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Phthalate exposure and allergic diseases: Review of epidemiological and experimental evidence

Anette Kocbach Bølling[a,*,1], Kam Sripada[b,*,1], Rune Becher[a], Gabriel Bekö[c,d]

[a] Department of Environmental Health, Norwegian Institute of Public Health, Oslo, Norway
[b] Centre for Global Health Inequalities Research, Department of Sociology and Political Science, Norwegian University of Science and Technology, Trondheim, Norway
[c] International Centre for Indoor Environment and Energy, Department of Civil Engineering, Technical University of Denmark, Kgs. Lyngby, Denmark
[d] Faculty of Civil Engineering and Architecture, Kaunas University of Technology, Kaunas, Lithuania

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ABSTRACT

Phthalates are among the most ubiquitous environmental contaminants and endocrine-disrupting chemicals. Exposure to phthalates and related health effects have been extensively studied over the past four decades. An association between phthalate exposure and allergic diseases has been suggested, although the literature is far from conclusive. This article reviews and evaluates epidemiological (n = 43), animal (n = 49), and cell culture studies (n = 42), published until the end of 2019, on phthalates and allergic diseases, such as asthma, rhinoconjunctivitis, and eczema. In contrast to earlier reviews, emphasis is placed on experimental studies that use concentrations with relevance for human exposure. Epidemiological studies provide support for associations between phthalate exposures and airway, nasal, ocular, and dermal allergic disease outcomes, although the reported significant associations tend to be weak and demonstrate inconsistencies for any given phthalate. Rodent studies support that phthalates may act as adjuvants at levels likely to be relevant for environmental exposures, inducing respiratory and inflammatory effects in the presence of an allergen. Cell culture studies demonstrate that phthalates may alter the functionality of innate and adaptive immune cells. However, due to limitations of the applied exposure methods and models in experimental studies, including the diversity of phthalates, exposure routes, and allergic diseases considered, the support provided to the epidemiological findings is fragmented. Nevertheless, the current evidence points in the direction of concern. Further research is warranted to identify the most critical windows of exposure, the importance of exposure pathways, interactions with social factors, and the effects of co-exposure to phthalates and other environmental contaminants.

1. Introduction

Phthalates are ubiquitous environmental chemicals used primarily as plasticizers, lubricants, binders, and solvents in a variety of consumer products globally. Due to their widespread use and ability to migrate from the source to the environment, human exposure is common; phthalate metabolites are detected in the majority of analyzed urine samples, with many detected in over 95% of samples (CDC, 2019; Heudorf et al., 2007).

Phthalates are diesters of phthalic acids. They have a wide range of physical and chemical properties. The physicochemical properties of phthalates determine their industrial applications, environmental kinetics, and consequently the dominant human exposure routes. Whereas both dermal absorption and inhalation may be important pathways for low molecular weight (LMW) phthalates, ingestion (including food, tap and bottled water, soil, and dust) is likely most important for high molecular weight (HMW) phthalates (Bekö et al., 2013; Koch et al., 2013; Wittassek et al., 2011; Wormuth et al., 2006; Luo et al., 2018).

Phthalate exposure has been associated with adverse health effects, including endocrine disruption, respiratory symptoms, and effects on reproduction and neurodevelopment (Bornehag et al., 2018; Braun et al., 2013; Braun et al., 2014; Cathey et al., 2020; Engel et al., 2010; Huang et al., 2017; Jurewicz and Hanke, 2011; Oulhote et al., 2020). Phthalates have been linked to asthma symptoms and asthma development in an increasing number of epidemiological studies (Bornehag and Nanberg, 2010). Early studies on phthalate exposure and respiratory conditions date back to the 1970s (Polakoff et al., 1975; Sokol et al., 1973). More recently, possible associations between phthalate exposure and allergic endpoints like eczema, rhinoconjunctivitis, and

* Corresponding authors.
E-mail addresses: anette.kocbach@fhi.no (A.K. Bølling), kam.sripada@ntnu.no (K. Sripada).
[1] Equal contributors.

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Nomenclature

BBzP	Butyl-benzyl phthalate
BDP	Butyl-dodectyl phthalate
DEHP	Di-ethyl-hexyl phthalate
DEP	Di-ethyl phthalate
DiDP	Di-iso-decyl phthalate
DiNCH	Di-iso-nonyl-cyclohexane-di-carboxylate
DiNP	Di-iso-nonyl phthalate
DnBP	Di-n-butyl phthalate
DPHP	Di-2-propylheptyl phthalate
FITC	Fluorescein isothiocyanate
HMW	High molecular weight
LMW	Low molecular weight
MBzP	Mono-benzyl phthalate
MCiNP	Mono-carboxy-iso-nonyl phthalate
MCiOP	Mono-carboxy-iso-octyl phthalate
MCMHP	Mono-carboxy-methyl-hexyl phthalate
MEP	Mono-ethyl phthalate
MECPP	Mono-ethyl-carboxy-pentyl phthalate
MEHP	Mono-ethyl-hexyl phthalate
MEHHP	Mono-ethyl-hydroxy-hexyl phthalate
MEOHP	Mono-ethyl-oxo-hexyl phthalate
MHiDP	Mono-hydroxy-iso-decyl phthalate
MHiNP	Mono-hydroxy-iso-nonyl phthalate
MnBP	Mono-n-butyl phthalate
MNICN	2-methoxy-4-nitrophenyl isocyanate
MOiNCH	Mono-oxo-iso-nonyl cyclohexanecarboxylic acid
MOiNP	Mono-oxo-iso-nonyl phthalate
OVA	ovalbumin
IgE	immunoglobulin E
CAE	cockroach allergen extract
PBMCs	Peripheral blood mononuclear cells
PEICN	Phenethyl isocyanate
PVC	Polyvinyl chloride
SVOC	Semi-volatile organic compounds
VOC	Volatile organic compounds

sensitization, have received increasing attention (Ait Bamai et al., 2014; Bekö et al., 2015; Choi et al., 2014; Hsu et al., 2012; Stelmach et al., 2015; Wang et al., 2014).

The symptoms of these allergic diseases manifest in the upper and lower airways and skin, which comprise the major epithelial interface between air and the body. Although the mechanisms behind development of allergic diseases are not completely understood, environmental exposures through airways and skin are suspected to contribute to disease development and exacerbation (Dick et al., 2014; Redlich, 2010; Searing and Rabinovitch, 2011). The route of exposure also affects to what extent cells and organs are exposed to the parent phthalate or its metabolites. While ingestion leads to first-pass metabolism of phthalates in the liver, this is not the case after inhalation and dermal uptake. Since parent phthalates and metabolites interact with different molecules and receptors, this is of major importance for the toxicological effects of phthalates on a molecular level (Bølling et al., 2013).

Phthalate exposure indicators commonly applied in epidemiological studies include presence of polyvinyl chloride (PVC) flooring, phthalates in indoor air or dust, and urinary phthalate metabolite levels. Pregnancy is a particularly vulnerable time for environmental exposures, and maternal phthalate metabolite levels in urine and serum are used to assess prenatal exposure (Just et al., 2012b; Ku et al., 2015; Stelmach et al., 2015; Whyatt et al., 2014).

This review comprehensively summarizes epidemiological studies, *in vivo* studies with animal models, and *in vitro* cell culture studies, in relation to human phthalate exposure and allergic disease. First, we present the epidemiological studies of phthalate exposure and allergic diseases in non-occupational settings for the four commonly applied exposure indicators (presence of PVC flooring, phthalates in indoor dust, urinary phthalate metabolite levels, maternal phthalate metabolite levels during pregnancy to assess prenatal exposure). Then, experimental studies from animal and cell culture models are summarized, and their relevance is evaluated in terms of the applied concentrations and exposure pathways. Finally, conclusions are drawn regarding the current evidence for associations between phthalate exposure and allergic diseases.

2. Methods

2.1. Epidemiological studies

A PubMed search was performed using all possible combinations of the search terms for (a) exposure indicators (PVC, Plasticizer, Phthalate, Phthalates, "Plastic materials", "Surface materials") and (b) study outcomes (Respiratory health, Asthma, Bronchial obstruction, Wheeze, Croup, Eczema, Atopic dermatitis, Allergy, Allergic, Sensitization, Rhinitis, Rhinoconjunctivitis) on studies published through 2019. Titles and abstracts were initially screened for inclusion, and then full texts were screened for relevant articles (either by A.K.B. or K.S.). Occupational health research, case studies, and literature reviews were excluded. Publications with a main focus on other exposures or health outcomes, such as pulmonary function or exhaled nitric oxide, were excluded. Studies on exposure to PVC material were excluded when less than 2% of the study population was exposed.

Potential bias in the selected studies was assessed by rating the inclusion of covariates from "1" (poor) to "4" (good). Rating "3" included the covariates age, sex, socioeconomic status (usually parental education or income), family history of allergic symptoms, and smoking or environmental tobacco smoke exposure. Studies that excluded one or more of these covariates were rated "2" or "1," respectively. Rating "4" was given to studies that also considered covariates related to predisposition (e.g., birth weight, maternal age at delivery, breastfeeding, type of daycare, single guardian) or other environmental exposures (e.g., pets, ventilation, dampness, cleaning frequency, occupational exposure).

Results from each article were categorized into four health outcome groups:

i) *Airway*; all asthma and wheeze outcomes, cough, phlegm, bronchial obstruction, bronchitis, croup.
ii) *Nasal and ocular*; all rhinitis outcomes, hay fever, rhinoconjunctivitis, allergic conjunctivitis.
iii) *Dermal*; all eczema outcomes. Since the terms "eczema" and "atopic dermatitis" are often used interchangeably, both are grouped under "eczema" in the review of the epidemiological literature.
iv) *Allergic disease indicators*; current allergy, allergic disease case status (as determined through a combination of reported symptoms of asthma, rhinitis/rhinoconjunctivitis and eczema specified in the individual study), sensitization, total immunoglobulin E (IgE), food allergy.

2.2. Animal studies

A PubMed search was performed using all possible combinations of the search terms for (a) model systems ("*in vivo*", Animal, Mouse, Rat) and (b) endpoints (Asthma, Eczema, Atopic dermatitis, Allergy, Sensitization, Rhinitis, Rhinoconjunctivitis, Conjunctivitis, Inflammation,

Immune response) or characteristics (Allergen, Adjuvant) in combination with (c) Phthalate. Titles and abstracts were screened for inclusion in this review (by A.K.B.). Studies concerning endpoints with relevance for allergic and respiratory outcomes considered in the epidemiological studies were included. Studies in animals other than mice and rats were excluded.

