Review

Relationship between flame retardants and respiratory health– A systematic review and meta-analysis of observational studies☆

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A R T I C L E   I N F O

A B S T R A C T

Chronic respiratory diseases are a dealing cause of death and disability worldwide. Their prevalence is steadily increasing and the exposure to environmental contaminants, including Flame Retardants (FRs), is being considered as a possible risk factor. Despite the widespread and continuous exposure to FRs, the role of these contaminants in chronic respiratory diseases is yet not clear. This study aims to systematically review the association between the exposure to FRs and chronic respiratory diseases.

Searches were performed using the Cochrane Library, MEDLINE, EMBASE, PUBMED, SCOPUS, ISI Web of Science (Science and Social Science Index), WHO Global Health Library and CINAHL EBSCO.

Among the initial 353 articles found, only 9 fulfilled the inclusion criteria and were included. No statistically significant increase in the risk for chronic respiratory diseases with exposure to FRs was found and therefore there is not enough evidence to support that FRs pose a significantly higher risk for the development or worsening of respiratory diseases. However, a non-significant trend for potential hazard was found for asthma and rhinitis/rhinoconjunctivitis, particularly considering urinary organophosphate esters (OPEs) including TNBP, TPHP, TCEP and TCIPP congeners/compounds. Most studies showed a predominance of moderate risk of bias, therefore the global strength of the evidence is low. The limitations of the studies here reviewed, and the potential hazardous effects herein identified highlights the need for good quality large-scale cohort studies in which biomarkers of exposure should be quantified in biological samples.

1. Introduction

Respiratory diseases are one of the leading causes of death worldwide, accounting for nearly 8% of all deaths (Union, 2018; Soriano et al., 2020). The most frequent are acute conditions, such as lower respiratory infections, but there is also increasing prevalence and incidence of chronic conditions, such as asthma and chronic obstructive pulmonary disease (COPD) (Union, 2018; Soriano et al., 2020) (Soriano et al., 2020). Chronic respiratory diseases, namely asthma and COPD, may be worsened and their prevalence and incidence increased by the exposure to various types of indoor and outdoor environmental contaminants (Jiang et al., 2016; Viegi and Taborda-Barata, 2022), including flame retardants (FRs).

There are limited observational studies on the effect of flame retardants on chronic respiratory disease, but there are many sources for exposure in daily life, and *in vivo/in vitro* assays have suggested the adverse effects on the respiratory system (Wang et al., 2020; Meng et al., 2022; Chen et al., 2022; Montalbano et al., 2020), with recent reviews

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highlighting the cellular and physiological mechanisms of FRs toxicity (Yan et al., 2021; Khani et al., 2023)and their contribution to oxidate stress (Chen et al., 2023). Flame retardants are synthetic chemicals usually applied to consumer products, such as furniture, textiles, and electronic and electric devices, to reduce their flammability and thus prevent the start of fire or slow down its progression (Coelho et al., 2016a; Esplugas et al., 2022). It is a wide group of chemicals composed of families of organic and inorganic chemicals and some of the organic FRs (e.g., different polybrominated diphenyl ethers (PBDEs) and hexabromocyclododecanes (HBCDs)) have been listed as persistent organic pollutants (POPs) by the Stockholm Convention, due to their toxicity and persistency in the environment (Sharkey et al., 2020). Therefore, their use was already banned or restricted, such as for the earliest flame retardants, polychlorinated biphenyls (PCBs), banned in the U.S. in 1977. In the last decades new alternatives have been used to replace them including organophosphate flame retardants, namely organophosphate esters (OPEs). However, many of these alternative FRs also bioaccumulate and can pose adverse effects to humans being considered as emerging POPs, such as tris(2-chloroethyl) phosphate (TCEP) (already banned by the European Union), tris(1,3-dichloro-2-propyl) phosphate (TDCIPP), and tris(2-chloroisopropyl) phosphate (TCIPP) (Lorenzo et al., 2019). Also, emerging evidence suggest a progressive increase, over the years, in the production of some FRs such as tributyl phosphate (TNBP), triphenyl phosphate (TPhP), TCEP and TCIPP (Greaves et al., 2016).

Such compounds may adversely affect the environment as well as human health, having the potential to cause or worsen acute or chronic conditions. They may act through direct toxicity, but also as endocrine disruptors, pro-carcinogenic or pro-inflammatory agents, and they are known to disrupt innate and adaptive immune systems (Khani et al., 2023; Alcock et al.). At the cellular/molecular level they are responsible for changes in membrane integrity, DNA damage, altered gene expression, disruption of the cell cycle and cell death (Khani et al., 2023). Humans may be exposed to FRs through several routes, including the ingestion of food or non-dietary ingestion and inhalation of dust, soil, and air (Coelho et al., 2016b; Li et al., 2022).

Some studies have pointed out the potential for POPs to be associated with an increased risk of respiratory diseases, considering that inhalation is one of the most relevant pathways for exposure (Gascon et al., 2013; Park et al., 2020). However, no previous systematic reviews have been performed to estimate the potential risk of FRs on respiratory health.

This systematic review aimed to fulfil this important research gap by identifying, critically appraising, and synthesizing the evidence from studies that have investigated the association between exposure to FRs and the onset or clinical worsening of chronic respiratory diseases.

Thus, the addressed main questions were:

1) Primary research questions: Is the exposure to FRs associated with chronic respiratory diseases or adverse respiratory health parameters? Does the exposure to FRs increase the risk of worsening clinical outcomes in patients with established chronic respiratory diseases?
2) Secondary research questions: Do specific FRs exert differential risks on chronic respiratory diseases or adverse respiratory health parameters? Are there specific exposure pathways to FRs associated with the risk of chronic respiratory diseases?

2. Methods and analysis

2.1. Eligibility criteria for study selection

2.1.1. Population

We included all studies involving human individuals of any context and age. Chronic respiratory diseases criteria for inclusion were applied as: i) established clinical and medical diagnosis; and ii) clinical features characterised by: a) self-report, validated questionnaires, b) symptom/ medication scoring systems, c) objective or structural functional measures (e.g., lung function, blood tests or from other biologic sources, imaging tests, hospitalizations, exacerbations).

2.1.2. FRs exposure

Exposure to any FRs (such as: high-molecular weight compounds - oligomers and polymers, phosphorus, brominated, organophosphorus, chlorinated and novel/alternative FRs) through any source (e.g., dust and air) and their levels in biological specimens (e.g., urine and blood) were assessed. When possible, exposure was assessed through biomarkers such as urinary metabolites, namely: 5-HO-EHDPHP (2-ethyl-5-hydroxyhexyl-diphenyl phosphate), BDCIPP (bis(1,3-dichloro isopropyl) phosphate), DBP (2,3-dibromopropanol), and DNBP (Di-n-butyl phosphate), or through parent compound itself such as TDCIPP/TDCP (tris(1,3-dichloro-2-propyl) phosphate), TBOEP (tris(2-butoxyethyl) phosphate), TCEP (tris(2-chloroethyl) phosphate), TCIPP (tris(2-chloroisopropyl) phosphate),TEHP (tris(2-ethylhexyl) phosphate), TNBP (tributyl phosphate), TPhP (triphenyl phosphate), TPP (tripropyl phosphate), DEHP (bis (2-ethylhexyl) phthalate), and TBPH (bis-(2-ethylhexyl) tetrabromophthalate).

