

Review article

Insights from human biomonitoring studies of children's exposure to indoor air pollutants in school and home environments: A systematic review

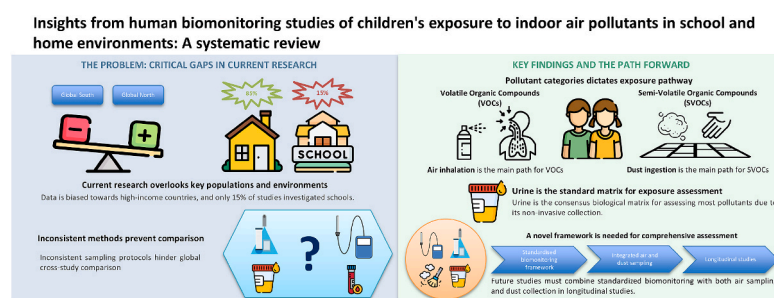
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HIGHLIGHTS

- Data is biased towards high-income regions, and only 15% of studies assessed schools.
- Inconsistent sampling protocols hinder global cross-study comparisons.
- Inhalation dominates for VOCs exposure, whereas dust ingestion drives SVOC exposure.
- Urine is a consensus biological matrix, but sampling timing requires standardisation.
- A novel framework is needed to combine biomonitoring with source-specific sampling.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Human biomonitoring offers critical insight into the total internal dose of indoor air pollutants, yet standardised protocols for school-age population remain undefined. This review systematically evaluated biomarkers, biological matrices, and analytical strategies for assessing school-aged children's exposure to volatile (VOCs) and semi-volatile organic compounds (SVOCs) in home and school environments.

Methods: A systematic search across four databases identified 79 peer-reviewed studies involving children aged 6–12. Data were synthesised to evaluate the performance of biomarkers relative to concurrent environmental monitoring data, with a focus on methodological applicability and study design heterogeneity.

Results: The analysis revealed a geographic bias toward high-income regions and a critical data gap regarding educational settings, with only 15% of studies investigating schools. Methodologically, urine emerged as the consensus biological matrix, though the utility of metabolites varies by half-life times. A key divergence was identified in exposure pathways: active air sampling effectively predicts the internal dose of VOCs, confirming inhalation as the primary pathway, while settled dust collection is a superior predictor for SVOCs, validating that accidental ingestion is dominant. Furthermore, clinical outcomes proved more sensitive than general oxidative stress markers for verifying the health risks of environmental tobacco smoke.

Conclusion: Currently, cross-study comparisons are hindered by methodological fragmentation and predominant cross-sectional designs that fail to capture peak exposure activities. Future research must adopt a novel methodological framework that combines harmonised longitudinal biomonitoring with source-specific environmental

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sampling. This integrated approach is crucial for attributing pollutant sources and accurately characterising the health risks of children in the indoor environment.

1. Introduction

Indoor air pollution (IAP) refers to pollutants present in non-industrial indoor environments that can adversely affect human health, including volatile organic compounds (VOCs) and semi-volatile organic compounds (SVOCs) (Li and Ma, 2021), (Tran et al., 2020). As one of the major environmental health risk listed by the U.S. Environmental Protection Agency (EPA) (Seguel et al., 2017), IAP contributes to an estimated 3.8 million deaths globally each year (Tran et al., 2020). The issue is particularly acute in modern society, as most people spend approximately 90% of their time indoors (Huang et al., 2022), and are often exposed to indoor pollutant concentrations 2 to 5 times higher than outdoor levels (Ferreira and Barros, 2022).

Children are the most vulnerable group to these exposures due to unique physiological and behavioural factors (Price et al., 2003). Compared to adults, children inhale more air relative to their body weight and possess a higher metabolic rate (Bearer, 1995), while their immature immune and neurological systems are more susceptible to toxic substances (WHO Regional Office for Europe, 2005), (Goldizen et al., 2016). Recent epidemiological evidence suggests a strong link between early-life indoor environmental factors and the onset of pneumonia, asthma, and allergic rhinitis (Norbäck et al., 2018a), (Norbäck et al., 2018b), (Norbäck et al., 2019), (Lu et al., 2023), highlighting the urgency for accurate assessment of children's exposure. Given that children spend the majority of their time at homes (55%–56%) and schools (30%) (Kalimeri et al., 2016), (Korhonen et al., 2021), characterising the “total exposome” across these two environments is critical for public health intervention (Abdel-Salam, 2022).

A major challenge in exposure assessment lies in the distinct physicochemical properties of the major pollutants. VOCs exist primarily in the gas phase, leading to inhalation exposure (Watson and Cleveland, 2004), while SVOCs partition between the gas phase and various condensed-phase reservoirs such as aerosols and settled dust (You et al., 2022). Traditionally, environmental monitoring has been the primary approach to assess these exposures (Ashmore and Dimitroulopoulou, 2009). However, this method is resource-intensive and often fails to account for individual variability in uptake via non-inhalation pathways (e.g., ingestion) (Watson et al., 1988). In contrast, Human Biomonitoring (HBM) offers a superior advantage by measuring the integrated internal dose from all routes of absorption (Manno et al., 2010), (Egorov, 2015). HBM relies on Biomarkers of Exposure (BoEXs) to quantify parent chemicals or their specific metabolites, and Biomarkers of Effect (BoEFs) to detect early physiological alterations induced by exposure (World Health Organization, 1993).

Despite the numerous advantages of HBM, there is currently no consensus on the optimal approach for assessing children's exposure. Previous systematic reviews have largely focused on general populations or outdoor environments (Hadei et al., 2021), (Liu et al., 2019), (Smith, 2008), (Wang et al., 2022), (Xu et al., 2022), (Zhu et al., 2021), leaving a gap in understanding the specific study designs required for children. Assessing exposure in this population is inherently complex due to ethical constraints on invasive sampling (e.g., blood collection) and the logistical challenges in school sampling (Needham and Sexton, 2000). Consequently, there is a need for a comprehensive resource that not only reports findings but also evaluates the tools applicable to this population.

This review systematically summarises the methodological approaches for assessing the exposure of school-age children (defined here as ages 6 to 12) to indoor air pollutants (VOCs and SVOCs) in home and school environments. Specifically, it evaluates the applicability of different biological matrices (e.g., urine, blood, exhaled breath) and

analytical protocols to identify knowledge gaps. Its goal is to provide a novel methodological framework to guide researchers in conducting robust and standardised biomonitoring studies of children's indoor exposure.

2. Methods

The study protocol for this review was registered in PROSPERO (PROSPERO, 2023 CRD42023410305) and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Page et al., 2021).

2.1. Search strategy

A systematic search of literature was conducted on the 30th of March 2023, across four electronic databases (PubMed, Web of Science, Scopus, and Embase), with no restrictions regarding publication years. Given the recent rapid development of IAQ-related biomonitoring studies for children, a second search was conducted on the 5th of March 2024, in the same 4 electronic databases for all literature published from the 30th of March 2023 to the 5th of March 2024. The language of articles was restricted to English. The search strategies combined keywords related to (1) school-age children (6–12 years), (2) school- and home-related indoor environments, (3) exposure to specific indoor air pollutants (i.e., VOCs or SVOCs), and (4) human biomonitoring studies. The pollutant list was selected based on the WHO guidelines for indoor air quality (World Health Organization, 2010) and previous reviews (Vardoulakis et al., 2020), (World Health Organization, 2021), targeting 17 VOCs, 9 SVOCs and 21 chemical families. However, this list was not exclusive; studies reporting other relevant VOCs or SVOCs pollutants were also considered during the screening process. Furthermore, the review covered all available biological matrices, including but not limited to urine, blood, exhaled breath, and hair, to ensure a comprehensive assessment of internal exposures. Details of keywords and search strategies are provided in Table S1.

2.2. Inclusion and exclusion criteria

Studies were included if they met the following criteria: (1) observational studies, or control groups data from non-observational studies; (2) reporting biomonitoring data for at least one indoor air pollutant from the VOC or SVOC groups; (3) reporting individual chemical pollutants rather than an aggregate total (e.g. TVOCs); (4) targeting children between the age of 6 to 12 years (or cohorts with an age range overlapping by at least 70% with this target); (5) assessing indoor exposure within school or home environments; (6) original peer-reviewed research; (7) published in English. Studies were excluded based on the following criteria: (1) lack of quantitative biomonitoring data (e.g., environmental-only studies); (2) animal studies/in vitro studies; (3) focusing exclusively on outdoor exposure, other indoor or occupational settings, or prenatal exposure, or non-inhalational exposure; (4) addressing pollutants solely from solid fuel combustion, indoor cooking, or biomass combustion; (5) duplicate data from studies already included in the review.

2.3. Study selection

All records searched from the four databases were deduplicated using the Systematic Review Automation (SRA) - Deduplicator (<https://sr-accelerator.com/#/deduplicator>) (Forbes et al., 2024), retaining only one record per article. Any two of the three investigators

(Wai Kei Chu, Thomas Celis, and Lama Said) independently screened the study titles and abstracts of the remaining articles against the inclusion and exclusion criteria. Subsequently, the full text of all potentially eligible articles was reviewed. If the full text of the article was not accessible, the record would be excluded. Any discrepancies were resolved through discussion between investigators.

2.4. Data extraction

Any two of the three investigators independently extracted data from all included articles and entered them into a standardised Microsoft Excel spreadsheet. The data comprised study characteristics (e.g., citation, design, demographics), exposure details (e.g., specific pollutants, emission sources), and methodological data for both biological and environmental sampling, including matrices, analytical methods, and detection limits. Statistical outcomes, including effect estimates and confidence intervals, were also recorded. Exposure classification relies on environmental monitoring: if a study included biomonitoring data as well as separate environmental air measurements from homes and schools, the biomonitoring data were considered an independent exposure to each environment, while biomonitoring data lacking specific environmental air measurements were classified as integral exposure across both environments. Moreover, all available data for total populations and eligible subgroups were extracted in their original statistical formats (e.g., means, medians) and units, and adjustments such as creatinine correction were noted where necessary.