A range of different exposure routes, models, and endpoints were applied in the included studies. They reflected the exposure measures and health outcomes assessed in the epidemiological studies to a varying extent. In order to relate the various study designs to the epidemiological studies, they were classified with regard to six outcome groups (L – lung/airways, N – nasal, S – sensitization, D – atopic dermatitis, C – contact hypersensitivity and I– inflammation) and 7 exposure routes (L – lung/airways (inhalation or instillation), N – nasal (instillation or injection), O – oral (gavage or feed), T – topical, I – injection (subcutaneous or intraperitoneal), M-O – maternal oral exposure (gavage, intragastric or feed), M-I – maternal injection (intraperitoneal)).

In order to assess whether the animal studies used doses reflecting human environmental exposures, the daily intake estimates reported in the literature for humans and the current tolerable daily intake (TDI) levels were considered. Although the daily intake estimates are much higher for DEHP than DnBP and BBzP, the maximum daily intake is generally below 100 μg/kg/day for all three phthalates (Clark et al., 2011; Wittassek et al., 2011). Thus, when evaluating studies in animal models, exposures above 100 μg/kg/day were considered to have limited relevance for human environmental exposure. These studies are listed in this review, but emphasized to a lesser extent in the discussion.

2.3. Cell culture studies

A PubMed search was performed using all possible combinations of the search terms for (a) model systems ("*in vitro*", "cell culture") and (b) endpoints (Asthma, Eczema, Atopic dermatitis, Allergy, Sensitization, Rhinitis, Rhinoconjunctivitis, Conjunctivitis, Inflammation, Immune response, Cytokine) or characteristics (Allergen, Adjuvant) in combination with (c) Phthalate. Titles and abstracts were screened for inclusion (by A.K.B.). Studies concerning endpoints with relevance for the allergic and respiratory outcomes considered in the epidemiological studies were included.

With regard to the relevance of the *in vitro* phthalate concentrations for human environmental exposure levels, we considered the reported serum levels of phthalates and their primary metabolites (Guo et al., 2012; Guo et al., 2012; Högberg et al., 2008; Frederiksen et al., 2020; Olsén et al., 2012; Lind et al., 2012), or the estimated pulmonary levels of phthalates based on reported indoor air levels (Bølling et al., 2013) (Appendix C, Table C1). Concentrations in the nano-molar range appear to be most relevant for human exposure, while exposures up to 10 μM may have relevance for airway exposures. Thus, these two levels ($\leq$1 μM and $\leq$10 μM) were considered potentially relevant for human exposure in this review.

3. Results and discussion

3.1. Epidemiological studies

The search yielded 601 studies, of which 43 met the inclusion criteria. There were 14 cross-sectional (32.5%), 12 case control (28%), and 17 longitudinal studies (39.5%). The largest sample size was n = 31,049 (Dong et al., 2014) and the smallest was n = 18 (Kim et al., 2017); the median sample size was n = 483 individuals. The studies differed in the number and choice of covariates. Six studies were rated "1" (poor), 10 studies were rated "2," 11 studies were rated "3," and 16 studies were rated "4" (good); the mean covariate rating was 2.9. The majority of studies rated "2" did not include a measure of socioeconomic status. Studies varied in method of identifying health outcome (e.g., symptoms, doctor-diagnosed, parent-reported, parent-reported doctor-diagnosed), time of diagnosis (e.g., current, last 12 months, ever), as well as the exposure indicator used. Seven studies used the presence of PVC flooring or wall covering as phthalate exposure indicator, eight studies used phthalate concentrations in indoor dust, 18 studies used concentrations of phthalate metabolites in urine, and 15 studies used phthalate metabolites in pregnant mothers. Some studies included more than one exposure indicator.

Tables 1–4 present for the four exposure indicators adjusted odds ratio (OR) and 95% confidence interval (CI) for each significant association, grouped by health outcome category and parent phthalate by increasing molecular weight. If a study reported multiple models for a given relationship, ORs are shown for the ones with the highest covariate rating. Non-significant results and other effect size measures (e.g., relative risk, percent difference, regression coefficient), together with full details of all included studies, are presented in Appendix A, Tables A1–A4.

3.1.1. Presence of PVC/plastic building materials

Three cross-sectional, two case-control, and two longitudinal studies used PVC flooring or wall covering as an exposure indicator (Table 1; see Table A1 for one additional study not reporting OR). Most of these had satisfactory control for covariates (rating 3 or 4). Four studies included populations with a high proportion of homes with PVC flooring (26 to 52%) (Jaakkola et al., 1999; Jaakkola et al., 2004; Larsson et al., 2010; Shu et al., 2014). In two studies, PVC building materials were rare (2.5 to 2.8%), resulting in a relatively small study population with exposure to PVC (Jaakkola et al., 2000; Jaakkola et al., 2006).

The literature reviewed here provides support for an association between the presence of PVC materials in the home and airway

Table 1
Summary of significant associations reported between the presence of PVC flooring/wall coverings and allergic disease. All associations are for children, except where indicated otherwise. Study design is indicated by C – case-control; L – longitudinal; or X – cross-sectional. See Table A1 for further details, non-significant results, and one additional study that did not provide OR.

Outcome	Study design	n	Covariate category	Adjusted OR (95% CI)	Reference
Airway					
Asthma	L	4779	3	1.7 (1.1–2.8)	Larsson et al. (2010)
Asthma	L	3228	2	2.4 (1.3–4.6)	Shu et al. (2014)
Asthma (adults)	C	1453	3	2.4 (1.0–5.8)	Jaakkola et al. (2006)
Bronchial obstr.	C	502	4	1.9 (1.1–3.1)	Jaakkola et al. (1999)
Cough	X	2568	3	2.4 (1.0–5.6)	Jaakkola et al. (2000)
Phlegm	X	2568	3	2.8 (1.0–7.4)	Jaakkola et al. (2000)
Wheeze	X	2568	3	3.4 (1.1–10.4)	Jaakkola et al. (2000)
Wheeze	X	5951	4	1.4 (1.0–1.9)	Jaakkola et al. (2004)
Allergic disease indicators					
Allergy	X	5951	4	1.5 (1.1–1.7)	Jaakkola et al. (2004)

Table 2
Summary of significant associations reported between phthalate concentrations in indoor dust and allergic disease. Associations are for all children in study, except where indicated. Study design is indicated by C–case-control; L–longitudinal; or X – cross-sectional. Negative associations are italicized. See Table A2 for further details, non-significant results, and one additional study that did not provide OR.

Phthalate	Outcome	Study design	n	Covariate category	Adjusted OR (95% CI)	Reference
Airway						
DnBP	Asthma	C	500	2	*0.7 (N/A)*	Callesen et al. (2014b)
DnBP*	Asthma	C	500	2	3.7 (1.1–12.5)	Bekö et al. (2015)
BBzP*	Asthma	C	500	2	2.0 (1.1–3.7)	Bekö et al. (2015)
DEHP	Asthma	C	400	1	2.9 (1.4–6.3)	Bornehag et al. (2004)
DEHP	Wheeze	C	184	2	3.7 (1.4–9.9)	Kolarik et al. (2008)
Nasal & Ocular						
DMP	Rhinitis	X	156	1	2.9 (1.5–5.5)	Ait Bamai et al. (2014)
DnBP*	Rhinoconjunctivitis	C	500	2	5.2 (1.4–18.7)	Bekö et al. (2015)
DnBP	Rhinoconjunctivitis (girls)	X	128	1	1.85 (1.12–3.06)	Ait Bamai et al. (2016)
DiBP*	Rhinoconjunctivitis	C	500	2	6.7 (1.8–25.4)	Bekö et al. (2015)
BBzP	Rhinitis	C	400	1	3.0 (1.3–6.9)	Bornehag et al. (2004)
BBzP	Rhinitis	C	101	4	7.0 (1.8–28.2)	Hsu et al. (2012)
DEHP	Conjuncivitis	X	156	1	9.3 (1.7–50.4)	Ait Bamai et al. (2014)
DEHP	Conjuncivitis (adults)	X	156	1	4.0 (1.3–12.6)	Ait Bamai et al. (2014)
DEHP	Rhinoconjunctivitis	X	128	1	1.97 (1.19–3.25)	Ait Bamai et al. (2016)
DEHP	Rhinoconjunctivitis (boys)	X	128	1	2.05 (1.03–4.08)	Ait Bamai et al. (2016)
DEHP	Rhinoconjunctivitis	C	500	2	3.5 (1.4–9.0)	Bekö et al. (2015)
Dermal						
DiBP	Eczema	X	156	1	15.0 (1.9–118.0)	Ait Bamai et al. (2014)
DiBP*	Eczema	C	500	2	*0.12 (0.02–0.65)*	Bekö et al. (2015)
BBzP	Eczema	X	156	1	6.6 (1.7–25.3)	Ait Bamai et al. (2014)
BBzP	Eczema (adults)	X	156	1	4.5 (1.06–19.4)	Ait Bamai et al. (2014)
BBzP	Eczema	C	500	2	3.1 (1.1–9.3)	Bekö et al. (2015)
BBzP	Eczema	C	400	1	2.6 (1.2–5.3)	Bornehag et al. (2004)
BBzP	Eczema	C	101	4	7.7 (1.7–35.6)	Hsu et al. (2012)
DEHP	Eczema	C	500	2	2.1 (1.0–4.5)	Bekö et al. (2015)
DEHP	Eczema (adults)	X	156	1	3.9 (1.1–13.8)	Ait Bamai et al. (2014)
Allergic disease indicators						
BBzP	Allergy	C	400	1	2.0 (1.0–3.7)	Bornehag et al. (2004)
BBzP	Disease cases	C	101	4	5.8 (1.5–22.3)	Hsu et al. (2012)
DEHP	Disease cases	C	184	2	2.9 (1.1–7.5)	Kolarik et al. (2008)

* Indicates exposure in daycare settings; otherwise exposure at home (Bekö et al., 2015).

outcomes. Dong et al. (2014) reported using a regression model (Table A1) that respiratory conditions (asthma, cough, phlegm) were significantly associated with exposure to PVC flooring. The evidence for other health outcome groups is insufficient. Studies in occupational settings provide further support for the positive association, as exposure to PVC fumes has been associated with respiratory symptoms and occupational asthma (Jaakkola and Knight, 2008). Several studies have reported that PVC flooring contributes significantly to phthalate exposure (Bornehag et al., 2005a; Just et al., 2015), providing support for the role of phthalates in the observed relationship. However, exposure to PVC materials is an indirect indicator of phthalate exposure. These studies could reflect health outcomes associated with other volatile and semi-volatile organic compounds (VOCs and SVOCs) emitted by PVC containing materials, or the combined effect of dampness and PVC materials (Bonisch et al., 2012; Bornehag et al., 2005b; Wieslander et al., 1999). Moreover, misclassification of building materials (e.g., PVC vs. linoleum) by questionnaire respondents may be a further limitation in these studies (Engman et al., 2007).

3.1.2. Phthalates in indoor dust

Three cross-sectional and five case-control studies investigated the relationship between allergic disease and phthalate mass fractions in indoor dust (Table 2, Table A2). Control for covariates was generally poor, most often rated 1 or 2. The only study with good control for covariates (rating 4) had a small study population (n = 101), resulting in even smaller subgroups of cases and controls available for analyses, high effect estimates, and wide confidence intervals (Hsu et al., 2012). The results from these studies should therefore be interpreted with caution.