2.1.3. Comparator

We aimed to compare FRs types, as well as different exposure pathways, and different levels of exposure (exposed vs non-exposed or different exposure doses).

2.1.4. Main outcomes

The main outcomes were defined according to criteria associated with the development or worsening of chronic respiratory diseases. Most chronic respiratory diseases were considered for inclusion, such as: asthma, COPD, asthma/COPD overlap, interstitial lung diseases, bronchiectasis, cystic fibrosis, emphysema, sarcoidosis, rhinitis, rhinosinusitis, etc. However, due to the paucity of studies found, only asthma, wheezing and allergic rhinitis/rhinoconjunctivitis were addressed.

We aimed to analyse all the variables that are associated with disease onset, clinical control (i.e. symptoms, quality of life) and disease severity, assessed in accordance with national/international guidelines and/or based on pre-defined criteria (e.g. exacerbations, hospitalizations or emergency department visits in the previous year, need for increased therapy in the previous year, use of rescue medication, symptoms scores and other control questionnaires), questionnaires on quality of life and any other outcome indicating clinical control, including lung function parameters (such as: forced expiratory volumes, forced vital capacity, peak expiratory flow), imaging features, or markers related to inflammatory parameters.

2.1.5. Types of studies included

We included all types of observational study designs including prospective and retrospective cohort, nested case-control, case control and cross-sectional studies.

We did not include non-human studies, narrative reviews, editorials, correspondence and/or letters, case reports/series or ecological studies.

2.1.6. Search strategy

We searched the Cochrane Library, MEDLINE, PUBMED, EMBASE, SCOPUS, ISI Web of Science (Science and Social Science Index), WHO Global Health Library and CINAHL EBSCO, to reach regular and grey literature. We included studies published from the inception of the databases up to February 2022. Search terms are detailed in "Appendix 1 - Search Strategy". We reviewed the bibliographies of all eligible studies in order to identify additional literature, and the search strategy was reconducted in April 2023 for inclusion of additional and recent published studies, before submission for publication. No language restrictions were imposed; however, no translations were necessary, considering that all studies were published in English.

2.1.7. Data extraction and selection process

Titles and abstracts of included papers were independently checked by two investigators (TM and SDC). The full texts of all potentially eligible studies were retrieved and independently assessed according to the inclusion criteria (see above) by two reviewers (TM and SDC). The reviewers decided which of the studies fitted the inclusion criteria: any disagreements were resolved by consensus, with a third reviewer arbitrating unresolved discrepancies (ACAS).

Data from included articles were collected from their original presentation to a proper form made in Microsoft Excel© software, with each study identified by a reference code. It was not necessary to collect indirect data from figures and charts, neither to contact additional authors of original articles for further information and data.

2.1.8. Data collected

For the articles selected we extracted the following information: Study design, number of participants and their sociodemographic characteristics, country of study, year of publication, follow-up (in cohort studies), imaging and/or lung function features, types of FRs, exposure pathway, exposure load, disease diagnosis criteria and types of outcomes.

Some features were not reported in any study, such as: time-related phenotypes (e.g., early onset; late onset), clinical phenotypes (e.g., frequent exacerbator, mild/severe disease degree) and inflammatory markers (e.g., eosinophilic, neutrophilic, etc.).

2.1.9. Risk of bias (quality) assessment

Risk of bias assessment were independently undertaken by two different reviewers (TM and SDC), using an adaptation of the GRADE quality assessment tool (Oxford Centre for Triple Value Healthcare Ltd, 2018; Morgan et al., 2019). Several components of each study were appraised, including confounding, selection, measurement of exposure, departures from exposure, missing data, measurement of outcomes and reported results. For each study, each individual component was evaluated and assigned with a category of risk of bias: low, moderate, severe, and critical. The global study grading was accessed by the average and relative weight of all individual components. All disagreements were resolved by consensus and arbitrated by a third reviewer (ACAS). Risk of publication bias was examined using forest plots. The subdomain "confounding" was accessed in a more detailed approach, by developing a confounder matrix assessment tool (Petersen et al., 2022). For that, a causal diagram was developed in order to identify potential confounder variables, and those were gathered in different core sets composing six confounding constructs, namely: sociodemographic and biological features (gender and age; body mass index; physical activity; renal function; baseline characteristics), housing characteristics (dampness/mildew, ventilation, particulate matter, type of mattress and kitchenware), socioeconomic features (income, education), history of allergy/atopy (parental or child) and tobacco or smoking exposure. Detailed evaluation is available in supplementary Appendix S3 – "Quality Assessment of included studies".

2.1.10. Data synthesis

We produced a narrative and descriptive synthesis of the data using raw values, and crude or adjusted estimates of effect (such as: odds ratios, risk ratios (RR), incidence rate ratios, hazard ratios, mean differences, etc.).

For studies with reasonable clinical and methodological homogeneity, and if the association between the exposure (regardless of the pathway) and the outcomes were reported in a quantitative manner, we performed meta-analyses using random-effects models. We performed analysis regarding estimations for specific groups and congeners/compounds of FRs or their metabolites (if two or more studies reported them), as well as for FRs full mixtures, either using the values reported by original studies or by performing additional mean estimations within each study (using the reported individual groups and congeners/

compounds of FRs). In the meta-analysis, estimates from studies not presented as RR, were converted to RR using the formulae provided by VanderWeele et al. (VanderWeele and Ding, 2017), to seek meta-analytical standardisation and coherence.

We quantified the heterogeneity between studies using the I^2 statistic. The meta-analyses were performed using Cochrane Review Manager Software© (available at http://community.cochrane.org). The PRISMA checklist was followed for reporting of the systematic review (Page et al., 2021).

Sub-group analysis was performed according to sample size, participants mean age, exposure pathways, sub-types of FRs and types of outcome measures.

3. Results

3.1. Description of studies

The search yielded 353 articles, and, after elimination of duplicates, 252 remained. From these articles, 235 were excluded after reading title and/or abstract. Thus, 19 studies were obtained, from which, 10 were excluded after reading the full text. The reasons for exclusion are described in Fig. 1.

Of the 9 eligible and unique studies, 6 were cross-sectional (Meng et al., 2016a; Meng et al., 2016b; Araki et al., 2014; Araki et al., 2018; Ait Bamai et al., 2018) and 3 were cohort studies (Canbaz et al., 2016; Leijs et al., 2018). A total of 3285 individuals were studied and most (n = 2298; 70%) were children. Only Zhu et al., 2022 (Zhu et al., 2022) was performed with adults, and Araki et al., 2014 (Araki et al., 2014) included a small proportion of adults (0–14 yrs: 24.4%; 15–29 yrs: 12.2%; 30–44 yrs: 26.9%; 45–59 yrs: 20.3%; 60+ yrs: 16.1%). Detailed information for all selected studies is available at supplementary Appendix S2 – "Complete data of selected studies", and Fig. 2 presents a summary of their main characteristics.