2.5. Quality assessment

The methodological quality of included studies was evaluated using the Effective Public Health Practice Project Quality Assessment Tool (EPHPP) (<https://www.ephpp.ca/quality-assessment-tool-for-quantitat>

ive-studies/) (Thomas et al., 2004). Any two of the three independent investigators rated studies as “Weak”, “Moderate”, or “Strong” based on selection bias, study design, confounders, blinding, data collection methods, and withdrawals. Any disagreement was resolved through discussions between investigators. These ratings were used to contextualise the strength of evidence but not for exclusion. Detailed information on EPHPP and the quality assessment results were presented in Tables S2 and S3, respectively.

3. Results

The systematic search was conducted in March 2023 and updated in March 2024, identifying a combined total of 14259 records across four electronic databases. After deduplication and title/abstract screening, 339 full-text articles were assessed for eligibility. Eventually, 79 studies met the inclusion criteria and were included in the systematic review. The detailed selection process was illustrated in the PRISMA flow diagram (Fig. 1).

3.1. Characteristics of included studies

The geographic distribution of the 79 included studies revealed a clear bias toward the Global North, with the majority of research conducted in high-income regions. Europe contributed the most studies (32 studies), followed by Asia (24 studies) and North America (19 studies), while data from Africa, South America, and Oceania were scarce. This tendency was also apparent at the national level, with the United States (17 studies), Germany (10 studies), and Japan (9 studies) dominating the relevant literature (Fig. 2). The geographic imbalance suggested that current exposure data may not adequately reflect the risks faced by children in low- and middle-income countries, where indoor air pollution is often more severe. The study designs were predominantly cross-

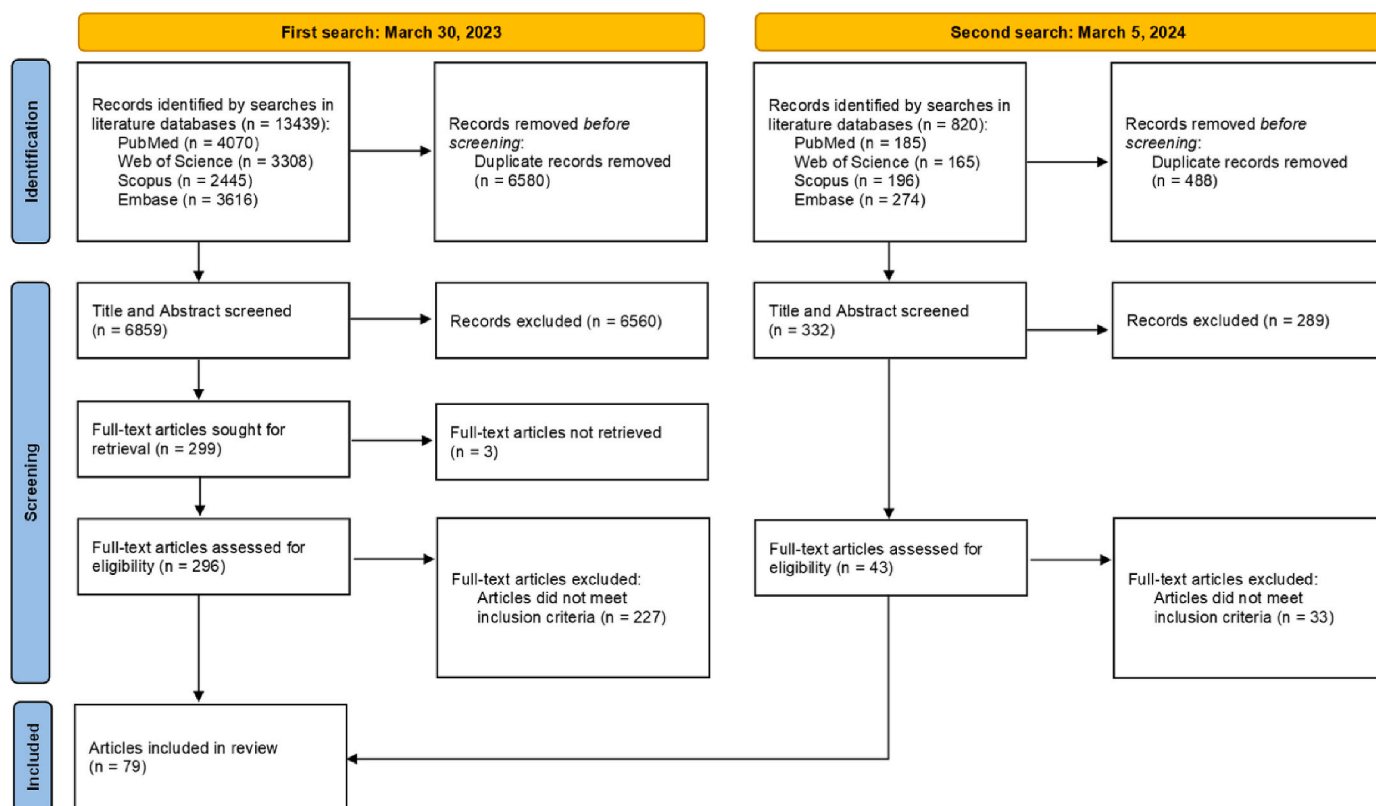


Fig. 1. PRISMA flow diagram of the systematic study selection process. The diagram outlines the identification, screening, eligibility, and inclusion phases for the systematic review. Data were aggregated from four electronic databases across two search periods (March 2023 and March 2024), ultimately including 79 eligible studies.

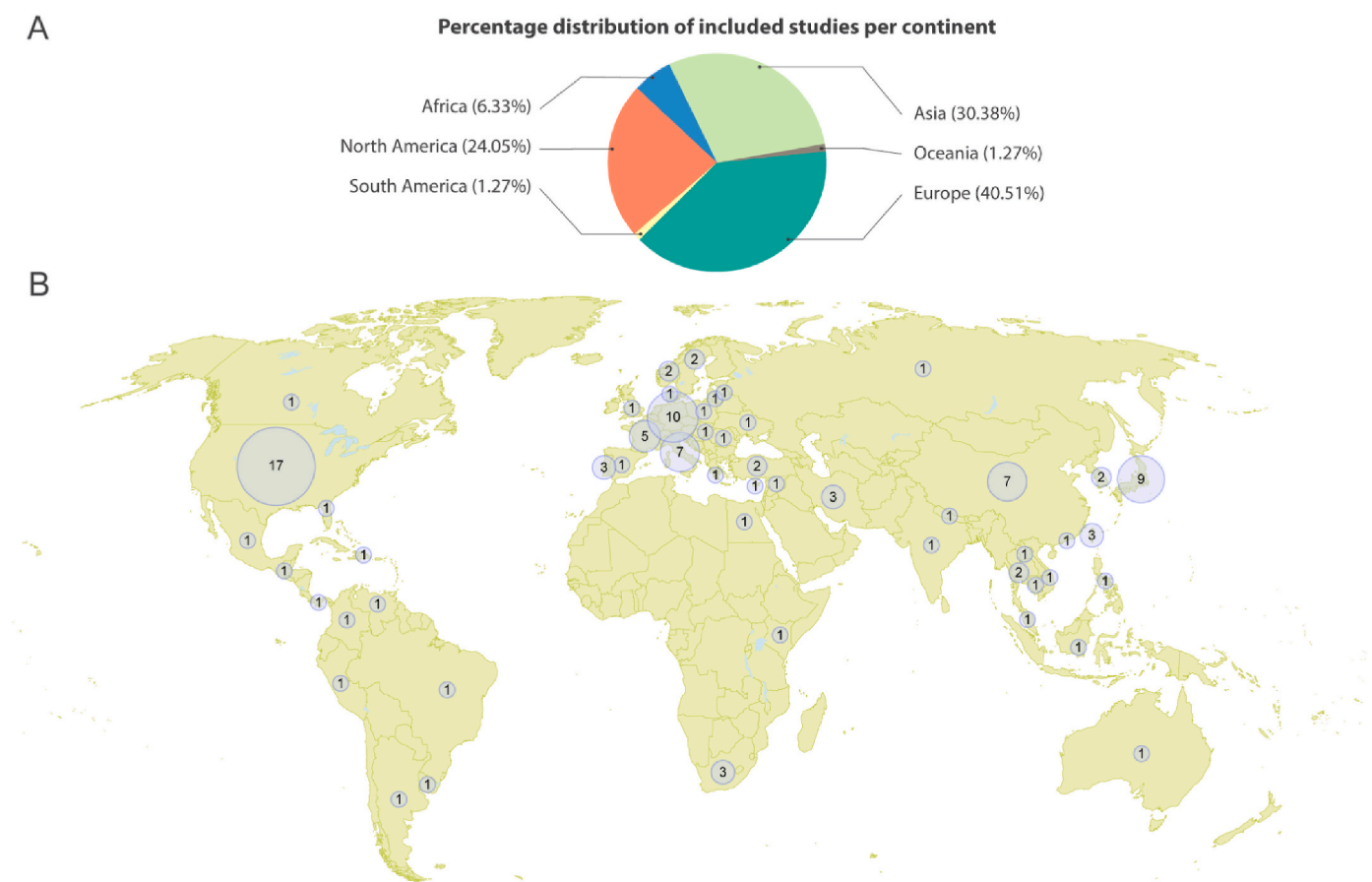


Fig. 2. Geographical distribution of included studies. (A) Number of studies per continent. (B) Number of studies per country. Percentages indicate the proportion of the total unique studies ($n = 79$). The data show a significant geographic bias toward high-income regions in the Global North (Europe, Asia, North America), with a notable scarcity of data from the Global South (Africa, South America, Oceania). Note: Cumulative percentages exceed 100% as multicentre studies conducted across multiple continents/countries were counted for each respective location.

sectional (46 studies) (Fig. 3a), which provided a snapshot of exposure but had limited ability to establish associations or track temporal changes compared to the 24 longitudinal cohort studies identified.