Significant positive associations were reported especially in the nasal and ocular and dermal outcome groups. BBzP, DEHP, and to a lesser extent DMP, DnBP, and DiBP were associated with negative health outcome measures. The majority of the ORs indicated moderate to strong associations. However, half of the studies had relatively small populations (n < 200), potentially leading to uncertainty in effect estimates (also indicated by some of the confidence intervals in Table 2 being very wide).

One study found no significant associations between allergic outcomes and exposure to phthalates in house dust (Ait Bamai et al., 2018a). Large number of statistical tests, misclassification of outcomes by parents, low observed phthalate mass fractions in dust, and lack of covariates present in other studies (e.g., PVC flooring) were suggested by study authors as possible reasons for discrepancies between studies.

SVOCs partition between the gas phase (air) and surfaces, which include settled dust, airborne particles, and other indoor surfaces (Weschler and Nazaroff, 2010). Higher molecular weight phthalates such as DEHP and BBzP are present indoors primarily in the condensed phase (on surfaces including dust), while lower molecular weight phthalates such as DEP and DBP are predominantly present in the gas phase (Heudorf et al., 2007). Dust mass fractions may represent exposure via dust ingestion, inhalation, and dermal absorption, assuming there is equilibrium between concentrations in the gas phase and in settled dust. However, for some SVOCs, especially those with high octanol-air partition coefficients, mass fraction in settled dust may not have time to equilibrate with the gas phase concentration (Weschler and Nazaroff, 2010). Simplified models to infer air concentrations from dust mass fractions work well in central tendency but may have uncertainties on a case-to-case basis (due to e.g., octanol-air partition

Table 3
Summary of significant associations reported between phthalate metabolite concentrations in urine and allergic disease. Associations are for all children in the study, except where indicated. Study design is indicated by C – case-control; L – longitudinal; or X– cross-sectional. Negative associations are italicized. See Table A3 for further details, non-significant results, and findings with other types of effect estimates.

Phthalate metabolite	Outcome	Study design	n	Covariate category	Adjusted OR (95% CI)	Reference
Airway						
MEP	Asthma	L	171	3	8.92 (1.9–42.5)	Ku et al. (2015)
MEP	Asthma (boys)	X	2180	1	2.00 (1.14–3.51)	Odebeatu et al. (2019)
MiBP	Wheeze	X	128	1	*0.62 (0.40–0.97)*	Ait Bamai et al. (2016)
MnBP	Asthma	X	418	2	1.84 (1.0, 3.3)	Franken et al. (2017)
MnBP	Wheeze	X	1596	1	*0.45 (0.20,0.98)*	Hoppin et al. (2013)
MnBP	Wheeze	X	419	4	2.27 (1.0–4.9)	Shi et al. (2018)
MBzP	Asthma	X	2180	1	1.54 (1.05–2.27)	Odebeatu et al. (2019)
MBzP	Asthma (adults)	X	1596	1	1.5 (1.0–2.1)	Hoppin et al. (2013)
MBzP	Wheeze (adults)	X	1596	1	1.8 (1.2–2.6)	Hoppin et al. (2013)
MEHHP	Asthma	C	453	3	1.33 (1.1–1.6)	Wang and Karmaus (2017)
MCNP	Asthma	X	1596	1	*0.50 (0.25, 0.97)*	Hoppin et al. (2013)
MCNP	Asthma	X	623	3	2.2 (1.2–4.0)	Bertelsen et al. (2013)
MCOP	Asthma	X	623	3	1.9 (1.0–3.3)	Bertelsen et al. (2013)
Σ_4LMW	Wheeze	X	419	4	2.15 (1.0–4.6)	Shi et al. (2018)
ΣDEHP	Asthma	X	1596	1	*0.26 (0.1, 0.5)*	Hoppin et al. (2013)
ΣDEHP	Asthma (age 2 years)	L	171	3	6.14 (1.2–32.1)	Ku et al. (2015)
ΣDEHP	Asthma (age 5 years)	L	171	3	4.36 (1.0–18.7)	Ku et al. (2015)
ΣDEHP	Asthma	X	418	2	1.94 (1.1, 3.5)	Franken et al. (2017)
ΣPhthalates	Wheeze	X	419	4	2.25 (1.1–4.8)	Shi et al. (2018)
Nasal & Ocular						
MiBP	Rhinitis	X	419	4	2.23 (1.08–4.62)	Shi et al. (2018)
MnBP	Rhinitis	X	419	4	2.14 (1.02–4.46)	Shi et al. (2018)
MBzP	Rhinitis	X	419	4	2.46 (1.17–5.14)	Shi et al. (2018)
MBzP	Rhinitis (adults)	X	1596	1	1.2 (1.0–1.5)	Hoppin et al. (2013)
Σ_4LMW	Rhinitis	X	419	4	2.28 (1.09–4.76)	Shi et al. (2018)
ΣPhthalates	Rhinitis	X	419	4	3.19 (1.49–6.82)	Shi et al. (2018)
Dermal						
MEP	Eczema	C	500	2	2.3 (1.1–4.6)	Callesen et al. (2014a)
MiBP	Eczema	X	419	4	2.96 (1.02–8.60)	Shi et al. (2018)
MnBP	Eczema (same day)[‡]	L	18	1	2.85 (1.12–7.26)	Kim et al. (2017)
MnBP	Eczema (1 day lag)[‡]	L	18	1	2.74 (1.21–6.20)	Kim et al. (2017)
MnBP	Eczema	X	419	4	2.98 (1.19–7.50)	Shi et al. (2018)
MBzP	Eczema	L	483	4	2.50 (1.08–5.79)	Wang et al. (2014)
MEOHP	Eczema (2 day lag)[‡]	L	18	1	3.11 (1.01–9.61)	Kim et al. (2017)
MEOHP	Eczema	X	419	4	2.63 (1.02–6.80)	Shi et al. (2018)
MEHHP	Eczema	X	419	4	3.10 (1.10–8.74)	Shi et al. (2018)
MEHP	Eczema	C	256	4	2.17 (1.03–4.56)	Wang et al. (2015)
MECPP	Eczema	X	128	1	*0.45 (0.21–0.95)*	Ait Bamai et al. (2016)
Σ_4LMW	Eczema	X	419	4	4.30(1.42–13.01)	Shi et al. (2018)
ΣPhthalates	Eczema	X	419	4	4.66 (1.52–14.30)	Shi et al. (2018)
Allergic disease indicators						
MEP	Sensitization (adults)	X	1596	1	*0.8 (0.7, 0.9)*	Hoppin et al. (2013)
MiBP	Hay Fever	X	1596	1	*0.1 (0.0, 0.4)*	Hoppin et al. (2013)
MnBP	Hay Fever	X	1596	1	*0.1 (0.0, 0.2)*	Hoppin et al. (2013)
MCPP	Hay Fever	X	1596	1	*0.1 (0.0, 0.6)*	Hoppin et al. (2013)
MCPP	Sensitization (adults)	X	1596	1	1.5 (1.1, 2.1)	Hoppin et al. (2013)
MBzP	Hay Fever	X	1596	1	*0.4 (0.2, 0.8)*	Hoppin et al. (2013)
MBzP	Hay Fever (adults)	X	1596	1	1.7 (1.1–2.6)	Hoppin et al. (2013)
ΣDEHP	Sensitization (adults)	X	1596	1	1.4 (1.1–2.1)	Hoppin et al. (2013)

Notes: Where table displays the name of a phthalate, studies examined its metabolites. ΣDEHP = MEHP + MEHHP + MEOHP. Σ_4LMW = MMP + MEP + MiBP + MnBP. ΣPhthalates = MMP + MEP + MiBP + MnBP + MBzP + MEHP + MECPP + MEHHP + MEOHP.

[‡] Pooled urinary phthalate levels were compared with atopic dermatitis symptom manifestation rate for the entire sample on the same day as well as after a 1- or 2-day lag.

coefficients, average indoor airborne particle concentrations, and density). Consequently, if inhalation or dermal uptake from air plays a more important role than dust ingestion of a phthalate, the dust mass fraction of that phthalate is not an appropriate exposure indicator.

3.1.3. Urinary phthalate metabolites

Urinary metabolite concentrations are the most commonly used exposure measure in epidemiological studies on phthalate health effects. Eight cross-sectional, seven case-control, and three longitudinal studies used urinary phthalate metabolites as an exposure indicator (Table 3; see Table A3 for six additional studies). These studies covered a wider range of health outcomes: allergic disease cases, asthma, eczema, food allergy, hay fever, IgE, rhinitis, rhinoconjunctivitis, and wheeze. Most studies only included children; three studies included adult participants (Odebeatu et al., 2019; Bai et al., 2017; Hoppin et al., 2013). Nine of 18 studies had satisfactory adjustment for covariates (categories 3 or 4).

The studies reviewed here provide evidence for potential associations between phthalate metabolite levels and airway, nasal and ocular, and dermal health outcome categories among children. A few associations were relatively strong and included good adjustment for covariates, but some, such as Ku et al. (2015) and Kim et al. (2017), had small populations (n < 200) and reported large confidence intervals, so these associations should be interpreted with caution. Allergic disease

Table 4
Summary of significant associations reported between maternal phthalate metabolite concentrations and allergic disease. All studies were longitudinal (L). Negative associations are italicized. See Table A4 for further details, non-significant results, studies using maternal blood, and findings with other types of effect estimates.