3.2. Chronic respiratory diseases

Five studies reported asthma as an outcome (Meng et al., 2016a; Meng et al., 2016b; Araki et al., 2014; Canbaz et al., 2016), two reported wheezing (Araki et al., 2018; Ait Bamai et al., 2018) and two reported allergic rhinitis/rhinoconjunctivitis (Araki et al., 2014; Araki et al., 2018). No studies were found for COPD, asthma/COPD overlap, interstitial lung diseases, bronchiectasis, cystic fibrosis, emphysema, sarcoidosis. Two studies (Leijs et al., 2018) evaluated lung function as an outcome.

Among the included studies, asthma prevalence varied between 4.7% (Araki et al., 2014) and 50% (Canbaz et al., 2016), being present in 559 participants of the full sample (17% global); allergic rhinitis/rhinoconjunctivitis prevalence varied between 18.6% (Araki et al., 2014) and 36.7% (Araki et al., 2018), being present in 143 participants (6.6% global); wheezing prevalence varied between 13.9% (Ait Bamai et al., 2018) and 22.7% (Araki et al., 2018), being present in 70 participants (3.3% global).

Different diagnosis criteria were used to define the outcomes. Two studies (Araki et al., 2018; Ait Bamai et al., 2018) used the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire (Mallol et al., 2013) definition for the diagnosis of respiratory diseases. Five studies (Meng et al., 2016a; Meng et al., 2016b; Araki et al., 2014; Canbaz et al., 2016) used participant's self-reporting of symptoms, medical diagnosis or medical treatment prescribed. One study (Leijs et al., 2018) did not reported the applied criteria.

3.3. Exposure to flame retardants

Only five studies evaluated the exposure to organophosphate esters (OPEs) (Araki et al., 2014; Araki et al., 2018; Ait Bamai et al., 2018), three to brominated flame retardants (BFRs), more specifically
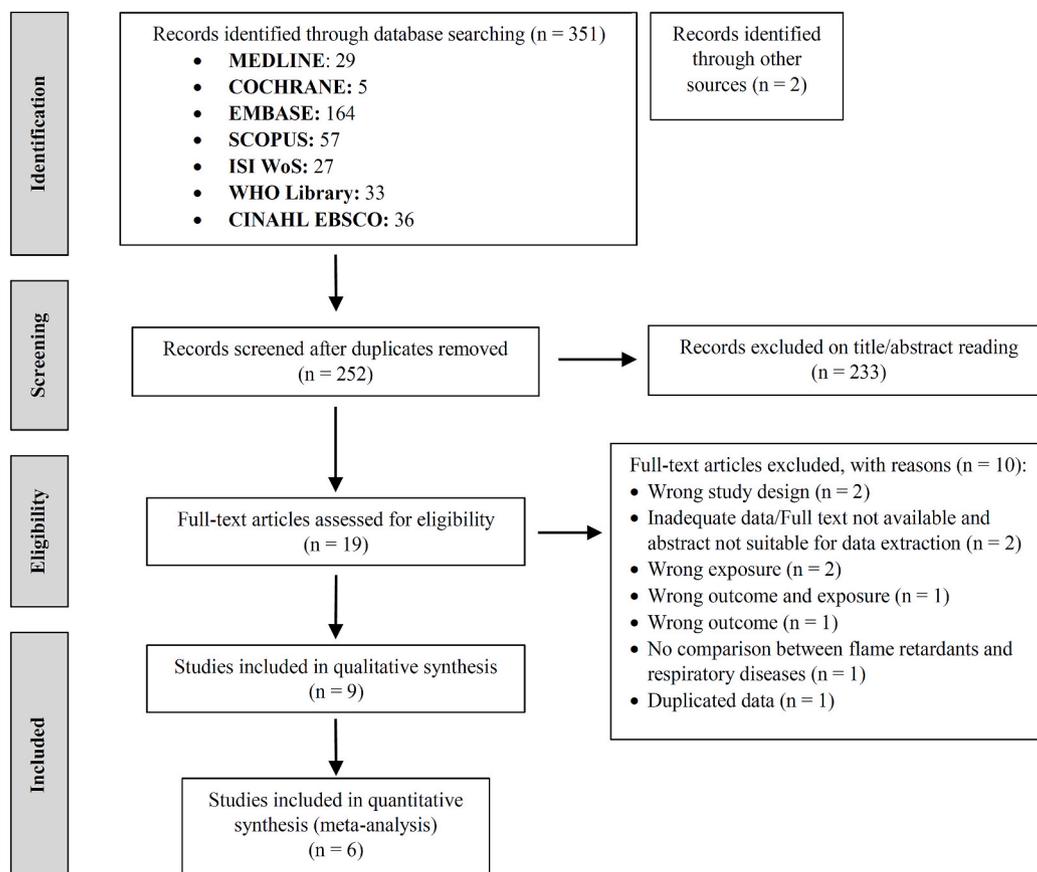
Fig. 1. Flow diagram on search and article inclusion, according to PRISMA statement.

polybrominated diphenyl ethers (PBDEs) (Meng et al., 2016a; Meng et al., 2016b; Leijs et al., 2018) and one to both (Canbaz et al., 2016). Supplementary Appendix S5 summarizes the target compounds addressed in this review.

Among the studies reporting OPEs, the compounds evaluated included several OPEs or OPE metabolites, namely: 5-HO-EHDPHP, BDCIPP, TDCIPP/TDCP, TDCPP, DBP, DNBP, TBOEP, TCEP, TCIPP, TEHP, TNBP, TPhP, TPP. Among the studies reporting BFRs, only TBPH and PBDEs were addressed, and among these BDE 28,47, 66 and 209 were the main studied congeners.

Most studies evaluated the exposure to FRs only through dust (present either on the floor or on multi-surfaces) (Meng et al., 2016a; Araki et al., 2014; Ait Bamai et al., 2018; Canbaz et al., 2016). Two studies (Meng et al., 2016b; Leijs et al., 2018) evaluated the concentrations of FRs in serum/blood samples, two studies evaluated metabolites levels in urine samples (Zhu et al., 2022; Louis et al., 2023) and one study evaluated metabolites levels in both matched dust and urine samples (Araki et al., 2018).

Concerning the description of the FRs concentrations, several approaches were employed. Two studies reported FRs concentrations based on quartiles (Araki et al., 2018; Ait Bamai et al., 2018). Four studies based on detection frequencies (Meng et al., 2016a; Meng et al., 2016b; Canbaz et al., 2016). Two studies (Araki et al., 2014) reported the exposure based on the "levels under the detection limit", and another study did not report the type of measure used (Leijs et al., 2018).