Although children spend most of their waking hours in educational

settings, the existing literature mainly focusses on the home environment. Sixty-seven studies assessed exposure in the home environment, whereas only 12 studies investigated the classroom environment, and only three studies integrated assessments of both. This disparity does

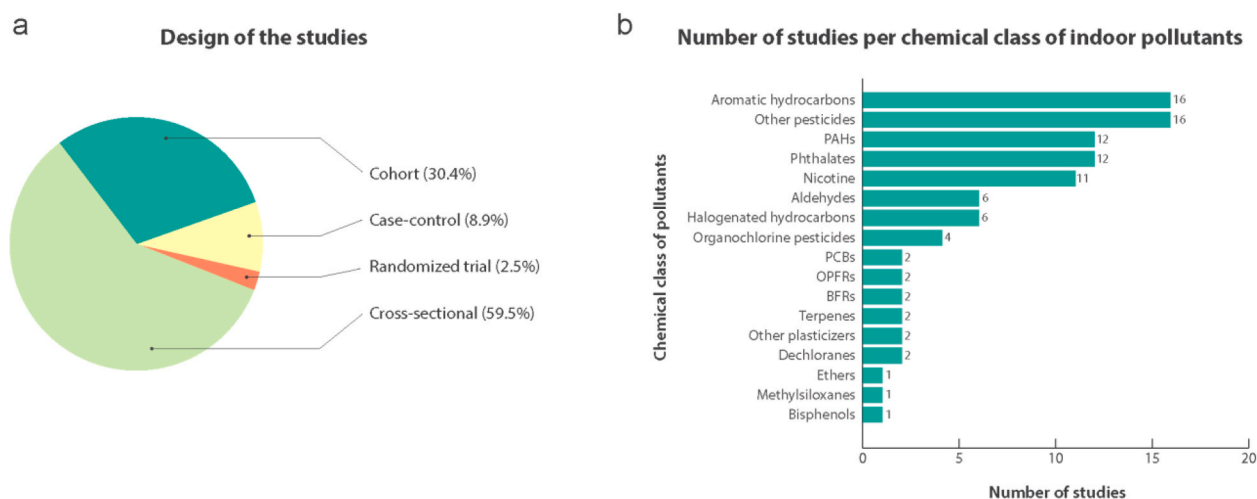


Fig. 3. Methodological characteristics of included studies. (a) Distribution of study designs. It highlights the predominance of cross-sectional studies (58%). (b) Frequency of studies investigating chemical groups. Research focus remains heavily on traditional pollutants (e.g. aromatic hydrocarbons, PAHs) compared to emerging pollutants (e.g., non-phthalate plasticizers). Note: Cumulative percentages exceed 100% as some individual studies employed mixed designs or assessed multiple chemical groups ($n = 79$).

vary by pollutant category; VOCs investigations were more evenly distributed between different settings, while SVOCs investigations were almost exclusively restricted to home environments (Fig. 4). This inequality highlights a significant gap in understanding of children's cumulative exposure, particularly to SVOCs, especially considering that pollutant concentrations in schools are often higher than in home environments due to higher occupancy density and insufficient ventilation (Sadrizadeh et al., 2022).

Regarding the study population, while some studies targeted large-scale, general population cohorts (Conrad et al., 2008), (Schwedler et al., 2020a), (Ketema et al., 2023), (Ketema et al., 2021), a significant portion of the studies explicitly focused on vulnerable groups of children to address specific susceptibility issues. For example, Galvez et al. (2018) specifically studied children living in low-income urban settings to assess how community factors influence chemical exposures, while Greenwald et al. (2013) recruited a group of asthmatic children attending schools near major border crossings to assess their respiratory responses to traffic-related pollution.

The biomarkers which were investigated in the included studies reflected a strong emphasis on “traditional” indoor air pollutants, potentially overlooking emerging pollutants. Aromatic hydrocarbons, particularly BTEX compounds, were the most extensively studied pollutants (16 studies), followed by polycyclic aromatic hydrocarbons (PAHs) and phthalates (both 12 studies). They still are of significant concern due to their known toxicity and prevalence in urban environments. In contrast, data on emerging chemicals of concern, such as organophosphate flame retardants (OPFRs) and non-phthalate plasticizers, were limited to only two and one studies, respectively (Fig. 3b). The methods to quantify these internal doses relied heavily on non-invasive matrices, with urine being the most common biological matrix (55 studies), followed by blood (15 studies). In terms of analysis, gas chromatography (GC) and liquid chromatography (LC) coupled with mass spectrometry (MS) were the main techniques employed, but heterogeneity in specific biomarkers and adjustment methods (e.g., creatinine correction) continues to pose challenges for direct comparison across studies.

3.2. Methodological overview of biomonitoring and environmental assessment

To comprehensively evaluate exposure assessment strategies, the following sections synthesize findings across the 79 included studies, categorised by chemical group (Fig. 3b). Detailed study characteristics and data are available in Table S4–S8.

Across the included studies, urine was the predominant biological matrix ($n = 55$), favoured for its non-invasive collection in school-age population, followed by blood ($n = 15$), exhaled breath ($n = 9$), and hair ($n = 5$) (Fig. 5). To interpret these internal doses, 45 studies (57%) performed concurrent environmental measurements. The environmental assessment strategies revealed a significant reliance on passive air sampling ($n = 29$) over active pump-assisted air sampling ($n = 10$) (Fig. 6), reflecting a methodological trade-off between logistical feasibility and temporal resolution. While 37 studies reported statistical associations between environmental concentrations and biomarkers (Table S8), the strength of these associations varied significantly depending on the type of pollutants, sampling duration, and the inclusion of non-inhalation pathways like dust ingestion.

The following subsections evaluate these methodological approaches for each major pollutant group, integrating the analyses of Biomarkers of Exposure (BoEXs), Biomarkers of Effect (BoEFs), and analytical and environmental assessment to identify best practices for future research.

3.2.1. Volatile organic compounds (VOCs)

3.2.1.1. Aromatic hydrocarbons (BTEX compounds). Sixteen studies investigated exposure to BTEX compounds, making it the most studied VOC group. Urine is the predominant matrix (utilised in 9 studies) (Barbieri et al., 2002), (Boniardi et al., 2023), (Cheng et al., 2023), (Chen et al., 2018), (Minoia et al., 1996), (Pilia et al., 2021), (Protano et al., 2012), (Ruchirawat et al., 2007), (Tabatabaei et al., 2022a) and is established as the standard for assessing children's exposure to aromatic hydrocarbons due to its non-invasive collection method (Cheng et al., 2023). The selection of specific urinary BoEXs for benzene involves a trade-off between sensitivity and specificity. Trans,trans-muconic acid (t,t-MA) is mainly utilised ($n = 2$) due to its high sensitivity, but its reliability is often compromised by dietary confounders, such as sorbic acid in food preservatives (Barbieri et al., 2002). Conversely, S-phenylmercapturic acid (S-PMA) was analysed in 3 studies, which offers high specificity to benzene but often lacks the sensitivity required for school-age children exposed to low levels. For instance, in a study of school-aged children in Taiwan, S-PMA was largely undetectable, whereas t,t-MA was frequently quantified (Cheng et al., 2023).

Distribution of the investigated survey sites for VOCs and SVOCs

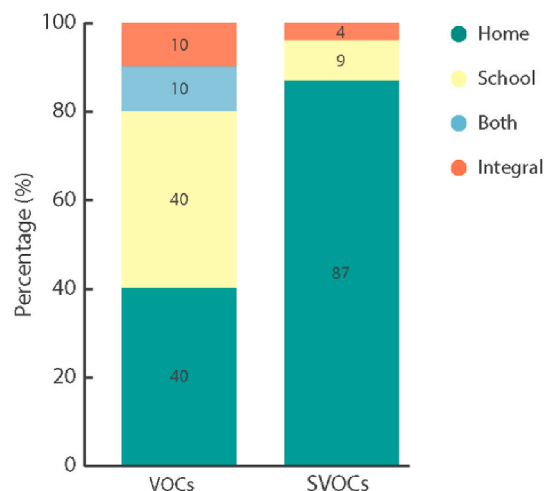


Fig. 4. Percentage distribution of survey sites by pollutant categories. The comparison highlights a critical methodological gap regarding educational settings. VOCs studies show an even distribution between home and school environments, while SVOCs studies are largely restricted to home settings, limiting our understanding of SVOCs exposure in classrooms.