Phthalate metabolite	Outcome	Study design	n	Covariate category	Adjusted OR (95% CI)	Reference
Airway						
MEP	Asthma	L	300	3	1.3 (1.0–1.7)	Whyatt et al. (2014)
MEP	Wheeze	L	159	4	*0.31 (0.15–0.66)*	Buckley et al. (2018)
MnBP	Asthma	L	371	4	1.24 (1.02–1.50)	Jahreis et al. (2018)
MnBP	Asthma	L	300	3	1.4 (1.1–1.9)	Whyatt et al. (2014)
MnBP	Wheeze	L	159	4	*0.40 (0.18–0.87)*	Buckley et al. (2018)
MBzP	Asthma	L	300	3	1.4 (1.1–1.9)	Whyatt et al. (2014)
MBzP	Wheeze	L	136	3	4.95 (1.08–22.63)	Ku et al. (2015)
MBzP	Croup (boys)	L	1062	4	3.35(1.49–7.54)	Shu et al. (2018)
MCOP	Asthma	L	392	4	1.54 (1.12–2.12)	Berger et al. (2018b)
MEHHP	Croup (boys)	L	1062	4	3.04(1.33–6.94)	Shu et al. (2018)
MEOHP	Croup	L	1062	4	2.27(1.23–4.19)	Shu et al. (2018)
MECPP	Croup	L	1062	4	2.46(1.32–4.61)	Shu et al. (2018)
MHiNP	Wheeze (girls)	L	1062	4	2.40 (1.26–4.54)	Shu et al. (2018)
MOiNP	Wheeze (girls)	L	1062	4	2.71(1.35–5.45)	Shu et al. (2018)
MCiOP	Wheeze	L	1062	4	1.72(1.17–2.54)	Shu et al. (2018)
MHiDP	Croup (boys)	L	1062	4	2.25(1.08–4.72)	Shu et al. (2018)
ΣLMW	Wheeze	L	159	4	*0.27 (0.13–0.59)*	Buckley et al. (2018)
Dermal						
MEP	Eczema	L	604	4	1.69 (1.05–2.73)	Soomro et al. (2018)
MiBP	Eczema	L	604	4	1.68 (1.16–2.45)	Soomro et al. (2018)
MEHP	Eczema	L	604	4	1.38 (1.03–1.85)	Soomro et al. (2018)
MECPP	Eczema	L	604	4	1.46 (1.04–2.06)	Soomro et al. (2018)
MCNP	Eczema	L	604	4	1.61 (1.00–2.59)	Soomro et al. (2018)
MCOP	Eczema	L	604	4	1.60 (1.16–2.23)	Soomro et al. (2018)
ΣDEHP[†]	Eczema	L	604	4	1.08 (1.00–1.18)	Soomro et al. (2018)
Allergic disease indicators						
MEP	Total IgE	L	371	4	1.14 (1.02–1.26)	Jahreis et al. (2018)
MnBP	Total IgE	L	371	4	1.21 (1.04–1.41)	Jahreis et al. (2018)
MBzP	Allergy	L	147	3	4.2 (1.2–17.9)	Stelmach et al. (2015)

Notes: Where table displays the name of a phthalate, studies examined its metabolites. For Soomro et al. (2018), ΣDEHP[†] = MECPP + MEHHP + MEOHP + MEHP. For Buckley et al. (2018), only results related to wheeze in the last 12 months are shown, and ΣLMW = MEP + MnBP + MiBP. For Soomro et al. (2018), only results from the youngest age with significant associations are shown; for other ages, see Table A4. For Whyatt et al. (2014), only results for history of asthma-like symptoms are shown; for other asthma-related endpoints, see Table A4.

indicators showed both positive and strong negative associations with phthalate urinary metabolites, but these results are based on a single study, judged to have poor adjustment for covariates (Hoppin et al., 2013). Two studies reported associations using regression coefficients for serum total IgE per unit log-urine metabolite levels (Table A3): Wang et al. (2014) reported that MEHP levels were positively correlated with specific IgE sensitization in boys, and Ku et al. (2015) found in allergic children that total IgE at 8 years of age was associated with MBzP exposure at 2 years of age and MEHP exposure at 5 years of age. Negative associations between urinary metabolites and health were also reported (Ait Bamai et al., 2016; Hoppin et al., 2013). Four studies reported null findings between urinary phthalate measures and various health outcomes: asthma (Bai et al., 2017); eczema (Choi et al., 2014); allergic disease cases, asthma, rhinitis, and eczema (Hsu et al., 2012); and eczema and food allergy (Stelmach et al., 2015).

Filaggrin (FLG) loss-of-function mutation has been linked to increased urinary phthalate metabolite levels (Joensen et al., 2014) and to higher odds of eczema in children with high urinary phthalate levels (Wang and Karmaus, 2015). Higher levels in urine may be due to increased dermal absorption caused by impaired skin barrier function or increased use of skin care products due to the skin condition. However, Overgaard et al. (2017) did not find an association between FLG loss-of-function mutation and urinary levels of phthalate metabolites, but did report that emollient use and eczema were associated with increased phthalate metabolite concentrations. On the other hand, Ait Bamai et al. (2018a) found clearer effects of indoor environmental exposures on eczema and wheeze in children without loss-of-function mutations in FLG compared to those with mutations, possibly owing to increased care or a different lifestyle among those with FLG mutation. In addition, two studies investigating phthalate levels and asthma proposed possible interactions with DNA methylation (Wang et al., 2015) and genetic variants (i.e., superoxide dismutase 2, SOD2) (Wang and Karmaus, 2017). Taken together, more research is needed in order to disentangle the relationship between phthalate exposure, genetic and epigenetic factors, and allergic diseases.

Several studies investigated the relationship between health outcomes and both phthalates in indoor dust and urinary phthalate metabolites. A Danish study did not observe strong associations between allergic disease outcomes and phthalate levels in dust (Callesen et al., 2014b) or their metabolites in urine (Callesen et al., 2014a). However, among children with allergic diseases, but not among healthy children, significant associations were found between IgE sensitization and mass fractions of several phthalates in indoor dust collected from homes and daycare centers (Bekö et al., 2015). Similar associations were found with the estimated daily indoor phthalate intakes from dust ingestion, inhalation, and dermal absorption (Bekö et al., 2015). No significant associations were however observed between phthalate metabolites in urine and allergic sensitization. Hsu et al. (2012) observed associations between allergic diseases and BBzP in dust, but not their metabolites in urine. Additionally, daily intakes of DEHP via floor dust, but not total intake estimates obtained from urinary metabolite levels, were associated with allergic rhinoconjunctivitis (Ait Bamai et al., 2016). These results indicate that exposures occurring in the indoor environment may play a more prominent role in allergic diseases than other sources.

Levels of phthalate metabolites in urine reflect the total phthalate exposure through ingestion, inhalation, and dermal uptake. They provide limited information regarding the contribution of exposure routes. This is especially the case for lower molecular weight phthalates. For high molecular weight phthalates, inhalation, and dermal exposure may contribute less to the urinary metabolite levels compared to

ingestion (Bekö et al., 2013; Clark et al., 2011; Koch et al., 2013). If fractional exposure through a given exposure pathway, as opposed to total exposure, happens to dominate a health effect, urinary metabolite concentrations will not capture the association. Moreover, phthalate metabolite levels in urine correspond to exposures that occurred over a relatively short period of time (1 to 2 days) prior to sampling and may vary throughout the day, between days, or among trimesters of pregnancy. A larger number of samples collected over a longer period of time may therefore be important to accurately assess exposure (Casas et al., 2018).

3.1.4. Maternal phthalate metabolites

Phthalate metabolite levels in pregnant mothers were used in 15 studies to longitudinally investigate the impact of prenatal phthalate exposure on allergic disease in children (Table 4; see Table A4 for five additional studies with urinary metabolites and two studies with serum metabolites). Age at follow-up ranged from 2 to 11 years. Almost all studies had satisfactory adjustment for covariates (categories 3 or 4).

For prenatal phthalate exposure, six studies reported positive associations with asthma or wheeze, three with allergy or total IgE, and one with eczema. Two studies with small sample sizes (n < 200) reported significant findings with relatively high ORs and large confidence intervals (Ku et al., 2015; Stelmach et al., 2015). Three studies did not report significant findings (Berger et al., 2018a; Vernet et al., 2017; Wang et al., 2014). Buckley et al. (2018) reported only negative associations (between wheeze and MEP, MnBP, and ΣLMW phthalates).

Several studies reported associations without reporting ORs (see Table A4). Just et al. (2012b) found that an interquartile range increase in log-MBzP was positively associated with eczema at 24 months (relative risk (RR): 1.52; 95% CI: 1.21–1.91). Ku et al. (2015) reported using regression coefficients that total IgE in allergic children was associated with urinary MEHP metabolites during the third trimester. In the same study, in all children regardless of health status, IgE was associated with urinary MBzP metabolites from the third trimester (Ku et al., 2015). In one of the larger longitudinal studies (n = 657), risk ratios were provided per doubling of maternal metabolite levels (Gascon et al., 2015). Increased levels of Σ_4DEHP (MEHHP, MEHP, MEOHP, and MECPP) corresponded to increased risk for asthma (RR: 1.4; 95% CI: 1.1–1.8), wheeze (1.3; 1.0–1.5), and bronchitis (1.2; 1.0–1.4), while increased levels of MBzP corresponded to increased risk for asthma (1.3; 1.0–1.8) and wheeze (1.2; 1.0–1.3). Additionally, Ait Bamai et al. (2018b) and Smit et al. (2015) both measured phthalate exposure using blood (see Table A4), which is considered a less reliable and informative medium for measuring phthalates compared with urine (Högberg et al., 2008; Calafat et al., 2013).

The literature regarding sensitive windows of exposure is limited. Only Gascon et al. (2015) compared prenatal exposure estimates at multiple time-points and found risk estimates for respiratory outcomes to be higher for urinary phthalate metabolite levels from first compared to third trimester. Three studies used levels of both prenatal maternal and childhood urinary phthalate metabolites. Wang et al. (2014) reported significant associations only for urinary phthalate metabolite levels at age 2, whereas Stelmach et al. (2015) found associations only for prenatal exposure and not at age 2, and Ku et al. (2015) for both prenatal exposure and urinary metabolites at ages 2 and 5 years.

3.1.5. General remarks

The epidemiological evidence suggests that phthalate exposure may play a role in the development or exacerbation of allergic diseases in children. While epidemiological studies most frequently presented positive associations between phthalate exposure and health outcomes, some studies reported both positive and negative associations. Two studies reported only negative associations, although for relatively small populations (n = 159 (Buckley et al., 2018) and n = 128 (Ait Bamai et al., 2016)); the latter also had poor adjustment for covariates (rating 1). Among the reported positive associations, some were relatively weak. Several studies had small study populations, inadequate adjustment for covariates in their statistical analyses, or low response rates (< 50%). Comparison of the reviewed studies is further complicated by differences in study populations and research methods (e.g., questionnaire verification, disease diagnosis, sampling, and analytical methods).

Studies frequently reported non-significant associations between allergic health outcomes and exposure to specific phthalates. Several studies reviewed here reported only null findings; most of these had small sample populations that may have limited statistical power. The largest study with only null findings in this review was Bai et al. (2017) (n = 2038), which only assessed total urinary phthalates, possibly masking associations with individual chemicals or specific exposure routes. Overall, the number of studies that consistently report effects of a particular phthalate or metabolite on a particular health outcome is limited.

The majority of studies concerned children, whose exposures are usually higher because of their hand-to-mouth behavior, crawling, mouthing, and higher intake of food and air relative to their body weight. Jaakkola et al. (2006) and Bai et al. (2017) used adult samples, while three studies investigated outcomes in both children and adults (Odebeatu et al., 2019; Ait Bamai et al., 2014; Hoppin et al., 2013). Overall, these three studies report conflicting results in terms of differences in effects of phthalate exposure between children and adults.

Several studies found gender differences in allergic disease outcomes among children. These differences may be explained by differences in behavior that contribute to phthalate exposure, as well as potential sex-specific mechanisms underlying development of allergic conditions (Fuseini and Newcomb, 2017). Future studies should be designed to elucidate the potential gender differences in health effects of phthalates, including for adults, since higher exposure to certain phthalates has been reported for women (Helm et al., 2018; N'Dri et al., 2014; Zota and Shamasunder, 2017).