3.4. Risk of bias in included studies

Two reviewers independently evaluated the risk of bias of the included studies and reached consensus in all evaluations (Fig. 3). Almost every study showed a predominance of low to moderate risk of bias in their risk assessment. Eight out of nine studies included in the

quality assessment (Meng et al., 2016b; Araki et al., 2014; Canbaz et al., 2016) (Meng et al., 2016a; Araki et al., 2018; Ait Bamai et al., 2018; Zhu et al., 2022; Louis et al., 2023) had a global moderate risk of bias and one (Leijs et al., 2018) was considered serious. The highest risk of bias was found regarding the confounding control, selection of participants, measurement of outcomes and selection of reported results. The dimension "departures from intended exposures" was not possible to evaluate in most studies, due to the cross-sectional design. The classification of exposures was globally well performed and missing data was rare. Detailed evaluation is available in supplementary Appendix S3 – "Quality Assessment of included studies".

3.5. Association between FRs exposure and chronic respiratory diseases

Among the selected follow-up studies, two cohort studies and one cross-sectional (Canbaz et al., 2016; Leijs et al., 2018) did not report enough data to be aggregated in a quantitative manner. There was no positive association between the FRs in mattress dust and the development of childhood asthma. In contrast, in one study (Canbaz et al., 2016), dust collected from mattresses of the households with children who would develop asthma contained significant lower levels of TPHP (419 vs 613 ng g-1, p = 0.007) and mmp-TMPP (meta, meta, para-tris (methylphenyl) phosphate) (192 vs 288 ng g-1, p = 0.026), compared with dust collected in those of the households with healthy participants. The other two studies addressed lung functions as an outcome of interest. One study (Leijs et al., 2018) performed in children found a statistically significant correlation between FRs exposure (dioxin and dioxin-like PCBs congeners, detected in serum/blood samples) and worse lung function levels, namely Forced expiratory volume in the first second [FEV1] (spearman's correlations $r = -0.539$, p = 0.032), the ratio of FEV1/Forced Vital Capacity [FVC] (spearman's correlation $r = -0.575$, p = 0.02) and Peak expiratory flow at 50% [FEF50]
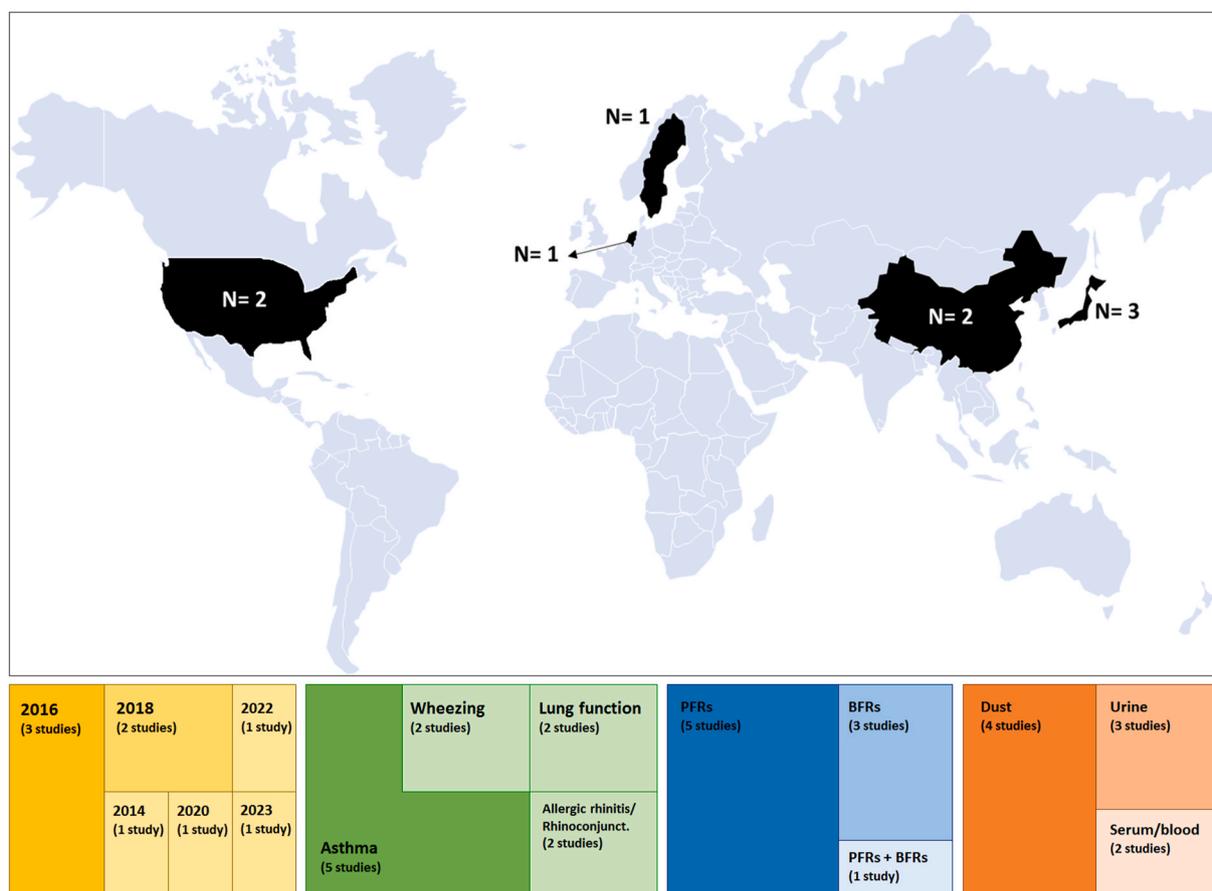
Fig. 2. Characteristics of the studies included in this systematic review: respiratory diseases studied; temporal and spatial distribution of the studies; type of FRs and type of matrices analysed.

	Risk of Bias adapted from GRADE Evaluation							Overall risk of bias
	1	2	3	4	5	6	7	
Araki A; et al 2014	?	+	+	NA	+	?	+	Moderate
Araki A; et al 2018	?	?	?	NA	+	+	?	Moderate
Ait Bamai Y; et al 2018	+	?	+	NA	+	+	?	Moderate
Canbaz, D.; et al 2016	?	+	+	?	+	?	?	Moderate
Leijs, M.M.; et al 2018	-	?	?	?	?	?	?	Serious
Louis, LM.; et al. 2023	+	?	+	?	+	+	?	Moderate
Meng, G.; et al 2016_1	?	+	+	NA	+	?	+	Moderate
Meng, G.; et al 2016_2	?	+	+	NA	+	?	?	Moderate
Zhu, H.; et al. 2022	?	?	+	NA	+	?	+	Moderate

1 - Confounding;
2 - Selection of Participants;
3 - Classification of Exposures;
4 - Departures from Intended Exposures;
5 - Missing Data;
6 - Measurement of Outcomes;
7 - Selection of Reported Results;

+ → Low risk of bias
? → Moderate risk of bias
? → Serious risk of bias
- → Critical risk of bias
NA → Not enough information to judge the risk of bias

Fig. 3. Risk of Bias assessment in included studies according to an adaptation of the GRADE quality assessment tool and including a detailed confounding assessment through a confounding matrix.