Distribution of the studied biological matrices

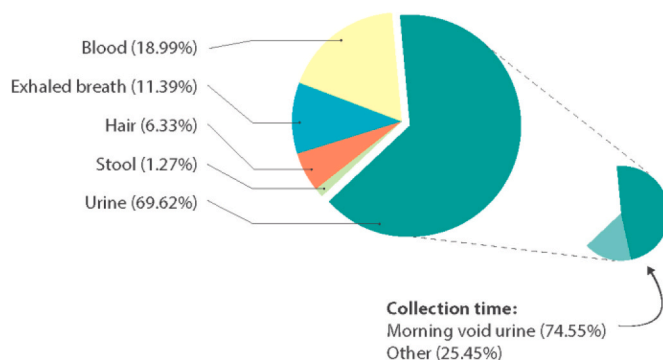


Fig. 5. Frequency of biological matrices utilised across the 79 included studies. Studies analysing multiple matrices were counted for each distinct matrix type. Urine (69.62%) serves as the popular matrix for assessing exposure, followed by blood (18.99%). Exhaled breath and hair represent novel non-invasive alternatives.

Number of studies conducting environmental assessments for each chemical group

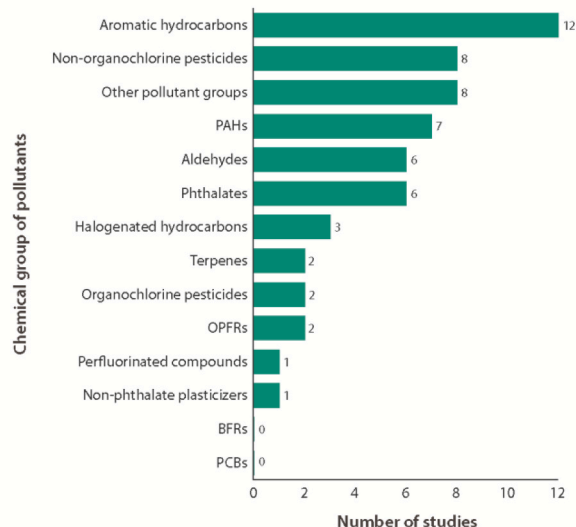


Fig. 6. Prevalence of concurrent environmental assessments by chemical group. Bars represent the number of studies performing concurrent environmental sampling alongside biomonitoring for each chemical group. Studies investigating multiple chemical groups were counted separately for each group.

Consequently, recent methodologies have turned to the detection of urinary unmetabolized BTEX, which were investigated in 8 studies and showed 100% detection rates in school-aged children and successfully differentiated between exposed and unexposed groups (Boniardi et al., 2023), (Tabatabaei et al., 2022b).

To validate the health impact of these pollutants, seven studies paired exposure data with physiological indicators of airway inflammation and oxidative stress, namely BoEF. Exhaled nitric oxide (eNO) is a marker of eosinophilic airway inflammation and the most studied BoEF ($n = 3$) used to demonstrate the acute respiratory responses of BTEX exposure. Specifically, an increase in the interquartile range of BTEX compounds was significantly associated with a 1–5% increase in eNO levels among asthmatic children (Greenwald et al., 2013). Lung function tests also corroborated the impact of these compounds, with a significant decrease in FEV1 associated with exposure to toluene and ethylbenzene. Since indoor concentrations of aromatic compounds were higher than outdoor concentrations, these findings highlight the obstructive effects of indoor emission sources on the respiratory system (Martins et al., 2012). Furthermore, oxidative stress markers to DNA, such as 8-hydroxy-2'-deoxyguanosine (8-OHdG), provide evidence of genotoxic effects at low exposure levels. A study from Italy found that urinary S-PMA was significantly correlated with the excretion of 8-OHdG, linking internal dose of benzene directly to oxidative DNA damage even if airborne levels were below regulatory limits (Pilia et al., 2021).

From an analytical perspective, the literature generally agreed that advanced chromatography can effectively detect low-level environmental exposures. For biological samples, gas chromatography-mass spectrometry (GC-MS), usually combined with headspace solid-phase microextraction (HS-SPME), was the standard for quantifying urinary unmetabolized BTEX (Boniardi et al., 2023), (Minoia et al., 1996), (Pilia et al., 2021), (Protano et al., 2012), (Tabatabaei et al., 2022a), while liquid chromatography-tandem mass spectrometry (LC-MS/MS) was required to achieve necessary sensitivity limits for polar metabolites like t,t-MA (Barbieri et al., 2002), (Cheng et al., 2023) and S-PMA (Cheng et al., 2023), (Chen et al., 2018), (Pilia et al., 2021) (Cheng et al., 2023). Environmental concentrations were assessed in 12 studies (Greenwald et al., 2013), (Barbieri et al., 2002), (Boniardi et al., 2023), (Chen et al.,

2018), (Minoia et al., 1996), (Pilia et al., 2021), (Ruchirawat et al., 2007), (Martins et al., 2012), (Erdei et al., 2003), (Garcia et al., 2021), (Scheepers et al., 2010), (Madureira et al., 2015a). Three studies (Chen et al., 2018), (Scheepers et al., 2010), (Madureira et al., 2015b) employed active air sampling using pumps and adsorption media (e.g., TENAX tubes) to capture BTEX compounds (Chen et al., 2018), yet passive diffusion samplers ($n = 8$) (Greenwald et al., 2013), (Barbieri et al., 2002), (Boniardi et al., 2023), (Minoia et al., 1996), (Pilia et al., 2021), (Ruchirawat et al., 2007), (Martins et al., 2012), (Erdei et al., 2003), such as the Radiello samplers, were the predominant method due to their lightweight and non-intrusive nature (Barbieri et al., 2002), (Boniardi et al., 2023), (Minoia et al., 1996). Analytically, GC-MS was the most frequent technique ($n = 6$) (Greenwald et al., 2013), (Barbieri et al., 2002), (Boniardi et al., 2023), (Chen et al., 2018), (Pilia et al., 2021), (Madureira et al., 2015a) for quantifying environmental samples, with GC-FID as a valid alternative utilised in 4 studies (Minoia et al., 1996), (Ruchirawat et al., 2007), (Erdei et al., 2003), (Scheepers et al., 2010). The correlation between air samples and internal biomarkers remains inconsistent across methodologies. In studies with active air sampling, researchers observed that children living near coal-chemical industries exhibited significantly higher urinary BTEX concentrations compared to controls, aligning with elevated indoor concentrations (Chen et al., 2018). On the other hand, the results were mixed for passive sampling, some studies reported significant positive correlations between airborne benzene and urinary benzene ($r = 0.31$) or S-PMA ($r = 0.379$) (Boniardi et al., 2023), (Pilia et al., 2021), while others indicated that passive air samples had a weak explanatory power for the variance of VOC concentrations in blood. This variability is likely attributed to the rapid metabolism of these compounds and the mismatch between the short-term nature of biological sampling, and the longer integration times required for passive air samplers (ranging from 16 h to one week) (Boniardi et al., 2023), (Pilia et al., 2021), (Sexton et al., 2005).

3.2.1.2. VOCs derived from indoor sources (Aldehydes, halogenated hydrocarbons, terpenes). The selection of biological matrices for indoor-sourced VOCs depends heavily on the metabolic pathway and volatility of the compound. Across the 11 studies (Galvez et al., 2018), (Greenwald et al., 2013), (Martins et al., 2012), (Erdei et al., 2003), (Madureira et al., 2015a), (Madureira et al., 2015b), (Sexton et al., 2005), (Andra et al., 2015), (Storm et al., 2011), (Flamant-Hulin et al., 2009), (Franklin et al., 2000) investigating this group, urine and exhaled breath were the primary matrices. For halogenated compounds like 1, 4-dichlorobenzene (1,4-DCB), urine was a preferred matrix due to the high detection frequency of its specific metabolite, 2,5-dichlorophenol (2,5-DCP), which correlates significantly ($r = 0.757$) with airborne concentrations in the home (Yoshida et al., 2021a). For highly volatile compounds such as tetrachloroethylene ($n = 3$) (Madureira et al., 2015b), (Sexton et al., 2005), (Storm et al., 2011), studies directly measured the parent compounds in exhaled breath and noted that samples must be corrected for alveolar carbon dioxide to account for physiological variability. Blood was also an essential matrix to assess internal dose in children (Storm et al., 2011), as air measurements were found to be strong predictors of 1,4-DCB levels ($R^2 = 0.79$) and moderate predictors of tetrachloroethylene levels ($R^2 = 0.19$) in blood (Sexton et al., 2005). While breath analysis allows the detection of volatile parent compounds, urinary metabolites like 2,5-DCP offer a more practical approach to assess exposure to indoor sources, such as moth repellents and toilet deodorisers, as these metabolites reflect integrated exposure and are readily collected from school-age populations (Barbieri et al., 2002), (Yoshida et al., 2021a). For aldehydes and terpenes, no specific BoEF were quantified in the included studies.

Clinical parameters could also show associations between indoor chemical emissions and respiratory irritation (Franklin et al., 2000). Exhaled nitric oxide (eNO), the most frequently used BoEF ($n = 6$)

(Flamant-Hulin et al., 2009), (Madureira et al., 2015a), (Madureira et al., 2015b), (Franklin et al., 2000), (Martins et al., 2012), (Greenwald et al., 2013) reflecting eosinophilic airway inflammation (Babadi et al., 2022), was significantly elevated in healthy children living in homes with formaldehyde concentrations exceeding 50 ppb (Franklin et al., 2000). Similarly, in school environments, higher exposures to ubiquitous indoor aldehydes (formaldehyde and acetaldehyde) were associated with increased eNO levels in both asthmatic and non-asthmatic children. (Madureira et al., 2015b), (Flamant-Hulin et al., 2009). However, lung function tests revealed a distinct pattern of effect, with studies finding no significant association between formaldehyde exposure and decreased FEV1. This divergence highlighted that the aldehydes are primarily linked to airway inflammation rather than lung function (Martins et al., 2012). No significant association between indoor terpene exposure (e.g., d-limonene and α -pinene) and inflammatory effects was observed in the general school-aged population (Madureira et al., 2015b). Functional assessments identified a distinct non-respiratory effect for tetrachloroethylene; elevated indoor levels were associated with decreased visual contrast sensitivity, indicating a potential subclinical neurotoxic effect on the central nervous system rather than the respiratory system (Storm et al., 2011).