In this review, we focused on the direct association between phthalate exposure and allergic diseases. The few controlled human exposure studies (not covered in this review) provide some support for the effects of airway exposure to phthalates. Inhalation of phthalates or PVC degradation products have been associated with a limited effect on airway inflammation (exhaled nitric oxide) and an increased incidence of airway symptoms the morning after exposure (Kolarik et al., 2009; Tuomainen et al., 2006). Nasal instillation of house dust containing DEHP altered nasal cytokine responses in house dust mite-allergic, but not healthy, participants (Deutschle et al., 2008). Studies that considered pulmonary function (Agier et al., 2019; Hoppin et al., 2004; Hu et al., 2019; Kim et al., 2018; Lin et al., 2018) or exhaled nitric oxide, a biomarker of airway inflammation (Just et al., 2012a), as health outcomes were not included in this review.

Social, ethnic, and lifestyle factors are associated with environmental exposures and health outcomes (Bloom et al., 2019). The relationship between phthalate exposure, socioeconomic status, and health is however unclear. Just et al. (2012b) reported a higher probability of eczema for African Americans compared to those of Dominican ethnicity across a range of urinary concentrations of MBzP. Additional studies addressing the relationship between socioeconomic factors, exposure, and health, especially in sensitive and high-risk populations, are warranted.

Exposure to phthalates varies across geographic regions (Kashyap and Agarwal, 2018; Wang et al., 2019), as demonstrated in a recent environmental exposure study collecting personal chemical exposure data via silicone wristbands in 14 communities in Senegal, South Africa, United States, and Peru (Dixon et al., 2019). Phthalates accounted for 18 to 42% of total chemical detections in the study, with Senegal having the highest proportion. The majority of the reviewed studies were conducted in high-income countries where some phthalates are subject to regulation. Corresponding epidemiological studies from low- and middle-income countries with potentially higher exposures are

Table 5
Animal studies with relevance for allergic diseases. Studies are grouped by health outcome. For studies that assess both effects in the lung (Lu) and systemic sensitization (S), these two outcomes are grouped together (Lu + S). For studies using doses likely to be relevant for environmental exposures, the phthalate is listed in bold. Underlined phthalate doses indicate significant positive effects, and underlined doses in italic indicate negative effects (i.e., a reduction of the allergen-induced responses). If the phthalate dose was not provided in the original article in μg/kg/day, our estimate is based on the information provided in the original study as specified in the footnotes. Applied dose refers to sensitization dose (as opposed to challenge dose). All studies used mice, except where indicated. Results for contact hypersensitivity and inflammation are listed in Table B1.

Administration route	Outcome specification	Phthalate[1]	Applied dose(s) [μg/kg/day]	Allergen [2]	Reference
Lung (Lu) and systemic sensitization (S)					
Airway	Lu + S	DEHP	– [3]	OVA	Larsen et al. (2007)
Airway	Lu + S	DEHP	30,000	OVA	You et al. (2014)
Airway	Lu + S	MEHP [4]	– [5]	OVA	Hansen et al. (2007)
Airway	Lu	**DEHP**	40	CAE	Alfardan et al. (2018)
Dermal	S	BBzP	2500	OVA	Dearman et al. (2009)
Dermal	S	DEHP	≈ 1250 [6]	OVA	Dearman et al. (2008)
Dermal	S	BBzP	≈ 6,250,000 [7,8]	–	Butala et al. (2004)
		DiHP	≈ 6,250,000 [7,8]	–	
		DiNP	≈ 6,250,000 [7,8]	–	
		DEHP	≈ 1,562,500; 3,125,000; 6,250,000 [7,8]	–	
Oral	Lu + S	**DEHP**	30; 300; 3000	OVA	Han et al. (2014)
Oral	Lu + S	**DEHP**	30; 300; 3000	OVA	Guo et al. (2012)
Oral	Lu + S	DiNP	20,000	OVA	Kang et al. (2018)
Oral	S	**DEHP**	30; 300; 3000	OVA	Han et al. (2019)
Maternal [R] (Oral)	Lu	DEHP	30,000; 300,000	OVA	Wang et al. (2018)
Maternal (Oral)	Lu	DEHP	*3880* [9]	OVA	Shin et al. (2014)
Maternal [R] (Oral)	Lu	DiNP	50,000	OVA	Chen et al. (2015)
Injection	S	**DOPT**	≈ 56; 556; 5556 [7]	OVA	Larsen and Nielsen (2008)
		BDP	≈ 56; 556; 5556 [7]	OVA	
		DEHP	≈ 56; 556; 5556 [7]	OVA	
Injection	S	**DnBP**	≈ 6; 56; 556; 5556 [7]	OVA	Larsen et al. (2002)
		DnOP	≈ 6; 56; 556; 5556 [7]	OVA	
		DiNP	≈ 6; 56; 556; 5556 [7]	OVA	
		DiDP	≈ 6; 56; 556; 5556 [7]	OVA	
Injection	S	**BBzP**	≈ 5; 53; 526; 5263 [7]	OVA	Larsen et al. (2003)
Injection	Lu + S	DEHP	≈ *5000* [10]	OVA	Larsen and Nielsen (2009)
Injection	S	DEHP	≈ 5556 [7]	OVA	Larsen and Nielsen (2007)
Injection	S	DEHP	≈ 5556 [7]	OVA	Larsen et al. (2001b)
Injection/ Airway	Lu + S	DiNP	50,000	OVA	Hwang et al. (2017)
Injection/ Airway	Lu + S	DiNP	50,000	OVA	Hwang et al. (2019)
Injection	Lu + S	DiDP	150; 1500; 15,000; 150,000	OVA	Qin et al. (2018)
Injection	S	**MnBP** [4]	≈ 5; 53; 526; 5263 [7]	OVA	Larsen et al. (2001a)
		MBnP [4]	≈ 5; 53; 526; 5263 [7]	OVA	
		MnOP [4]	≈ 5; 53; 526; *5263* [7]	OVA	
		MEHP [4]	≈ 5; 53; 526; *5263* [7]	OVA	
		MiNP [4]	≈ 5; *53*; 526; *5263* [7]	OVA	
		MIDP [4]	≈ 5; 53; *526*; *5263* [7]	OVA	
Nasal endpoints					
Airway		**DEHP**	0.018; 0.36; 7.3; 145	OVA	He et al. (2013)
Atopic dermatitis					
Dermal		DBP	– [11]	OVA	Matsuo et al. (2019)
Oral		DEHP	≈ 353; 7077; 141,489 [7]	Dp	Sadakane et al. (2014)
		DiNP	≈ 281; 5587; 111,702 [7]		
Injection		**DEHP**	≈ 34; 170; 851; 4255 [7]	Dp	Takano et al. (2006)
Maternal (Inj.)		**DEHP**	4.8; 24; 120; 600	Dp	Yanagisawa et al. (2008)

[R] Rat rather than mouse model system applied.
[1] When DBP is listed rather than DnBP or DiBP, the study did not provide specification regarding the DBP isomer applied.
[2] In some animal models the administration route for the allergen differs from the administration route of the phthalate (not indicated).
[3] Exposure measured as air concentration of aerosolized DEHP; 0.022; 0.094; 1.7; 13 mg/m^3 (significant effects reported for the highest dose only). The estimates of μg/kg/day doses were based on deposited fractions reported for solid particles, which must be considered as very approximate. The authors report that the 13 mg/m^3 concentration would reflect a dose of 275 μg/kg/day.
[4] Animals were exposed to primary metabolite rather than the parent phthalate.
[5] Exposures measured as air concentrations of aerosolized MEHP; 0.03 and 0.4 mg/m^3. Estimates of μg/kg/day doses were not provided by the authors.
[6] Estimate based on the provided dose of 50 mg DEHP applied topically, and an assumption of same mouse weight/dose relationship as in next study by the same group (Dearman et al., 2009), where a 100 mg dose of BBzP corresponded to a dose of 2500 μg/kg/day.
[7] Estimate based on i) phthalate dose (as provided in the original publication or calculated based on provided injection volume, by conversion to weight assuming unit density) and ii) approximate mice body weight (as provided in original publication, or assumed to be 20 g if no data was provided).
[8] Applied challenge dose is lower than sensitization dose.
[9] Maternal dose provided by authors; the daily dose for pups was 4780 μg/kg/day.
[10] Estimate based on the provided dose of 100 μg DEHP and an assumption of same mouse weight as in Larsen et al. (2002) of 18 g from the same laboratory using the same model system.
[11] Applied volume of DBP/Tween solution is not provided in the publication. Thus, dose calculation is not possible.

lacking (Suk et al., 2016; Rocha et al., 2017; Wu et al., 2020).

3.2. Animal studies

The search yielded a total of 263 studies, of which 49 experimental studies used animal models with relevance for allergic and respiratory outcomes, including inflammation. These studies focused primarily on adjuvant effects of phthalates, in terms of the ability of phthalates to potentiate the allergic effects induced by a model allergen or hapten. Haptens are small molecules that may elicit the production of antibodies when combined with larger carrier molecules, such as phthalates. A number of studies assessed the effects of the phthalates *per se*, but generally limited or no effects were observed in the absence of a model allergen or hapten (Bornehag and Nanberg, 2010; Dearman et al., 1996; Li et al., 2014; Matsuda et al., 2010b).

The majority of the animal studies reviewed here focused on effects of phthalates on the lung and systemic sensitization in mouse models using ovalbumin (OVA) as an allergen. Only a few studies applied models relevant for nasal and skin health outcomes (Table 5). Several studies also assessed the impact of phthalates on contact hypersensitivity and various aspects of inflammation using different animal models (Appendix B, Table B1). Animal models provide some support for the health effects of phthalates suggested by the epidemiological studies.

3.2.1. Lung and systemic sensitization

Asthma is a complex disorder associated with cell recruitment and inflammation, which result in airway hyperresponsiveness (AHR). Despite the limitations of murine models of allergic respiratory diseases, they mimic several hallmarks of human asthma, such as allergen-dependent sensitization, Th2-dependent allergic inflammation, and AHR (Aun et al., 2017). Since mice do not develop asthma spontaneously, a model allergen OVA is administered through various routes to induce airway symptoms in a sensitization phase and a challenge phase. Sensitization reflects the first exposure to an allergen and is characterized by production of allergen-specific IgE by B cells. Challenge reflects further exposures to the same allergen and is characterized by IgE activation of effector cells in the airways (mast cells and basophils), rapid synthesis of histamine, and bronchospasm, edema, and mucous secretion in the lower airways. Of the 24 studies assessing effects of phthalates on lung and systemic sensitization, 14 applied environmentally relevant administration routes, while 10 used injection (subcutaneous or intraperitoneal).