(spearman's correlation $r = -0.699$; p = 0.003). The other study (Zhu et al., 2022), performed with adults, also found a statistically significant correlation between urinary levels of OPE metabolites and worse lung function levels, namely: a reduction of 91.52 ml and 79.34 ml in the FVC levels with every logarithm unit increase in the levels of BDCIPP and BCEP; as well as a reduction of FEV1, FVC and Peak expiratory flow [PEF] levels by 130.86 ml, 153.56 ml and 302.26 ml, for each one-unit elevation in BCIPP, respectively.

Among the remaining studies, five cross-sectional studies (Meng et al., 2016a; Meng et al., 2016b; Araki et al., 2014; Araki et al., 2018; Ait Bamai et al., 2018) and one cohort (Louis et al., 2023) provided enough data to be analysed quantitatively. Figs. 4–6 present the main findings for asthma, wheezing and rhinitis/rhinoconjunctivitis, respectively. Full data of meta-analyses is available on supplementary Appendix S4 - "Complete data of meta-analysis".

Regarding asthma, we found significant results regarding exposure to TNBP in one study (Araki et al., 2014), with an elevated risk of asthma (Risk Ratio: 2.31; 95%CI: 1.20–4.44; p = 0.01), and regarding TPHP in the pooled estimate of two studies (Araki et al., 2014; Louis et al., 2023), also with an elevated risk (Risk Ratio: 1.13; 95%CI: 1.03–1.24; p = 0.01). Overall, a relative risk higher than 1, although not significant, was observed for asthma, for most of the OPEs compounds in the other studies. In the global pooled results, the meta-analysis showed no statistically significant risk estimation. No relevant patterns were found in the remaining subgroup analyses, namely other sub-type of FRs,

pathway/source, participants age or country. Concerning PBDEs, the results were divergent and heterogeneous, with no relevant patterns.

No statistical significance was observed for the association between FRs and wheezing although in some studies the relative risk was higher than 1.0 (Araki et al., 2018; Ait Bamai et al., 2018). Evaluating different FRs subtypes and their metabolites, we found no relevant trend patterns nor statistically significant risk differences. The exception is for 5-OH-EHDPHP, reported in the Araki et al., 2018 study (Araki et al., 2018) with a trend for higher risk. This trend was found in this study only when analysing the levels of this urinary metabolite of EHDPHP, but not its levels in dust.