To characterise indoor concentrations of these diverse pollutants, researchers predominantly employed passive diffusive samplers (e.g., Radiello). For aldehydes ($n = 6$) (Martins et al., 2012), (Erdei et al., 2003), (Madureira et al., 2015a), (Madureira et al., 2015b), (Flamant-Hulin et al., 2009), (Franklin et al., 2000), specific cartridges containing 2,4-dinitrophenylhydrazine (DNPH) were used, and analysed by High-Performance Liquid Chromatography (HPLC) coupled with an ultraviolet (UV) detector (Madureira et al., 2015a), (Madureira et al., 2015b), (Franklin et al., 2000) or photometric method (Erdei et al., 2003). For other indoor VOCs, such as halogenated hydrocarbons ($n = 3$) (Greenwald et al., 2013), (Madureira et al., 2015b), (Storm et al., 2011) and terpenes ($n = 2$) (Greenwald et al., 2013), (Madureira et al., 2015b), studies utilised Tenax TA tubes or general diffusive samplers analysed by GC-MS to determine indoor time-weighted average (TWA) during the sampling period (Conrad et al., 2008), (Greenwald et al., 2013), (Franklin et al., 2000). Source tracking identified distinct indoor drivers: moth repellents were the primary source of 1,4-DCB (Yoshida et al., 2021a), while co-located dry cleaners drove tetrachloroethylene concentrations significantly above background levels (Storm et al., 2011). For terpenes, d-limonene presented indoor/outdoor concentration ratio greater than 6, confirming indoor sources (e.g., cleaning activities) as the primary contributors to exposure (Madureira et al., 2015b). While passive air sampling effectively demonstrated that indoor concentrations of these pollutants significantly exceeded outdoor levels due to internal sources (Storm et al., 2011), the reliance on aggregate averages limited the ability to capture short-term peak exposures caused by episodic activities like cleaning or renovation, which are likely the major drivers of acute respiratory effects. (Madureira et al., 2015a), (Storm et al., 2011).

3.2.2. Semi-volatile organic compounds (SVOCs)

3.2.2.1. Polycyclic aromatic hydrocarbons (PAHs). Urine was and still is the gold standard matrix for assessing children's exposure to PAHs. Across the 12 studies investigating this group, 11 studies (Chen et al., 2018), (Ruchirawat et al., 2007), (Tabatabaei et al., 2022b), (Yoshida et al., 2021a), (Bae et al., 2010), (CIRILLO et al., 2006), (Heudorf and Angerer, 2001a), (Jung et al., 2014), (Peters et al., 2017), (Kim et al., 2023), (Suter et al., 2018) utilised urine due to non-invasive collection and the rapid metabolism of these compounds (Chen et al., 2018), (Tabatabaei et al., 2022b). There was a strong consensus ($n = 9$) (Chen et al., 2018), (Ruchirawat et al., 2007), (Tabatabaei et al., 2022b), (Bae et al., 2010), (CIRILLO et al., 2006), (Heudorf and Angerer, 2001a), (Jung et al., 2014), (Kim et al., 2023), (Suter et al., 2018) on using

1-hydroxypyrene (1-OHP) as the main surrogate BoEX for total PAH exposure because pyrene is ubiquitous in PAH mixtures and 1-OHP acts as a sensitive, integrated indicator of exposure from multiple sources (Ruchirawat et al., 2007), (Suter et al., 2018). However, researchers also emphasized the necessity of measuring hydroxylated naphthalene metabolites to capture specific exposure profiles. For instance, in children living near coal chemical industries or exposed to hookah smoke, urinary 1-Naphthol (1-OH-NAP) and 2-Naphthol (2-OH-NAP) levels were significantly elevated, and together with 1-OHP, they served as key indicators between the exposed and unexposed groups (Chen et al., 2018), (Tabatabaei et al., 2022b).

Four studies (Ruchirawat et al., 2007), (Tabatabaei et al., 2022b), (Madureira et al., 2015b), (Bae et al., 2010) validated the physiological effects of PAHs by linking internal dose to genotoxicity and oxidative stress. A study of school-aged children in Bangkok found that, compared to rural controls, high-dose exposure not only led to elevated urinary 1-OHP, but also resulted in a five-fold increase in DNA adducts in lymphocytes and significantly higher DNA strand breaks (assessed via the Comet assay), which indicated that internal dose was directly associated with genomic instability (Ruchirawat et al., 2007). Two studies validated the link between PAH exposure and oxidative stress; urinary 1-OHP was significantly associated with urinary MDA level in school-aged children, demonstrating that PAHs act synergistically with particulate matter to induce oxidative cell damage (Bae et al., 2010). Similarly, regression analyses in children exposed to hookah smoke confirmed that 2-OH-NAP was a significant predictor of elevated MDA levels, establishing a direct pathway between specific PAH uptake and lipid peroxidation (Tabatabaei et al., 2022b). eNO was utilised in one study to assess airway inflammation related to PAH exposure (Madureira et al., 2015b).

The environmental drivers of PAH exposure vary significantly by region, distinguishing between outdoor traffic emissions and indoor combustion sources. In urban Bangkok, traffic was the primary driver, with environmental PAH levels at school roadsides measuring 30-fold higher than in rural areas (Ruchirawat et al., 2007). In northern China and specific residential settings, indoor sources such as heating systems and environmental tobacco smoke (ETS) were the main drivers, resulting in indoor PAH concentrations exceeding outdoor levels (Chen et al., 2018), (Willers et al., 2005). Seven studies conducted concurrent environmental measurements. Unlike VOC studies that relied on passive samplers, active air sampling using pumps was the dominant method for PAHs ($n = 6$) (Chen et al., 2018), (Ruchirawat et al., 2007), (Madureira et al., 2015b), (CIRILLO et al., 2006), (Heudorf and Angerer, 2001a), (Jung et al., 2014). Only one study used passive sampling (Yoshida et al., 2021a). This methodological preference reflects the need to capture PAHs bound to particulates. Analytically, High-Performance Liquid Chromatography with Fluorescence Detection (HPLC-FD) ($n = 3$) (Ruchirawat et al., 2007), (Bae et al., 2010), (CIRILLO et al., 2006) was utilised for 1-OHP detection due to its high sensitivity, while recent studies increasingly employed GC-MS or LC-MS/MS to simultaneously quantify a broader spectrum of metabolites, including hydroxylated naphthalene and phenanthrenes (Chen et al., 2018), (Tabatabaei et al., 2022b). GC-MS was also the most frequent technique ($n = 5$) (Chen et al., 2018), (Madureira et al., 2015b), (Yoshida et al., 2021a), (Heudorf and Angerer, 2001a), (Jung et al., 2014) for the quantitative analysis of environmental samples.

3.2.2.2. Plasticizers and consumer additives (Phthalates, non-phthalates plasticizers, bisphenols, methylsiloxanes, and ethers). Urine was established as the gold standard matrix for assessing exposure to non-persistent plasticizers and consumer additives due to their rapid metabolism and excretion (Ketema et al., 2023), (Gys et al., 2020). Across the 16 studies (Schwedler et al., 2020a), (Ketema et al., 2023), (Ketema et al., 2021), (Galvez et al., 2018), (Bonardi et al., 2023), (Babadi et al., 2022), (Gys et al., 2020), (Ait Bamai et al., 2016), (Becker et al., 2004),

(Hsu et al., 2012), (Just et al., 2015), (Liao et al., 2018), (Schwedler et al., 2020b), (Sears et al., 2024), (Yoshida et al., 2020), (Guo et al., 2021) investigating this cluster, the vast majority ($n = 14$) (Schwedler et al., 2020a), (Ketema et al., 2023), (Ketema et al., 2021), (Galvez et al., 2018), (Boniardi et al., 2023), (Babadi et al., 2022), (Gys et al., 2020), (Ait Bamai et al., 2016), (Becker et al., 2004), (Hsu et al., 2012), (Just et al., 2015), (Liao et al., 2018), (Schwedler et al., 2020b), (Yoshida et al., 2020) utilised urine samples. For phthalates ($n = 12$) (Schwedler et al., 2020a), (Ketema et al., 2021), (Galvez et al., 2018), (Babadi et al., 2022), (Ait Bamai et al., 2016), (Becker et al., 2004), (Hsu et al., 2012), (Just et al., 2015), (Liao et al., 2018), (Schwedler et al., 2020b), (Sears et al., 2024), (Yoshida et al., 2020) and non-phthalate alternatives (e.g., DINCH, $n = 2$) (Schwedler et al., 2020a), (Ketema et al., 2023), a critical methodological necessity emerged regarding the selection of specific metabolites to ensure data validity. Although primary monoesters (e.g., MEHP) were measured in the past, they are susceptible to abiotic formation during sampling and storage, leading to false positive results (Becker et al., 2004). To avoid this, current methods prioritise the quantification of oxidized secondary metabolites, such as 5OH-MEHP and 5oxo-MEHP for DEHP, or 5cx-MEPTP for DEHTP, because these compounds are exclusively generated through human metabolism (Ketema et al., 2023), (Becker et al., 2004). This urinary approach was also successfully applied to bisphenols ($n = 1$) (Gys et al., 2020) and ethers ($n = 1$) (Boniardi et al., 2023). For instance, bisphenol A (BPA) was detected in 89% of urine samples in a cohort of Japanese children, with alternative bisphenols (BPF and BPS) also showing detection rates exceeding 50% (Gys et al., 2020). A notable methodological exception was methylsiloxanes ($n = 1$) (Guo et al., 2021), for which plasma is the primary matrix for assessing internal dose, with cyclic congeners (D4–D6) frequently detected in exposed children (Guo et al., 2021).