Airway administration of phthalates, through inhalation of aerosolized phthalate (droplets) or nasal or lung instillation, enhanced allergen-induced sensitization. DEHP or MEHP, in doses not likely to be relevant for environmental exposures, increased OVA-specific IgG1 (Hansen et al., 2007; Larsen et al., 2007) or IgE (You et al., 2014), and increased recruitment of inflammatory cells (Hansen et al., 2007; Larsen et al., 2007). However, nasal instillation of 40 μg/kg/day of DEHP in combination with a cockroach allergen extract (CAE) resulted in significant adjuvant effects of DEHP in the lung, but sensitization was not assessed (Alfardan et al., 2018). DEHP alone induced a neutrophilic inflammation, while DEHP and CAE in combination resulted in a conversion of the eosinophilic CAE-induced inflammation to a mixed granulocytic inflammation with a higher number of neutrophils (Alfardan et al., 2018). In parallel, an activation of Th2/Th17 immune cells and dendritic cells was observed, as well as increased levels of interleukin (IL)-17 and IL-6 in the lung and dysfunction of the epithelial barrier (Table B2). The study highlighted the importance of applying an environmentally relevant allergen, as well as the application of the same administration route for allergen and phthalate.

The airway administration methods applied in these animal studies may have limited relevance for human airway exposure, during which phthalates are inhaled both in the gas phase and adsorbed to airborne particulate matter. Nevertheless, the studies point towards a possible role of airway exposure in respiratory effects of phthalates. Further models using inhalation of phthalates in combination with aeroallergens relevant for human exposures are warranted.

Three studies assessed the effects of phthalates after **dermal** administration. Significant adjuvant effects on sensitization were reported in one study, in which BBzP increased OVA-specific IgG1, but not OVA-specific IgE sensitization. Although IgG1 is often used as a surrogate for IgE antibody production in mouse models, it is a less efficient inducer of mast cell degranulation. The study expressed less concern for phthalate-induced effects on IgG1 relative to IgE (Dearman et al., 2009). Only same-site application of allergen and BBzP enhanced sensitization; no adjuvant effect was observed in the model using subcutaneous OVA injection (Dearman et al., 2009). The other two studies did not use a model allergen (Butala et al., 2004) or used different sites of administration for allergen and phthalate (Dearman et al., 2008). Thus, animal studies do not support the role of dermal phthalate exposure in allergen-induced sensitization reported in epidemiological studies. Further studies using environmentally relevant allergens, concentrations, and same-site application would be useful.

Of the four studies using **oral** administration to study sensitization and lung effects, three reported effects of doses likely to have relevance for environmental exposures (Guo et al., 2012; Han et al., 2014; Han et al., 2019). Oral exposure of DEHP from 30 μg/kg/day by gavage induced adjuvant effects on total serum levels of IgE, indicative of sensitization (Guo et al., 2012; Han et al., 2014) (Table B2). Airway effects, including adjuvant effects on inflammation and AHR, were only observed for higher concentrations (300 and 3000 μg/kg/day) (Guo et al., 2012). As a possible cellular mechanism for the adjuvant effects of DEHP, it was proposed that DEHP leads to expansion of an important subset of T cells (T follicular helper (Tfh) cells), which modifies the functionality of antibody producing B cells (Han et al., 2014). The specific molecules involved in these cellular responses were identified in the follow-up study (Han et al., 2019).

Maternal oral phthalate exposure increased OVA-induced airway inflammation and recruitment of inflammatory cells in the offspring in two studies (Chen et al., 2015; Wang et al., 2018), while similar parameters decreased in another study (Shin et al., 2014). However, none of these studies applied doses likely to be relevant for environmental exposures. Given the large number of epidemiological studies assessing the effects of maternal phthalate exposure on allergic outcomes, such animal studies using environmentally relevant doses and aeroallergens are necessary.

Among the ten studies that used subcutaneous or intraperitoneal **injection** for phthalate administration, four included doses likely to have relevance for environmental exposures, and two of these reported significant effects on OVA-induced sensitization (Table 5, Table B2). Overall, studies that administered phthalates through injection have no or limited relevance for human phthalate exposure and thus provide little support for the associations reported in the epidemiological studies.

The majority of the animal studies assessing effects of phthalates on airways and sensitization applied the BALB/c mouse strain with OVA for sensitization and challenge. Although this reflects the most commonly applied murine models over the last decades, more recent protocols apply aeroallergens with relevance for human allergen exposure, e.g., house dust mite (Aun et al., 2017; Haspeslagh et al., 2017). Only one of the phthalate studies used a different model allergen (CAE) (Alfardan et al., 2018). While the OVA mouse models are skewed towards Th2-driven eosinophilic inflammation, other models, such as the CAE mouse model, exhibit other cell and cytokine profiles (Alfardan et al., 2018). Thus, further studies with a variety of mouse models and allergens are required.

In summary, animal studies indicate possible sensitization and airway effects of DEHP doses likely to have relevance for environmental exposure. Three studies reported significant effects for oral exposure, although the model allergen OVA was used rather than an

environmentally relevant aeroallergen (Guo et al., 2012; Han et al., 2014; Han et al., 2019). One study reported significant airway effects for airway exposure (nasal administration) (Alfardan et al., 2018), and this study used the more relevant cockroach allergen. However, the applied nasal instillation method is not fully representative of environmental inhalation exposure. The studies using injection, dermal, or maternal administration provide limited support for the associations reported in the epidemiological studies. The knowledge is also limited about the effects of phthalates other than DEHP, as well as about the relative potency of various phthalates. Further animal studies using environmentally relevant doses, aeroallergens, and a wider range of phthalates are needed to clarify the impact of phthalate exposure in allergic disease.

3.2.2. Nasal endpoints

Only one animal study examined the effects of phthalate exposure on nasal endpoints. The study applied phthalate doses comparable to environmental exposures. In an allergic rhinitis model using OVA as a model allergen, nasal instillation of 0.36 to 145 μg/kg/day of DEHP and OVA, respectively, increased the nasal levels of IL-13 compared to OVA alone (He et al., 2013). IL-13 plays an important role in allergic rhinitis. However, DEHP did not induce adjuvant effects on nasal histology, recruitment of inflammatory cells, or the levels of other cytokines (Table B2). Further studies using other phthalates and administration routes are needed to support these findings.

3.2.3. Atopic dermatitis

Atopic dermatitis is associated with infiltration of eosinophils and mast cells, and is most often associated with IgE-mediated sensitization and increased production of allergic mediators (Th2) like IL-4, IL-13, and IL-5 (Leung et al., 2004). To assess the effects of phthalates, mite allergen (Dp) was applied in three studies to induce atopic dermatitis-like skin lesions (Sadakane et al., 2014; Takano et al., 2006; Yanagisawa et al., 2008), while one study used an OVA model (Matsuo et al., 2019). Exposure to DEHP or DiNP worsened the mite allergen-induced skin lesions and increased infiltration of eosinophils and mast cells, as well as the levels of inflammatory mediators involved in cellular recruitment (eotaxin, MIP-1α). The total serum IgE level was not affected by the phthalate exposures. In the OVA model, similar results were seen for DBP, in addition to increased recruitment of Th2 cells and increased total serum IgE (Matsuo et al., 2019). Although two of these studies included phthalate doses likely to be relevant for environmental exposures, only doses above 100 μg/kg/day induced significant effects. Moreover, two of the studies used injection rather than administration routes relevant for environmental exposure. Further animal studies probing the association between phthalate exposure and atopic dermatitis or eczema observed in epidemiological studies should use environmentally relevant doses and additional phthalates and relevant administration routes.

3.2.4. Contact hypersensitivity

Thirteen studies used contact hypersensitivity models, in which a hapten and a phthalate are applied in combination to the skin of mice to induce sensitization and formation of skin lesions (Table B1). Two studies reported effects of oral administration of DiNP and DiDP (Kang et al., 2016; Shen et al., 2017). All studies except one (Dearman et al., 1996) used doses well above environmentally relevant exposures (Table B1). DBP was the most commonly applied phthalate, while fluorescein isothiocyanate (FITC) was most frequently used as hapten. DBP in combination with FITC induced infiltration of eosinophils and mast cells, increased levels of Th2 cytokines like IL-4, IL-13, and IL-5, as well as increased serum IgE (Li et al., 2014; Shigeno et al., 2009). Dendritic cell activation mediated through thymic stromal lymphopoietin (TSLP) was important for the development of the Th2-type contact hypersensitivity in these models (Larson et al., 2010; Shigeno et al., 2009).

Comparative studies were performed both in terms of different phthalates and haptens (Table B1). Different haptens can be used in models dominated by Th1 or Th2 immune responses, or a mixture of these. When comparing the effects of DBP and DPP with various haptens, it was evident that the presence of an isothiocyanate group on the hapten determined whether an adjuvant effect was induced, as opposed to whether the hapten induced a Th1 or a Th2 response (Matsuda et al., 2010b). With regard to the direction of the T cell polarization (Th1 or Th2) induced by different phthalates, it also appears to depend on the hapten applied, rather than being an intrinsic property of the phthalate (Matsuda et al., 2010a). Moreover, the relative potency of phthalates may depend on the applied hapten. DEHP, which did not induce an adjuvant effect in the FITC model, was more potent than DBP in the 2-methoxy-4-nitrophenyl isocyanate (MNICN) and phenethyl isocyanate (PEICN) models (Matsuda et al., 2010a).

Although the FITC contact hypersensitivity model shares many features with human atopic dermatitis (Leung et al., 2004), the infiltrating immune cells are not well characterized, vary between mouse strains and differ from the immune responses in human atopic dermatitis skin lesions (Hvid et al., 2009; Martel et al., 2017). Moreover, the phthalate doses applied in the contact hypersensitivity models are generally very high. Therefore, the contact hypersensitivity model has limited relevance for human atopic dermatitis or eczema, and these studies do not directly support the associations between phthalate exposure and eczema observed in epidemiological studies. However, these studies provide insights into how the interplay between phthalates and haptens may affect immunological responses.

3.2.5. Inflammation

Inflammation plays a critical role in allergic health outcomes. The complex cascades of inflammatory mediators involved vary between the health outcomes and between disease phenotypes. The eight studies concerning inflammation focused on various endpoints related to systemic inflammation, and exhibited various phthalate administration routes (Table B1). The inflammatory endpoints included serum peritoneal lavage levels of cytokines, as well as cytokine release from *in vitro* stimulation of immune cells to assess their immune function. Although the studies provide some information about the effect of phthalates on systemic inflammation and immunity, it is not straightforward to link these endpoints to the allergic outcomes assessed in the epidemiological studies. The only study using doses likely to be relevant for environmental phthalate exposures reported that DEHP exposure perinatally (during pregnancy and postnatally) or chronically by oral injection significantly altered the functionality of peritoneal macrophages from mice (Li et al., 2018). Based on *in vitro* exposures to the primary DEHP metabolite MEHP, the authors hypothesized that the modulations of inflammatory and phagocytic responses in peritoneal macrophages after *in vivo* exposures were due to chromatin modifications and changes in methylation (Li et al., 2018).