We found divergent and heterogeneous results in the global analysis, as well as among all analysed FRs exposure levels, for rhinitis/rhino-conjunctivitis. The exceptions were TCEP and TCIPP, both detected in urine and dust samples, showing a trend for higher risk, although not statistically significant (detailed information about risk estimates is presented at Appendix S4 - "Complete data of meta-analysis"). The study by Araki et al., 2018 (Araki et al., 2018) showed a significant marginal risk, when analysing the levels of urinary FRs metabolites (pooled estimate for all 14 OPEs metabolites reported) (Risk Ratio: 1.44; 95%CI: 1.10–1.88; p = 0.08), but not for FRs dust levels.
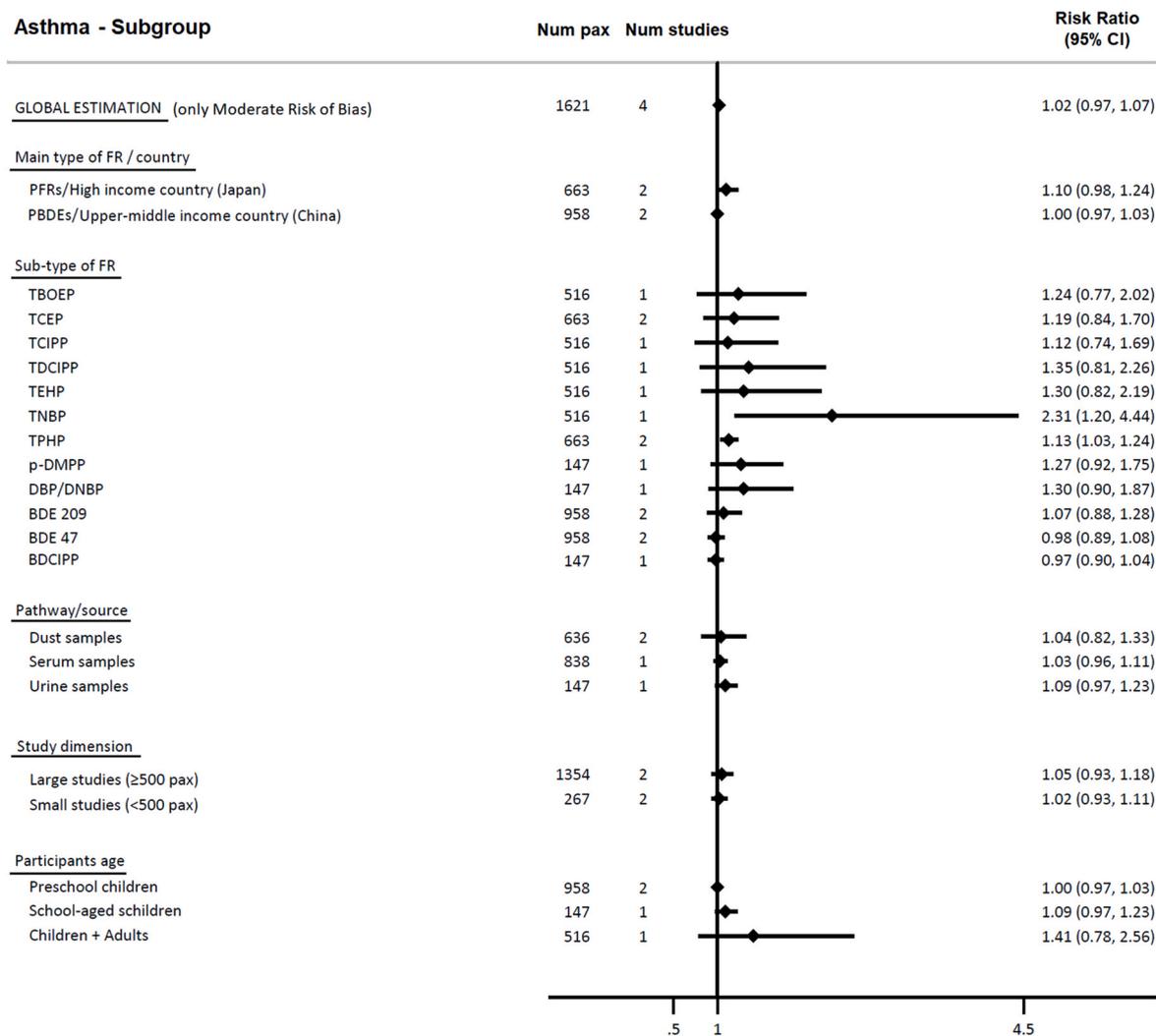
Fig. 4. Forest plot of results on the risk of asthma according to Flame Retardants exposure and the most relevant sub-group analysis.
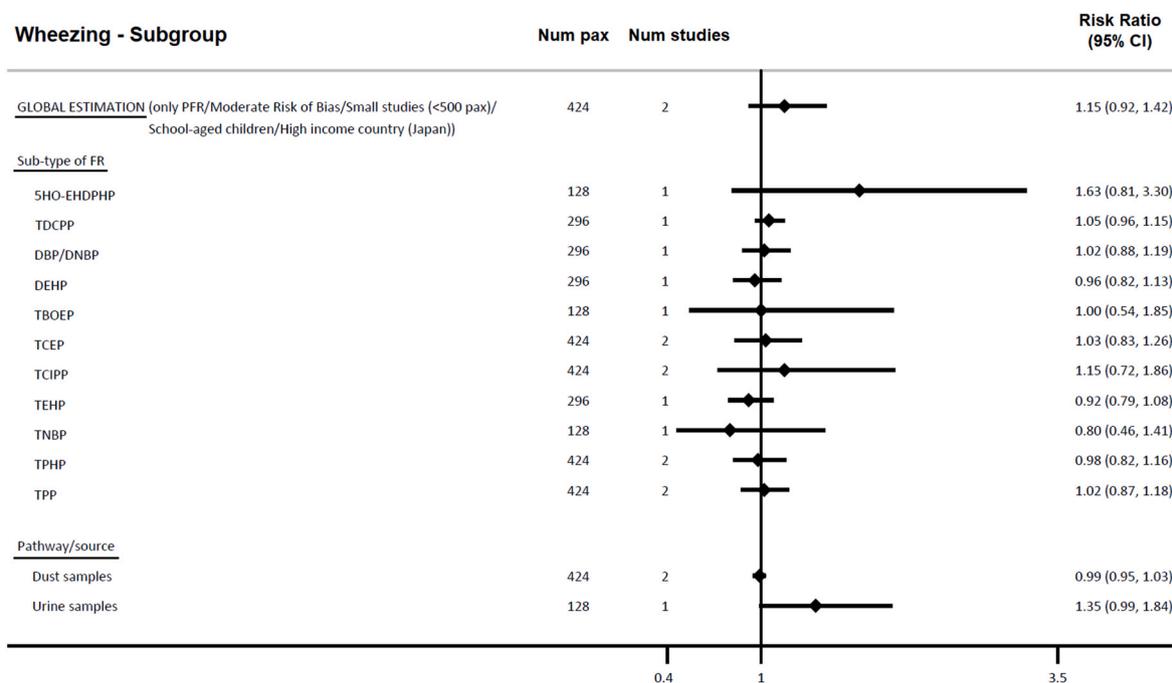
Fig. 5. Forest plot of results on the risk of wheezing according to Flame Retardants exposure and the most relevant sub-group analysis.
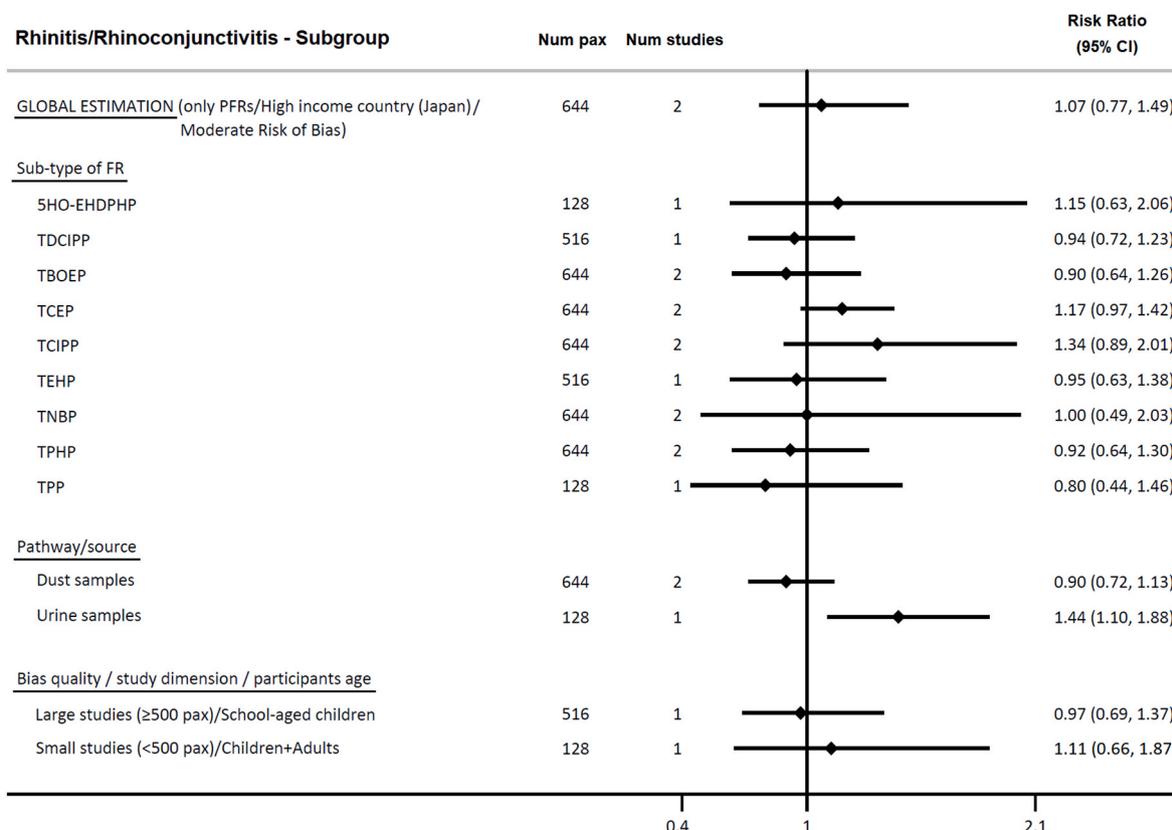
Fig. 6. Forest plot of results on the risk of rhinitis/rhinoconjunctivitis according to Flame Retardants exposure and the most relevant sub-group analysis.

4. Discussion

4.1. Summary of key findings

Considering the persistency and widespread use of current POPs and emerging POPs, including FRs, it is of paramount importance to assess their potential health impacts. This is particularly relevant in respiratory diseases, known to be highly susceptible to environmental pollution, while considering the increasing disease burden in the last decades (Union, 2018; Soriano et al., 2020). Thus, this is the first systematic review addressing the role of FRs in chronic respiratory diseases.