Three studies (Babadi et al., 2022), (Gys et al., 2020), (Sears et al., 2024) validated the physiological impact of these consumer additives using markers of oxidative stress and inflammation. For bisphenols, recent biomonitoring utilised urinary oxidative stress markers, such as 8-OHdG and hexanoyl-lysine (HEL), to evaluate potential cellular damage (Gys et al., 2020). A longitudinal study of Japanese children identified that the substitute Bisphenol F (BPF) was significantly associated with higher concentrations of 8-OHdG (Gys et al., 2020). This finding suggested that structural analogues used to replace BPA may exert similar or more pronounced genotoxic effects via oxidative stress pathways (Gys et al., 2020). For phthalates, the validation of health risks focused on markers of airway and systemic inflammation, such as eNO and urinary leukotriene E4 (uLTE4) (Babadi et al., 2022). In a longitudinal assessment of children with asthma, urinary phthalate metabolites, specifically those of di(2-ethylhexyl) phthalate (DEHP) and diethyl phthalate (DEP), were significant predictors of increased eNO and uLTE4 levels, with uLTE4 showing consistent positive associations across all tested metabolites (Babadi et al., 2022). These physiological BoEFs were more sensitive to phthalate-induced inflammatory processes than caregiver-reported symptoms or standardized asthma control tests, highlighting their utility in capturing subclinical pathophysiological changes driven by environmental plasticizer exposure (Babadi et al., 2022).

The analytical paradigm for assessing urinary metabolites of phthalates and alternative plasticizers (e.g., DEHTP, DINCH) and bisphenols underwent a methodological shift. While GC-MS is a valid approach utilised in 4 studies (Schwedler et al., 2020a), (Gys et al., 2020), (Ait Bamai et al., 2016), (Yoshida et al., 2020), LC-MS/MS became more popular and was employed in 8 studies (Schwedler et al., 2020a), (Ketema et al., 2023), (Ketema et al., 2021), (Babadi et al., 2022), (Becker et al., 2004), (Just et al., 2015), (Liao et al., 2018), (Schwedler et al., 2020b). This preference reflects the advantages of LC-MS/MS, which can directly analyse polar metabolites without derivatisation and chromatographically separate structural isomers (e.g., DEHTP) and complex mixtures (e.g., DINCH) (Ketema et al., 2023), (Schwedler et al., 2020b). Regardless of the interface, the use of isotope-dilution

techniques emerged as the rigorous standard across methodologies to ensure the high sensitivity required to detect trace-level exposures for biomonitoring in children (Ketema et al., 2023), (Babadi et al., 2022), (Gys et al., 2020), (Just et al., 2015), (Liao et al., 2018), (Schwedler et al., 2020b). Conversely, for volatile methylsiloxanes (e.g., D4, D5, D6), the analytical technique shifted to GC-MS to effectively quantify these compounds in plasma and environmental samples (Guo et al., 2021). Regarding environmental sampling, a key finding is that settled dust sampling (specifically from floors) had greater predictive value for internal exposure compared to air sampling. Studies comparing sampling locations demonstrated that floor dust is a better predictor of internal dose compared to multi-surface dust (collected >35 cm above the ground) or indoor air (Ait Bamai et al., 2016). For example, while vinyl flooring is a known source of butyl benzyl phthalate (BBzP) in indoor air (Just et al., 2015), the correlation between daily intake and environmental levels of heavy phthalates like DEHP and BBzP is significantly stronger for floor dust (Ait Bamai et al., 2016). This distinction validated the “dust ingestion” pathway as a primary route of exposure for children, driven by their hand-to-mouth behaviours and frequent contact with floor surfaces where these heavier compounds accumulate (Ait Bamai et al., 2016).

3.2.2.3. Pesticides (Organochlorines and non-organochlorines). Methodological approaches for pesticide biomonitoring are determined by the physicochemical properties and metabolic pathways of the specific class of compounds. Across the 19 studies investigating this cluster, the choice of matrix varied significantly. For persistent organochlorine pesticides (OCs) ($n = 4$) (Lepetit et al., 2024), (Martínez et al., 2012), (Seifert et al., 2000), (Tagne-Fotso et al., 2023) such as dichlorodiphenyltrichloroethane (DDT) and dichlorodiphenyldichloroethylene (DDE), blood serum remained the requisite matrix ($n = 3$) (Lepetit et al., 2024), (Martínez et al., 2012), (Tagne-Fotso et al., 2023) because these lipophilic compounds bioaccumulate and partition into lipid-rich tissues, allowing researchers to detect significant body burdens years after environmental application (Martínez et al., 2012). In contrast, non-organochlorine pesticides ($n = 16$) (Lepetit et al., 2024), (Becker et al., 2006), (Dereumeaux et al., 2022), (English et al., 2012), (Glorennec et al., 2017), (Heudorf and Angerer, 2001b), (Khademi et al., 2023), (Lioy et al., 2000), (Morgan et al., 2008), (Mthethwa et al., 2023), (Veludo et al., 2024), (Werthmann et al., 2021), (Yoshida et al., 2022), (Zhang et al., 2015), (Aprea et al., 2000), including organophosphates (OPs) and pyrethroids, are rapidly metabolized and excreted, requiring the use of urine as the standard matrix ($n = 13$) (Becker et al., 2006), (Dereumeaux et al., 2022), (Glorennec et al., 2017), (Heudorf and Angerer, 2001b), (Lioy et al., 2000), (Morgan et al., 2008), (Mthethwa et al., 2023), (Veludo et al., 2024), (Werthmann et al., 2021), (Yoshida et al., 2021b), (Yoshida et al., 2022), (Zhang et al., 2015), (Aprea et al., 2000) for detecting metabolites like dialkyl phosphates (DAPs) or 3-phenoxybenzoic acid (3-PBA) (Glorennec et al., 2017), (Mthethwa et al., 2023). Considering that spot urine samples only capture recent exposure windows (often <24 h), hair analysis ($n = 2$) (Lepetit et al., 2024), (Khademi et al., 2023) was validated as a non-invasive alternative for assessing the cumulative chronic exposure to compounds such as chlorpyrifos, diazinon, and pyrethroids (Dereumeaux et al., 2022), (Khademi et al., 2023). Notably, a significant number of studies ($n = 6$) (Lepetit et al., 2024), (Tagne-Fotso et al., 2023), (Dereumeaux et al., 2022), (Khademi et al., 2023), (Mthethwa et al., 2023), (Veludo et al., 2024) have specifically investigated secondary exposure using these BoEXs, confirming that children are exposed to these substances not only through direct spraying, but also through contaminated clothing and dust brought into the home (Martins et al., 2012), (Lepetit et al., 2024), (Tagne-Fotso et al., 2023), (Khademi et al., 2023), (Mthethwa et al., 2023), (Veludo et al., 2024).

Two studies (Lepetit et al., 2024), (English et al., 2012) validated the health risks associated with these exposures by incorporating BoEF, with

particular attention to neurotoxicity and genotoxicity. Blood-based assays measuring acetylcholinesterase (AChE) activity were utilised to quantify neurotoxic risk, with studies demonstrating that AChE depression correlated with higher OPs exposure in children (Lepetit et al., 2024). Innovatively, researchers used hair follicle assays to link these neurotoxic markers with genotoxicity. The results showed that children with detectable OPs exposure exhibited significantly higher frequency of DNA double-strand breaks (DSBs) in follicular cells compared to non-exposed peers, thus establishing an association between pesticide exposure and genome instability (Lepetit et al., 2024). This genotoxic assessment was complemented by urinary markers of oxidative stress, such as 8-OHdG and malondialdehyde (MDA) to assess cellular damage, which showed positive associations with exposure to pyrethroids and OPs (Tabatabaei et al., 2022b).

The evolution of instrumentation reflects the chemical properties of the targets. For legacy OCs, older methodologies relied on High-Resolution Gas Chromatography-Electron Capture Detector (GC-ECD) because of their high to halogenated compounds (Osius et al., 1999), while recent studies shifted to the use of GC-MS and Gas Chromatography-High Resolution Mass Spectrometry (GC-HRMS) to ensure specificity (Martínez et al., 2012), (Tagne-Fotso et al., 2023). A similar shift occurred for modern non-organochlorines, earlier studies employed Gas Chromatography with Flame Photometric Detection (GC-FPD) for OPs (Aprea et al., 2000) or GC-MS for pyrethroids (Becker et al., 2006), LC-MS/MS became the requisite standard for quantifying polar urinary metabolites (Glorennec et al., 2017), (Morgan et al., 2008). Environmental sampling was conducted in 10 studies, with four using active (Seifert et al., 2000), (Morgan et al., 2008), (Yoshida et al., 2021b), (Yoshida et al., 2022) six using passive sampling methods (Martínez et al., 2012), (Becker et al., 2006), (Glorennec et al., 2017), (Heudorf and Angerer, 2001b), (Lioy et al., 2000), (Veludo et al., 2024) to capture pesticide residues. Methodologies utilising dust samples and surface wipes proved essential in distinguishing between agricultural drift and residential application. Significant correlations were observed between pyrethroid concentrations in floor dust and urinary metabolites, confirming that dust ingestion and dermal contact were the main secondary exposure pathways for children, particularly where indoor insecticides were used (Glorennec et al., 2017). Conversely, other studies using indoor air sampling showed that the inhalation contribution was relatively low compared to overall absorption (Yoshida et al., 2022).