3.2.6. General remarks

In animal models assessing lung effects and systemic sensitization, DEHP has been applied far more commonly than other phthalates, while DBP has been the primary phthalate applied in the contact hypersensitivity models. The studies reporting significant effects of doses likely to be relevant for environmental exposures are dominated by DEHP. Thus, there is a considerable gap between animal and epidemiological studies in terms of phthalates for which scientific evidence is available.

The question of environmentally relevant exposure levels for phthalates is complex, since several exposure routes and exposure sources must be considered. Also, the conversion of exposure dose per bodyweight from laboratory animal to humans differs between species (Nair and Jacob, 2016). Several other aspects differ between laboratory models and humans, such as metabolic pathways and capacity, as well as genetic variability. As a pragmatic and simplified approach to assess whether the doses used in animal studies have relevance for human

environmental exposures, we chose to consider the current TDI levels for humans. Although this choice might result in inclusion of studies using doses somewhat higher than those reflecting environmental exposures for a particulate phthalate or pathway, we believe it allows us to roughly distinguish between studies that use doses clearly not relevant for human environmental exposures, and studies that use doses likely to be relevant.

Relatively few studies included more than one phthalate. Moreover, the studies addressing the relative potency of several phthalates either applied administration routes, phthalate concentrations, or model systems that have limited relevance for human environmental exposures (Table 5, Table B1). Thus, comparative studies of adjuvant effects of

Table 6
Cell culture studies in cell models with relevance for allergic diseases. Studies are grouped by cell type. The main endpoints assessed in the study are listed, as well as the applied phthalates, phthalate concentrations, information regarding cell model (P – primary or CL – cell line) and species (H – human or M – mouse). For studies using concentrations likely to be relevant for environmental exposures, the phthalate is listed in bold (≤10 μM) or italic bold (≤1 μM). Underlined phthalate doses indicate significant effects. For studies that assessed a range of endocrine disrupters, only phthalates are listed. If several phthalates did not have a significant effect on cell function, only one phthalate is listed and the rest appear in the footnotes. Studies using primary cells are listed first, followed by cell line studies. Results for mast cells, neutrophils, basophils, monocytes, and innate immune cells from blood, as well as epithelial, endothelial, and smooth muscle cells are listed in Table C2.

Specification of cell type: Main endpoint(s)	Phthalate	Applied concentration(s) [μM]	Primary cells or cell line	Species	Reference
Macrophage-like cells					
Peritoneal macrophages: cytotoxicity, mediator, production, surface markers, phagocytosis	***DBP***[1]	1; 5; 10; 50; 100	P	M	Li et al. (2013)
Monocyte-derived macrophages: mediator release, migration, transcription factors, intracellular pathways	***DnBP***	1	P	H	Teixeira et al. (2016)
	DEHP	1			
Peritoneal macrophages: mediator release, surface markers, T cell activation	***DEHP***	0.01; 0.1; 1	P	M	Yamashita et al. (2005)
Peritoneal macrophages: mediator expression (stimulated), surface markers, chromatin modification	***MEHP***	0.007; 0.07; 0.7	P	M	Li et al. (2018)
Alveolar macrophages: cytotoxicity, mediator release, intracellular pathways	MEHP	100, 300, 500, 1000	P	M	Rakkestad et al. (2010)
RAW264.7 monocyte-macrophage: cytotoxicity and NO production	**DEP**	2, 20, 200	CL	M	Kim et al. (2015)
	DnBP	2, 20, 200			
	DCHP	2, 20, 200			
	DPrP	2, 20, 200			
RAW264.7 monocyte-macrophage: promotor activation (gene transcription)	DEP	100	CL	M	Ohnishi et al. (2008)
	DPrP	100			
	BBzP etc. [2]	100			
THP-1 monocyte-derived macrophages: mediator expression (stimulated), phagocytosis, intracellular pathways. Combined exposures (other chemicals).	***DBP***[1]	0.001; 0.1; 1; 10	CL	H	Couleau et al. (2015)
	DEHP	0.001; 0.1; 1; 10			
RAW264.7 monocyte-macrophage: mediator expression (stimulated)	DEP etc. [3]	100	CL	M	Igarashi et al. (2006)
RAW264.7 monocyte-macrophage: cytotoxicity, nitrite	**BBzP**	2, 20, 200	CL	M	Kim et al. (2014)
RAW264.7 monocyte-macrophage: mediator and NO release (stimulated)	BBzP	32	CL	M	Hong et al. (2004)
THP-1 monocyte-derived macrophages: mediator release (stimulated)	DEHP	200	CL	H	Nishioka et al. (2012)
RAW264.7 monocyte-macrophage: mediator release, differentiation, intracellular pathways	MEHP	100, 300, 500, 1000	CL	M	Bølling et al. (2012)
THP-1 monocyte-derived macrophages: cytotoxicity, cytokine release, phagocytosis	***DiNP***	0.2, 2, 5, 10	CL	H	Bennasroune et al. (2012)
Dendritic cells					
Plasmacytoid dendritic cells: cytotoxicity, mediator release (stimulated), intracellular pathways, epigenetic regulation, T cell interactions	***BBzP***	0.001; 0.01; 0.1	P	H	Kuo et al. (2013)
	DEHP	0.001; 0.01; 0.1			
Plasmacytoid dendritic cells: differentiation (surface markers)	***DEHP***	0.1; 1; 10	P	M	Ito et al. (2012)
	MEHP	0.1; 1; 10			
Bone marrow-derived dendritic cells: differentiation (surface markers), antigen presenting activity	***DEHP***	0.1; 1; 10; 100	P	M	Koike et al. (2009)[4]
Bone marrow-derived dendritic cells: antigen presenting activity	***DiNP***	0.1; 1; 10; 100	P	M	Koike et al. (2010)[4]
Lymphocytes					
Lymphocytes from spleen: stimulated mediator release, proliferation, IgG	***DEHP***	0.001; 0.01, 0.1, 1	P	M	Yamashita et al. (2002)
Lymphocytes and T cells: stimulated mediator release	***DEHP***	0.1; 1; 2; 5; 10	P/CL	M	Lee et al. (2004)
	DiNP	0.1; 1; 2; 5; 10			
T cells from spleen: cytotoxicity, stimulated mediator production, Th1/Th2 phenotyping	***DiNP***	0.001; 0.01, 0.1, 1	P	M	Hwang et al. (2017)
Lymphocytes from spleen: stimulated mediator release, intracellular pathways	***DEHP***	1; 10; 50	P	M	Pei et al. (2014)
	MEHP	5; 40; 80			
T cells from lymph nodes: mediator expression, intracellular pathways	DEHP	100	P	M	Oh and Lim (2009a)
Lymphocytes from thymus and spleen: proliferation, stimulated mediator release	***DEHP***	0.001; 0.01, 0.1, 1	P	M	Yamashita et al. (2003)
Lymphocytes from thymus: mediator expression, intracellular pathways	DEHP	100	P	M	Oh and Lim (2009b)
Lymphocytes from spleen: proliferation, surface marker expression, stimulated mediator release	***DEHP***	0.1; 1; 10; 100	P	M	Koike et al. (2009)[4]
Lymphocytes from spleen: proliferation, stimulated mediator release	***DiNP***	0.0001; 0.001; 0.01; 0.1; 1; 10; 100	P	M	Koike et al. (2010) [4]
PBMCs: stimulated mediator release (T cell stimuli)	***DEP***	0.1; 100	P	H	Hansen et al. (2015b)[4]
	DnBP	0.1; 100			
	MnBP	0.1; 100			

[1] When DBP is listed rather than DnBP or DiBP, the study did not provide specification regarding the DBP isomer applied.
[2] A number of phthalates were tested without significant effects in this study; BBzP, DBP, DCHP, DOP, DHP, DPP.
[3] A number of phthalates were tested without significant effects in this study; DEP, DBP, DCHP, DOP, DHP, DPP, DPrP.
[4] Also listed under a different cell type.

different phthalates have not been performed under appropriate experimental conditions, and therefore there is currently insufficient data to draw specific conclusions with regard to the relative potency of phthalates. Moreover, we could not identify any study that investigated the effects of combined exposures to several phthalates, although such studies would be highly relevant, considering that humans are often exposed to several phthalates simultaneously.

Except for one study using CAE (Alfardan et al., 2018), all studies assessing the adjuvant effects of phthalates used OVA as a model allergen. The impact of different model allergens on the adjuvant effect of phthalates is therefore currently unknown. However, the studies comparing different haptens in the contact hypersensitivity model suggest that the potency of phthalates depends on the applied hapten (Matsuda et al., 2010a).

Animal models do not seem to unequivocally support the findings of epidemiological studies. They strongly indicate, however, that DEHP doses likely to reflect human environmental exposures may affect sensitization and allergic responses in the airways, particularly due to oral and airway exposure. Future animal studies are recommended to use relevant phthalate concentrations and a wider selection of phthalates, phthalate administration routes, allergens, and health endpoints. Finally, comparative studies of several phthalates and studies that apply various aeroallergens with relevance for human environmental allergen exposure are of major importance.

3.3. Cell culture studies

The search yielded a total of 79 studies, of which 42 studies used cell culture models with relevance for phthalate exposure and allergic and respiratory outcomes. Effects of phthalates in innate immune cells have received most attention (Hansen et al., 2015a), and macrophages are by far the most commonly applied cellular model (Table 6). Cells from the adaptive immune system have also been applied to study effects of phthalates *per se* or their impact on effects induced by model allergens (Bornehag and Nanberg, 2010; Jaakkola and Knight, 2008).

Phthalate exposure has been reported for a range of cell types in addition to macrophages, including dendritic cells, mast cells, neutrophils, basophils, monocytes, lymphocytes including T cells (extracted from spleen, thymus, and peripheral blood mononuclear cells (PBMCs)), epithelial cells, and endothelial cells. All these cell types are to a varying extent involved in the development, progression, or pathogenesis of respiratory allergy, allergic rhinitis, and eczema (Eyerich et al., 2019; Small et al., 2018; Verstraelen et al., 2008). The endpoints most commonly assessed in the *in vitro* phthalate literature include cytokine release or expression, phagocytosis, surface marker expression, and differentiation, with relevance for both adaptive and innate immune responses. Thus, the literature regarding cell culture studies is more diverse than that on animal models, which mainly focuses on allergic responses.

