance has recently launched[100], are needed to reduce exposure to organic pollutants in the community and particularly in pregnant women.

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DISCLOSURES

Dr. Abellan and Dr. Casas have nothing to disclose.

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