3.2.2.4. Persistent and emerging industrial pollutants (PCBs, PFAS, BFRs, OPFRs, Dechlorane Plus). Across the 7 studies investigating this cluster, biological matrix selection revealed a clear divergence between legacy persistent and emerging pollutants. For persistent, bioaccumulative compounds such as polychlorinated biphenyls (PCBs, $n = 2$) (Osius et al., 1999), (Egsmose et al., 2016), brominated flame retardants (BFRs, $n = 2$) (Guo et al., 2018), (Martínez et al., 2024) and Dechlorane Plus (DPs, $n = 2$) (Guo et al., 2018), (Martínez et al., 2024), blood serum or whole blood remained the standard matrix, as these lipophilic chemicals partition between adipose tissue and the circulatory system, providing a stable measure of long-term body burden (Osius et al., 1999), (Martínez et al., 2024). However, researchers also explored alternative matrices to assess internal dose, with one study quantifying BFRs in stool (Martínez et al., 2024). Yet, for modern organophosphate flame retardants (OPFRs, $n = 2$) (Bastiaensen et al., 2019), (Kucharska et al., 2015), which are rapidly metabolized, urine was the primary matrix used to quantify specific metabolites, such as hydroxylated metabolites (HO-PFRs), to reflect recent exposure (Bastiaensen et al., 2019). Emerging methodologies have also validated the use of hair analysis in the detection of per- and polyfluoroalkyl substances (PFAS, $n = 1$) (Sears et al., 2024) and OPFRs ($n = 1$) (Kucharska et al., 2015), with hair serving as an comprehensive matrix that captures both endogenous deposition from the bloodstream and exogenous adsorption from the environment,

offering a non-invasive alternative for assessing cumulative exposure over months (Sears et al., 2024), (Kucharska et al., 2015).

Three studies confirmed the systemic toxicity of these pollutants, focusing on endocrine and stress responses. The primary endpoint was the alteration of thyroid hormone homeostasis ($n = 2$) (Osius et al., 1999), (Guo et al., 2018). In school-aged children, serum concentrations of PCBs were significantly associated with disrupted thyroid function, manifesting as a positive association between the mono-ortho congener PCB 118 and thyroid-stimulating hormone (TSH), and negative associations between higher chlorinated congeners (e.g., PCB 138, 153, 180) and free triiodothyronine (FT3) (Osius et al., 1999). Similarly, studies of children living near petrochemical complexes found that the sum of PBDEs and novel flame retardants (NFRs) was significantly associated with elevated T3 levels, an effect largely driven by high concentrations of BDE-209 (Guo et al., 2018). One study utilised hair cortisol as a BoEF of physiological stress, linking PFAS exposure to hypothalamic-pituitary-adrenal (HPA) axis dysregulation (Sears et al., 2024). This suggested that for persistent pollutants, BoEFs are crucial for detecting systemic disruption that air monitoring alone cannot reveal.

The selection of analytical instruments followed the volatility and polarity of the target analytes. GC-ECD was utilised for legacy PCBs (Osius et al., 1999), (Egsmose et al., 2016), while GC-MS was required for BFRs and DPs (Guo et al., 2018), (Martínez et al., 2024). For the more polar urinary metabolites of OPFRs, LC-MS was the essential standard method (Bastiaensen et al., 2019), (Kucharska et al., 2015). Environmental source tracking has identified settled dust, particularly from floors, as the primary predictor of exposure over indoor air measurements for these heavy, semi-volatile compounds. Studies on flame retardants have shown that urinary metabolites and hair biomarkers significantly correlate with their parent compounds in floor dust, confirming accidental dust ingestion and hand-to-mouth contact as the dominant exposure routes for children (Becker et al., 2006), (Bastiaensen et al., 2019), (Kucharska et al., 2015).

3.2.2.5. Environmental tobacco smoke and nicotine. Urinary cotinine is widely considered the “gold standard” for assessing nicotine exposure in children, particularly from environmental tobacco smoke (ETS). Across the 11 studies investigating nicotine, most studies ($n = 9$) utilised urinary cotinine due to its greater stability and specificity compared to parent nicotine (Conrad et al., 2008), (Galvez et al., 2018), (Protano et al., 2012), (Willers et al., 2005), (Butz et al., 2011a), (Butz et al., 2011b), (Kaviani et al., 2023), (Quintana et al., 2019), (Kim et al., 2009), (Thaqi et al., 2005), (Willers et al., 2004). Nicotine is rapidly metabolized with a half-life of approximately 2 h, while cotinine exhibits a significantly longer half-life in children, ranging from 16 to 20 h, making it a reliable indicator of exposure over the preceding 2 to 4 days (Butz et al., 2011a), (Butz et al., 2011b). To assess the cumulative history of long-term exposure, one study employed hair analysis (Kim et al., 2009), because nicotine accumulates during hair growth, providing a retrospective window of exposure over months. This study demonstrated that nicotine concentrations in children's hair were significantly associated with indoor air nicotine levels and parental smoking behaviours, thus distinguishing exposure levels across different regions and household conditions (Kim et al., 2009). Additionally, serum cotinine was utilised in one study to validate systemic dose (Kaviani et al., 2023).

Validating the physiological effect of ETS presents a methodological challenge. A critical negative result was reported in a study that measured urinary 8-OHdG in schoolchildren, which found that while this oxidative stress marker correlated with the benzene metabolite S-PMA, it showed no significant correlation with urinary cotinine (Pilia et al., 2021), suggesting it an unreliable BoEF for ETS exposure (Pilia et al., 2021). Therefore, researchers relied on clinical and functional outcomes to validate the health risks of ETS. In asthmatic children, the Asthma Therapy Assessment Questionnaire (ATAQ) served as a sensitive clinical indicator; for every 10-fold increase in airborne nicotine levels,

the ATAQ score increased by 0.25 points, and for every 10-fold increase in serum cotinine levels, the ATAQ score increased by 0.54 points, establishing a clear dose-response relationship (Kaviani et al., 2023). Similarly, symptom frequency was proven to be an effective morbidity metric, with urinary cotinine concentrations trending significantly higher (28.1 vs. 16.2 ng/mL) in children reporting frequent symptom days compared to those with fewer symptoms (Butz et al., 2011a). Therefore, for children's ETS exposure, current clinical assessment tools are more sensitive and valid than general oxidative stress biomarkers in determining harm.

Environmental source tracking was conducted in six studies, predominantly using passive air sampling to correlate external concentrations with internal dose (Willers et al., 2005), (Butz et al., 2011a), (Butz et al., 2011b), (Kaviani et al., 2023), (Kim et al., 2009), (Willers et al., 2004). The studies consistently found strong positive correlations between passive air sampling for nicotine (using diffusive badges) and urinary cotinine levels, validating the effectiveness of indoor air monitoring as a proxy for individual uptake (Bonardi et al., 2023), (Butz et al., 2011a). Analytically, urinary cotinine was typically quantified using isotope dilution LC-MS/MS or HPLC, which offered high sensitivity with limits of detection as low as 0.036 ng/mL, enabling the detection of low-level exposures (Protano et al., 2012), (Butz et al., 2011b). For environmental samples, such as passive air badges, GC remained the standard method. Three studies utilised Nitrogen-Phosphorus Detection (NPD) for its specificity to nicotine (Butz et al., 2011a), (Butz et al., 2011b), (Kim et al., 2009), while other studies did not mention the detectors used (Willers et al., 2005), (Kaviani et al., 2023), (Willers et al., 2004).

4. Discussion

4.1. Methodological heterogeneity and the need for standardization

This systematic review highlights a critical barrier in the field of children's exposure assessment: the lack of standardized protocols. While robust analytical methods like GC-MS and LC-MS improved sensitivity, the variability in sample collection precludes a valid global meta-analysis across studies.

There is a significant lack of consensus on urine collection protocols. For examples, Mazhitova et al. used 24-h urine collection to capture a full day's exposure (Osius et al., 1999), Morgan et al. and Ketema et al. relied on first-morning voids (FMV) (Ketema et al., 2021), (Morgan et al., 2008). Veludo et al. collected spot samples during school breaks (Veludo et al., 2024), and Protano et al. collected samples before bedtime (Protano et al., 2012). This variability critically affects the comparability of results for short-half-life VOC metabolites, such as S-PMA. Pilia et al. found statistically significant differences between morning and evening urinary benzene concentrations, attributing evening levels to cumulative daytime exposure (Pilia et al., 2021). Consequently, studies relying on single-spot urine samples without standardised collection times fail to adequately reflect the variability of daily exposure or distinguish between school and home exposure sources (Veludo et al., 2024).

The inconsistencies in urinary dilution adjustment methods across studies, particularly the use of creatinine versus specific gravity (SG), present a methodological challenge for comparisons of school-age populations. While creatinine adjustment is commonly used for adults (Ketema et al., 2021), it is methodologically problematic for children aged 6 to 12 years, as creatinine excretion is directly dependent on muscle mass, which varies significantly with age, gender, and ethnicity (Andra et al., 2015). Morgan et al. explicitly stated that creatinine correction is "likely not a reliable adjustment measure for young children" due to these physiological variations (Morgan et al., 2008). In contrast, SG offers a more stable measure of dilution that is largely independent of children's physiological variables (Kucharska et al., 2015). The lack of uniformity in adjustment methods introduces systematic

bias, thereby compromising dose estimation and risk assessment when directly comparing populations from different studies.

To facilitate global cross-study comparisons, future studies must prioritise a harmonised sampling framework, such as the COPHES/DEMOCOPHES protocol and the HBM4EU initiative in Europe, which mandate timed collection windows and consistent adjustment methods (Schindler et al., 2014), (Gilles et al., 2021).