Overall, we found no statistically significant increase in the risk for

chronic respiratory diseases with higher exposure to FRs, with the exception for asthma, mainly regarding exposure to TNBP that was associated with a significantly increase in the relative risk of a 131% (in one single study), and regarding exposure to TPHP that was associated with a significant increase in the relative risk of a 13%, pooling two studies. Nevertheless, existing data support the hypothesis that some FRs may be associated with a higher risk for asthma, although no statistically significance was observed in the meta-analysis quantitative estimation of the overall risk. The remaining studies, not included in the meta-analysis (Canbaz et al., 2016; Leijs et al., 2018), reinforced such potential effect, particularly a significant risk for worsening of several lung function parameters, with a potential dose-response effect for FRs exposure. Similar results were found regarding wheezing when analysing the levels of urinary OPEs metabolites. For rhinitis/rhino-conjunctivitis, TCEP and TCIPP have also shown a trend for risk higher than 1, although not statistically significant, and, again, this was more pronounced when analysing the levels of urinary OPEs metabolites (potential increase of 44% risk).

Most studies showed a predominance of moderate risk of bias in their risk assessment; and, due to the cross-sectional design of most of the studies included in the meta-analysis, the global strength of the findings evidence is low.

4.2. Strengths and limitations of the review

This systematic review highlights the lack of enough evidence to establish a harmful relationship between exposure to FRs and asthma and rhinitis. However, this lack of association might be explained by some limitations.

First, there are still few studies published reporting this association, and most of them are cross-sectional. We found only 2 cohort studies (Canbaz et al., 2016; Leijs et al., 2018), and those studies reported different results when comparing with the cross-sectional ones, showing a deleterious effect upon asthma, probably as a consequence of the exposure to TPHP and mmp-TMPP. Overall, the global strength of the evidence regarding the meta-analysis estimations was low. These studies were not appropriate to study FRs impact because they obtained only one exposure assessment.

Also, most studies included considerably small sample sizes, which hampers the ability to detect marginal and low increases in the risk, and therefore, they may be underpowered. The methodological heterogeneity and the diversity of diagnosis (outcome) criteria may also pose some limitations in the true effect detection.

Another limitation is the fact that most studies were performed in Asian countries, such as Japan and China, with the exception for one study performed in USA, and this may not represent the real burden worldwide, as it may differ significantly across different countries. As well as the levels, patterns, and distribution of specific FRs may vary due to the FRs countries' legislation, building material employment, furniture, and devices variations (Esplugas et al., 2022; Li et al., 2019). The concentrations of FRs might also exhibit seasonal variations, yet the real impact of temperature and seasonal variability on the concentrations of FRs and consequently on exposure are still not fully understood. Several studies from diverse geographical locations (e.g. Asia, North America, Europe) have described that higher temperatures, which correspond to summer months, are responsible for higher OPEs concentrations in the atmospheric gas-phase (Saini et al., 2019; Ohura et al., 2006; Prats et al., 2022; Wong et al., 2018; Yaman et al., 2020). However, in other studies, this association was less robust or even absent with no significant impacts of temperature on OPEs partition (Liu et al., 2023; Shoeib et al., 2014; Zhao et al., 2023). Nevertheless, these results should be interpreted with caution as they are deeply dependent on the study design and/or characteristics of the built environment as recently highlighted by (Rodgers et al., 2023). In fact, the physical and chemical properties of OPEs and the climatic characteristics are important factors, but the characteristics of the built environment also play a determinant role on

the behaviour and release of contaminants and should not be ruled out (Rodgers et al., 2023). Further studies examining the mechanisms behind the partition of OPEs are necessary.

Lastly, we must notice that most studies evaluated the exposure through house dust. Although being one of the main exposure sources of FRs, levels in house dust may not represent the real internal dose of FRs, considering that many factors affect the real and final bioavailability. Among those we may highlight that the following information should be considered and adjusted as confounding factors when assessing the exposure: i) the different country policies regarding the use of FRs in all industrial and commercial settings, ii) the housing characteristics, cleaning procedures, amount of plastic furniture/objects, among others (Gravel et al., 2019; Sugeng et al., 2017), iii) Individual exposure differences (eg. dust exposure frequency) and the several pathways of exposure, such as the ingestion and inhalation of dust, the inhalation of air, the dermal absorption, and the dietary ingestion (Chupeau et al., 2020). Only three out of nine studies involved internal exposure measurements. While internal exposure measurement is more reliable in assessing actual exposure levels in the human body, the literature included here may not adequately represent the outcomes under investigation. Concerning the description of the FRs concentrations, several approaches were employed among the included studies (continuous (log2) concentrations, median values, geometric mean SG-corrected concentrations, quartiles, cut-offs for LOQ and LOQ), and, considering the heterogeneity found, future studies should address this important technical gap, and seek harmonization, either on methodological features related to detection rates, either on data-analysis methods and their report.

Importantly, we detected a higher risk when analysing the exposure to FRs through urine metabolites. This means that future studies should also consider biological samples, in addition to the environmental samples, as a better surrogate for the real exposure. Xu et al., 2019 (Xu et al., 2019), evaluated the occurrence of several OPEs metabolites in different biological samples (human hair, serum, and urine) and correlated them with the OPEs present in environmental samples (including air and dust) observing that urinary OPEs metabolites are associated with parent OPEs present in dust and air. However, it is well-known that since house dust is extremely heterogeneous, levels in dust do not necessarily reflect the internal dose. In fact, the reported bioaccessibility of FRs in dust shows relatively large variation. In this regard, biomonitoring approaches, which assess the exposure by analysing biological samples such as blood, urine, and hair, would be suitable as a surrogate for internal dose if relevant biomarkers are available (Fang and Stapleton, 2014; Wannomai et al., 2020; Wannomai et al., 2021). Further studies on the reliable and reasonable method for exposure assessment of FRs are warranted. Such studies should include the measurement of FRs in biospecimens from large-scale cohort studies.

Two studies, reporting exposure to TNBP and TPHP, revealed a significantly elevated risk for asthma (Araki et al., 2014; Louis et al., 2023). These studies had some positive design features (large sample size or cohort design), but overall, a moderate risk of bias, and the outcome was evaluated by participants self-reporting of having previous medical treatment for bronchial asthma or allergic rhinitis at any time during the preceding years, which may lead to overdiagnosis, and therefore, may result in overestimate this association. In addition, regarding TNBP, its exposure seems to be associated with a higher risk for Asthma than the exposure measured through the metabolite DNBP. This may be related to the studies design itself and some potential bias. The estimate for TNBP exposure is reported by Araki et al., 2014) (Araki et al., 2014), whereas exposure measured through DNBP was evaluated by Louis et al., 2023) (Louis et al., 2023). The study from Araki et al. has a larger sample and with data collected from a significantly larger follow-up population, which may allow a better detection of the hazardous effects in a long-term exposure.

Despite these limitations, this review has several strengths. First, the reported estimations resulted in a combination of adjusted risk ratios,

considering that all studies performed confounding adjustment in their risk estimations, namely for gender, age, tobacco smoking, housing characteristics, household income, creatinine levels, parental history of atopy, non-stick pan use and house ventilation. In addition, this review was conducted with high methodological quality, in accordance with the PRISMA recommendations (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) (Page et al., 2021). A broad, but concrete, study inclusion criteria (PICO) was designed, reaching consensus among all reviewers on a rigorous way. The inclusion of broad criteria allowed to develop a highly comprehensive review with a significant diversity of FRs included, with more generalised results.