3.3.1. Macrophages

Fourteen studies assessed effects of phthalates in various macrophage models, including primary macrophages from the peritoneum or lung, differentiated primary monocytes, and different cell lines (Table 6). Eight of these studies included concentrations likely to be relevant for environmental exposures ($\leq$10 μM), and six studies reported significant effects of such concentrations. Relevant concentrations of phthalates either increased release of pro-inflammatory mediators (Bennasroune et al., 2012; Couleau et al., 2015; Yamashita et al., 2005), induced a mixed response (both increased and reduced levels) (Li et al., 2018; Teixeira et al., 2016), or reduced release of pro-inflammatory mediators after stimulation with a bacterial component (Li et al., 2013). Comparison across the different studies is difficult due to differences in applied model systems and phthalates. For phagocytosis, the reported data are more consistent, as all studies report that phthalates reduce phagocytosis or molecules involved in phagocytosis (Couleau et al., 2015; Li et al., 2013; Li et al., 2018). Overall, these studies support that concentrations of phthalates likely to be relevant for environmental exposures can modulate macrophage functionality in terms of altered release of pro-inflammatory mediators and decreased phagocytosis. Possible implications are impaired innate immune responses and altered crosstalk with the adaptive immune system (Li et al., 2013; Yamashita et al., 2005).

3.3.2. Dendritic cells

All four studies assessing effects in dendritic cells used primary cells and concentrations likely to be relevant for environmental exposures (Table 6). Both DEHP and DiNP enhanced the differentiation of bone marrow-derived dendritic cells, and also their ability to stimulate T cells (Koike et al., 2009; Koike et al., 2010). In contrast, DEHP inhibited the stimulated expression of differentiation markers and release of inflammatory mediators from plasmacytoid dendritic cells (Ito et al., 2012; Kuo et al., 2013), but the differences in model systems (non-stimulated vs. stimulated) could explain this discrepancy. Both DEHP and BBzP also modulated the T cell stimulatory function of the dendritic cells promoting Th2 polarization (Kuo et al., 2013). Overall, these studies support that relevant concentrations of phthalates can modulate the differentiation of dendritic cells and their interaction with T cells, with aggravation of allergic responses as a possible implication (Koike et al., 2009; Koike et al., 2010; Kuo et al., 2013).

3.3.3. Lymphocytes

Various lymphocyte models were used to assess effects of phthalates in ten studies, including lymphocytes or T cell populations isolated from lymph nodes, spleen, thymus, or blood (Table 6). Eight studies included concentrations likely to be relevant for environmental exposures ($\leq$10 μM) and seven of them reported significant effects of these exposures. In general, DEHP and DiNP increased IL-4 release from lymphocytes in all studies, including murine splenocytes (Koike et al., 2009; Koike et al., 2010; Pei et al., 2014; Yamashita et al., 2002), thymocytes (Yamashita et al., 2003), primary lymph node cells (Lee et al., 2004), and T cells from spleen (Hwang et al., 2017). Other inflammatory mediators were also increased in presence of relevant concentrations of phthalates, including IFNγ (Pei et al., 2014; Yamashita et al., 2002; Yamashita et al., 2003), IL-3 (Yamashita et al., 2003) and IL-6 (Pei et al., 2014). Some studies also reported increased pro-inflammatory (Th1) cell differentiation (Hwang et al., 2017) and increased cell proliferation (Koike et al., 2010; Yamashita et al., 2002; Yamashita et al., 2003). Overall, these studies support that concentrations of DEHP and DiNP likely to be relevant for environmental exposures increase the release of Th2-associated mediators from lymphocytes, with modulation of the Th1/Th2 balance and enhanced allergic responses as possible implications (Hwang et al., 2017; Lee et al., 2004; Pei et al., 2014).

3.3.4. Other cell types

Effects of phthalates have also been studied in other innate immune cells like mast cells, neutrophils, basophils, and monocytes. Increased expression of inflammatory mediators, surface markers, and histamine release were reported, but mainly for high concentrations (Table C2). In monocytes or PBMCs, concentrations of DEP or DBP likely to be relevant for environmental exposures modulated release of pro-inflammatory mediators after stimulation with a bacterial component in line with the studies in macrophages (Hansen et al., 2015b; Maestre-Batlle et al., 2018). Environmentally relevant concentrations of DEP, DBP, BBzP, and DEHP have been reported to affect endothelial cells, bronchial epithelial and smooth muscle cells, and thyroid epithelial cells (Table C2). Endothelial cells and airway epithelial cells play an important role as mediators and regulators of immune responses (Schleimer et al., 2007; Sturtzel, 2017). However, the low number of studies for each cell type does not allow for drawing conclusions regarding possible links between these cellular effects of phthalates and allergic responses.

3.3.5. General remarks

Cell culture studies have focused on DEHP more than on other phthalates. Consequently, studies reporting significant effects of phthalate concentrations likely to be relevant for environmental exposures are dominated by DEHP, although several studies also report significant effects for relevant concentrations of DnBP and DiNP. It is difficult to draw conclusions with regard to the relative potency of phthalates based on the reviewed cell culture studies. Seven of the 14 studies that included multiple phthalates reported effects of concentrations likely to be relevant for environmental exposures, but these exhibited different selections of phthalates and did not show any general patterns in potency. Combined exposures to multiple phthalates were not reported.

Respiratory allergy, allergic rhinitis, and atopic dermatitis are all allergic diseases caused by complex interactions between immunological cells and mediators, as well as various structural cells. Although these allergic reactions are initiated and occur in different tissues, similar cell types and mediators are involved in their development, progression, or pathogenesis. Thus, studies of phthalate-induced effects in monocultures of various cell types are appropriate, but are not representative of the complex processes underlying these allergic diseases. Co-culture models (combining different cell types), as applied in some of the studies (Koike et al., 2009; Kuo et al., 2013; Li et al., 2013; Yamashita et al., 2003, 2005), but also the more recently developed 2D and 3D models, might provide a better understanding of the cellular and mechanistic pathways of phthalate-induced effects on allergic diseases (Castellani et al., 2018; Eyerich et al., 2019).

Overall, cell culture studies confirm that environmentally relevant concentrations of certain phthalates may affect the functionality of innate and adaptive immune cells. More specifically, they may affect the release of inflammatory mediators from macrophages and decrease their phagocytic activity, modulate the differentiation of dendritic cells and their interaction with T cells, and increase the release of Th2 mediators from lymphocytes. Possible implications of these cellular effects are either enhanced allergic responses or impaired innate immune responses. These findings provide indirect support to the findings of epidemiological studies. Future cell culture studies are recommended to use relevant phthalate concentrations, a wider selection of phthalates and cell models, and include comparative and combinatory exposures to multiple phthalates.

4. Concluding remarks

Both epidemiological and experimental studies provide some support for an association between phthalate exposure and allergic diseases, while there is insufficient epidemiological evidence to support the role of phthalates with regard to sensitization. Epidemiological evidence is limited by the relatively weak (although significant) associations and the inconsistencies in the reported associations for any given phthalate. However, considering the ubiquitous nature of phthalates, even weak significant associations can have a substantial impact across widely exposed populations. Most epidemiological studies reviewed here focus on children. There is little research on the long-term effects of early phthalate exposure on adult health. As a result, latent health effects following early exposure, which may not appear until adolescence or adulthood (Grandjean et al., 2019), are likely to be missed by cross-sectional or childhood study designs. Future epidemiological studies should identify the most critical windows of exposure by monitoring exposure at different time points.

Experimental studies provide plausibility for adjuvant effects of phthalates at levels likely to be relevant for environmental exposures, as well as for altered functionality of innate and adaptive immune cells. However, the phthalate exposure regimes applied in animal studies reflect human environmental phthalate exposures to a limited extent with regard to the selection of phthalates, exposure routes, and the use of single phthalates rather than combined exposures. Moreover, the applied animal models do not reflect the state-of-the-art models for allergic diseases.

Several possible molecular triggering mechanisms have been suggested for phthalate-induced effects, including receptor binding, oxidative stress, and transcriptional and epigenetic regulation (Bølling et al., 2013; Ito et al., 2012; Kuo et al., 2013; Lee et al., 2004; Pei et al., 2014; Teixeira et al., 2016). The underlying molecular mechanisms are however largely unknown. Due to the large variation in the chemical structure of phthalates, the mechanisms are likely to differ between LMW and HMW phthalates (Teixeira et al., 2016). Although not covered by this review, it is evident that further mechanistic studies using relevant concentrations of phthalates are necessary in order to identify a more robust causal relationship.

The relative role of exposure pathways (ingestion, inhalation, dermal uptake), as opposed to total exposure reflected by urinary metabolite levels, in the development and exacerbation of allergic diseases warrants attention. Certain phthalates can enter the body through the skin directly from air or clothing, and transdermal exposure can, under some conditions, be as large as, or larger than, that via inhalation (Morrison et al., 2016; Weschler et al., 2015). Only one of the reviewed epidemiological studies modelled indoor phthalate exposures via the three pathways, including the dermal route from air (Bekö et al., 2015). Most experimental studies assessing the effects of airway or dermal exposures applied methods with limited relevance for human exposures (e.g., instillation, droplets). The relative importance of each exposure pathway for allergic diseases is still to be determined.

Future epidemiological and experimental studies should not only examine the effects of individual compounds, as has been the case in most of the reviewed literature, but also consider possible confounding from exposure to chemical mixtures and cumulative risks of compounds that act in a dose-additive manner (Howdeshell et al., 2007; Howdeshell et al., 2008a; Howdeshell et al., 2008b). Some recent studies used sums of phthalates with similar properties to describe exposure, e.g., ΣLMW phthalates (Buckley et al., 2018; Gascon et al., 2015; Shi et al., 2018; Vernet et al., 2017) or ΣHMW phthalates (Vernet et al., 2017). Alternatively, an exposome approach could be applied to evaluate the associations between complex environmental exposures, including exposure to phthalates, a broad range of other factors, and allergic diseases (Agier et al., 2019).

The majority of the reviewed studies focused on a small number of phthalates, mostly traditional ones, which receive increasing attention in terms of their health effects and regulation. Their use is expected to decrease. Over the past 15 years, policy regulations have come into effect in multiple countries limiting or banning the use of certain phthalates, such as DEHP, DBP, DEP, BBzP, and DnOP, resulting in a declining trend in daily intakes (Helm, 2007; Katsikantami et al., 2016). At the same time, the application of alternative plasticizers (e.g., newer phthalates, adipates, DiNCH, terephthalates, epoxy, aliphatics, trimellitates, polymerics, benzoates, phosphates) is increasing (Dodson et al., 2012; IHS Markit, 2018) and may result in increasing body burdens (Bui et al., 2016; Sackmann et al., 2018). A recent study indicated, however, that despite new exposure patterns, human body burden of traditional phthalates is still higher than of substitutes (Frederiksen et al., 2020). Data regarding human exposure to emerging substances and their health effects are limited, and future studies should address these knowledge gaps. Until then, policy makers are recommended to apply the precautionary principle, which attempts to reduce potential risks before scientific evidence of possible health effects (or their absence) becomes available (Harremoës et al., 2002; Kriebel et al., 2001; Martuzzi and Tickner, 2004).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary material

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