4.3. Comparison with other studies

Comparison with previous systematic reviews reporting on FRs health effects is not possible, considering this is the first one on this topic. Nevertheless, previous studies have shown a potential adverse effect of POPs, as well as FRs, in different health conditions. A recent study suggests that female exposure to at least some POPs may reduce fecundability (Kahn et al.), affecting the time needed to achieve pregnancy. Two other systematic reviews found sufficient evidence supporting an association between developmental PBDEs exposure and reduced child cognitive, behavioural, and motor development (Lam et al.; Gibson et al., 2018), and that may be possibly through the perturbations in thyroid function either in the pregnant woman or in the child. This endocrine disruption theory was previously developed in a review including 36 epidemiological studies, that found a potential role of BFRs on diabetes, cancer, and thyroid function (Kim et al., 2014). Those systematic reviews included a larger number of well-designed studies, while in our review all the included studies presented some key limitations.

Moreover, recent evidence starts to propose some possible mechanisms underlying the role of FRs in some respiratory diseases, such as childhood asthma, and those may be associated to a disrupting inflammatory effects on lipid and fatty acid metabolism (Chen et al., 2024). In fact, studies from rural areas of industrialised countries suggest that exposure to some indoor pollutants might be protective in early life but are associated with adverse respiratory effects in adulthood (Hulin et al., 2012). Furthermore, *in vivo* and *in vitro* evidence with lung cell lines suggest that FRs have major implications in oxidative stress, and DNA damage with consequences in inflammatory responses (Montalbano et al., 2020; Chen et al., 2023). Studies with mice (Meng et al., 2022), suggested that oxidative stress and inflammatory responses mediated by the *Fkbp5/Nos3*/MAPK/NF-κB signal pathway are responsible for pulmonary damage and that TNBP intensified OVA-simulated asthmatic response, inducing the proliferation of goblet cells, the recruitment of inflammatory cells, and the overexpression of IgE. Recently, an Adverse Outcome Pathway (AOP) framework was developed to elucidate the mechanism of pulmonary disfunction caused by OPEs (Zhu et al., 2022). The evidence indicates that pulmonary dysfunction caused by chlorinated OPEs was associated with the IL-6/JAK/STAT pathway, which resulted in airway remodeling, and consequently in the impairment of the lung function. Also, a recently published study, including participants from an U.S. nationwide survey, revealed a potential association of OPEs exposure and the risk for worse lung function parameters, such as lower FEV1 and FVC levels, thus, reinforcing our findings (Hu et al., 2023).

4.4. Interpretation and implications of the findings

The importance of indoor and outdoor pollution and their role in the development and worsening of chronic respiratory diseases is well established and there are several international guidelines available on this topic (Reddel et al., 2019; Bousquet et al., 2020; Hoy, 2012). Generally, most recommendations call for a reduction of the exposure. Yet, to reduce exposure it is necessary to first identify the chemicals

associated with chronic respiratory diseases and to assess their real impact on disease onset and worsening. It is particularly relevant for widely used chemicals to which we are continually exposed, such as FRs. This systematic review presents a wide, inclusive, and comprehensive approach, including all available studies worldwide on FRs and respiratory health, and therefore we have found the results timely and relevant. Nevertheless, a comprehensive meta-analysis to estimate the associations cannot be performed due to lack of information despite the public concern and previous (*in vivo/in vitro*) reports implying adverse effects (Abdallah et al., 2015; Wang et al., 2021; Bajard et al., 2019). So, conducting large-scale observational studies is of paramount importance. Considering this, future studies should be designed on a longitudinal cohort base, with long-term follow-up, to assess these causal relationships over time, to control for potential confounders, and to assess the risk of synergic or collinear effects among different groups and congeners/compounds of FRs. These should consider the chronic exposure to FRs and the fact that the daily intakes of FRs are higher in early life (newborns and toddlers) due to the highest dust intake rates and smaller body weights comparing to adults (Kim et al., 2019). Therefore, this exposure might influence the respiratory health on a long term.

Finally, by identifying a potential, yet underdetermined, hazardous effect of FRs, this systematic review highlights the need for future interventions that may reduce this risk. These future interventions should be addressed at a global scale of health policies (Gravel et al., 2019; Souto-Miranda et al., 2020) and should focus on the substitution of the toxic chemicals for safer ones as contemplated in the European "Green deal" and disclosed in the European Commission "Chemicals Strategy for Sustainability Towards a Toxic-Free Environment" (CSS) (COM, 2020). In a scenario where the replacement of toxic chemicals is not yet possible, the implementation of urban design policies to reduce exposure should also be considered (Rodgers et al., 2023). Future interventions should also focus on educational programs to empower patients to reduce exposure in their everyday life. Previous works already demonstrated that simple interventions can decrease exposure levels and that patient empowerment is an important tool to reduce exposures and improve patients' health (Gravel et al., 2019; Souto-Miranda et al., 2020; Rodgers et al., 2021; Bryant-Stephens et al., 2009; Gibson et al., 2019).

5. Conclusions

Available data do not allow to support that exposure to Flame Retardants poses a significant higher risk for respiratory diseases. However, a trend was observed for a potential risk regarding asthma and rhinitis/rhinoconjunctivitis. This trend may be present with the OPEs: TNBP, TPHP, TCEP and TCIPP, and was more pronounced when FRs exposure was accessed through urinary metabolites.

Overall, the strength of the evidence is low, considering the lack of longitudinal, and robust well-designed studies. Future studies must be designed as cohorts, with large follow-ups, using more accurate bioavailability measures, and adjusted to potential confounders.

Ethical considerations

This work was not submitted to ethical board approval, considering it in a systematic review, and therefore, there was no human participation, and no personal data was used.

Data sharing

All data used in this systematic review is detailed and available at Supplementary Appendices.

Differences between protocol and review

The protocol of this systematic review was registered in PROSPERO

with the number CRD42022315231 Available at:
https://www.crd.york.ac.uk/prospero/display_record.php?
ID=CRD42022315231.

The study protocol has no methodological differences from the final work.

Prospero protocol registration no

CRD42020220805.

CRediT authorship contribution statement

Sónia D. Coelho: Writing – review & editing, Writing – original draft, Validation, Methodology, Formal analysis, Data curation, Conceptualization. **Tiago Maricoto:** Writing – review & editing, Writing – original draft, Validation, Software, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Luís Taborda-Barata:** Writing – review & editing, Writing – original draft, Validation, Software, Resources, Methodology, Conceptualization. **Isabella Annesi-Maesano:** Writing – review & editing, Writing – original draft, Validation, Methodology, Conceptualization. **Tomohiko Isobe:** Writing – review & editing, Writing – original draft, Validation, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Ana C.A. Sousa:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Formal analysis, Data curation, Conceptualization.

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.

Data availability

Data of public access already.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2024.123733.

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