4.2. Critical evaluation of matrices and exposure pathways

The selection of biological matrices in exposure assessment reflects the necessary trade-off between physicochemical suitability and the practical constraints of sampling vulnerable populations. Urine remains the dominant matrix for assessing children's exposure to both VOCs and non-persistent SVOCs due to the rapid metabolism of these chemicals and the non-invasiveness of collection. For VOCs like BTEX compounds, urine provides a reliable medium for quantifying specific metabolites such as S-PMA and t,t-MA, which serve as sensitive BoEXs for low-level environmental exposure (Barbieri et al., 2002), (Tabatabaei et al., 2022a). Similarly, for rapidly metabolized SVOCs, including phthalates, OPFRs, and pyrethroids, urinary metabolites are the standard BoEXs for estimating daily intake and cumulative exposure risks (Ketema et al., 2023), (Werthmann et al., 2021), (Bastiaensen et al., 2019). However, the utility of alternative matrices diverges based on physicochemical properties. For volatile compounds, exhaled breath has been validated as an effective alternative for measuring parent compounds, reflecting recent inhalation exposure and alveolar concentrations of pollutants like benzene and tetrachloroethylene (Scheepers et al., 2010), (Storm et al., 2011). In contrast, for persistent lipophilic SVOCs such as PCBs, blood plasma remains the requisite matrix to capture the cumulative body burden and long-term exposure that are undetectable in urine (Egsmose et al., 2016), (Sexton et al., 2005).

A critical synthesis of the reviewed studies reveals a fundamental difference in the environmental drivers of internal dose between VOCs and SVOCs. For VOCs, the internal dose is primarily driven by airborne concentrations, confirming inhalation as the dominant exposure pathway. As such, Tabatabaei et al. confirmed inhalation as the main exposure route for BTEX and established a direct link between hookah smoke emissions and urinary biomarkers (Tabatabaei et al., 2022a). Similarly, Sexton et al. demonstrated that air measurements explained a significant proportion of the variance of VOC concentrations in blood, particularly for compounds like 1,4-DCB (Sexton et al., 2005). On the other hand, for SVOCs, the internal dose is strongly associated with settled dust, implicating accidental ingestion as a key exposure pathway. Bastiaensen et al. found significant correlations between PFRs (e.g. TBOEP and TCIPP) in house dust and their corresponding urinary metabolites, identifying dust as a primary exposure source (Bastiaensen et al., 2019). This was further supported by Ait Bamai et al., who demonstrated that phthalate concentrations in floor dust, rather than multi-surface dust, were significantly associated with allergic outcomes and internal exposure, likely due to children's proximity to the floors (Ait Bamai et al., 2016). Yoshida et al. calculated that while inhalation contributes significantly to VOC intake, it accounts for as little as 1% of the total intake for certain phthalates like DEHP, where dust ingestion dominates (Yoshida et al., 2020).

The distinct exposure pathways identified for these chemical groups dictate that researchers cannot adopt a "one-size-fits-all" environmental sampling strategy. To accurately predict children's exposure, study designs must align the environmental sampler with the volatility of the target compounds. For VOCs, pump-assisted active air sampling or passive diffusive samplers are essential to capture the gas-phase fraction that drives inhalation exposure (Bonardi et al., 2023), (Sexton et al., 2005). In contrast, for SVOCs, the use of dust wiping or vacuum sampling is methodologically required to collect settled dust in order to capture the particle-bound fraction available for ingestion (Ait Bamai et al., 2016), (Morgan et al., 2008). Future protocols must therefore

integrate passive and active air sampling with dust collection to avoid misclassification of primary exposure pathways in multi-pollutant studies.

4.3. Public health policy and the built environment

Although children spend a substantial portion of their waking hours in classrooms, this review reveals a profound data gap: only 15% of studies investigated school environments. Given that schools often feature higher occupancy and lower ventilation rates compared to residential buildings (Madureira et al., 2015a), neglecting the school environment leads to a systematic underestimation of the total exposures, particularly for compounds emitted by building materials and cleaning activities in school settings.

The urgency of addressing this gap is underscored by recent epidemiological findings from the “China, Children, Homes, Health (CCHH)” study, confirming that indoor pollutant exposure is a major contributing factor to respiratory diseases in children. Norbäck et al. demonstrated that exposure to chemicals from home renovation and new furniture significantly increased the risk of lifetime-ever pneumonia in preschoolers (Norbäck et al., 2018b). Norbäck et al. Also found that indoor factors such as renovations were associated with increased onset and decreased remission of wheeze and rhinitis (Norbäck et al., 2019). Lu et al. further solidified the association between early-life indoor exposure and the onset of early allergic symptoms (Lu et al., 2023). While these studies utilised a wider range of environmental metrics and younger age groups than the primary focus of this review, they validated the direct link between indoor chemical exposures and the genesis of respiratory disease in children (Norbäck et al., 2018b).

Based on these findings, we propose three targeted policy actions to mitigate children's indoor exposure in schools: (1) Considering the clear link between new furniture or renovation and respiratory disease (Norbäck et al., 2018b), (Norbäck et al., 2019), strict regulations should be placed on the materials used in school construction and refurbishment. This includes purchasing low-emitting furniture and implementing “Green Cleaning” guidelines that mandate the use of low-emission, non-chlorinated cleaning agents to prevent students from inhaling volatile byproducts (Madureira et al., 2015a); (2) Given that natural ventilation often fails to maintain proper IAQ in high-density classrooms (Madureira et al., 2015a), schools should install mechanical ventilation systems that can consistently capture or flush out indoor VOCs. This is essential to prevent the accumulation of pollutants derived from building materials and occupants' activities (Madureira et al., 2015a); (3) To address the infiltration of outdoor traffic-related air pollutants such as benzene (Greenwald et al., 2013), urban planning policy should mandate “buffer zones” that prohibit the construction of new schools within close proximity to major roadways (Kaviani et al., 2023). For existing schools in busy traffic areas, the installation of high-efficiency filtration systems is necessary to reduce the infiltration of outdoor pollutants (Madureira et al., 2015a).

4.4. Risk characterization

To contextualise the potential health risks associated with the reported exposure levels, we benchmarked the aggregated data against the Human Biomonitoring Health-Based Guidance Value (HB2GV) Dashboard published by the International Human Biomonitoring (i-HBM) Working Group in 2023 (Nakayama et al., 2023). This analysis focused on compounds for which both biomonitoring and environmental data were available, including BTEX compounds, carbon tetrachloride, tetrachloroethylene, trichloroethylene, phthalates, DDT, DDE, cyfluthrin, and deltamethrin (Table S9). A key difference emerged in the risk characterisation: regardless of the pollutant category (VOCs or SVOCs), the biomarker concentrations predominantly fell within the HB2GV range. In contrast, the corresponding indoor environmental concentrations frequently exceeded established exposure guidance values. This

discrepancy suggested that current air quality guidelines function as conservative precautionary thresholds that do not always correlate linearly with “unsafe” internal doses in children, highlighting the necessity of integrated biomonitoring to provide a more accurate assessment of physiological risk.

5. Conclusions and future perspectives

To our knowledge, this is the first systematic review to comprehensively synthesize methodological approaches for assessing children's exposure to indoor VOCs and SVOCs in home and school environments. By evaluating data from 79 studies, this review identified critical deficits that currently limit global risk assessment.

Evidence confirmed that urine is the most practical and informative biological matrix in the school-age population, providing a non-invasive way to understand exposure to both volatile and semi-volatile compounds. Analytically, LC-MS/MS is the requisite standard for quantifying metabolites of semi-volatile pollutants, while GC-MS remains the standard for volatile compounds. Furthermore, the integration of BoEFs, particularly clinical outcomes for ETS and genotoxicity markers for PAHs, is crucial for validating the physiological relevance of low-level indoor exposures.

Despite these advancements, several systemic limitations hinder the practical applicability of current children's biomonitoring data. Firstly, biomonitoring integrates exposure from all sources (Arnold et al., 2013). However, only 57% of the included studies performed concurrent environmental monitoring, and reliance on passive air sampling often fails to capture “peak exposure activities” such as cleaning or renovation, making it still difficult to clearly attribute internal doses to specific indoor sources or outdoor infiltration. Secondly, the predominance of cross-sectional study designs (59%), and the use of spot urine samples provide only a snapshot of exposure (Sexton et al., 2004). This approach fails to capture the temporal variability of short-lived pollutants (e.g., VOCs) or establish causal relationships between chronic exposure and health outcomes. Thirdly, the profound imbalance in study locations, with 85% of research focused on home environments, meaning that children's exposure in school environments remains largely uncharacterised, despite schools often exhibiting higher pollutant concentrations due to high population density and poor ventilation (Lee et al., 2002), (Oeder et al., 2012). Furthermore, The review process itself is limited by the restriction to English publications and the four peer-reviewed databases, which exclude grey literature and national biomonitoring surveys reported in other languages. Additionally, the 70% age-overlap criterion for the 6-12 age group might introduce selection bias, as precise participant age distributions were not always available to verify strict age matching. Access issues also prevent the full-text retrieval of some older articles. However, the included studies remain representative of the broader literature on children's indoor biomonitoring, ensuring the validity of the overall conclusions.

To resolve these disparities, future study designs must move beyond descriptive, cross-sectional monitoring. We propose a novel methodological framework to guide the next generation of children's indoor exposure assessments. Firstly, future research should adopt standardised sampling time protocols (e.g., COPHES), prioritising 24-h collection or timed spot urine samples and reporting in standard units. This is essential to eliminate variability caused by diuresis and short biological half-lives, thereby enabling the global meta-analyses that are currently impossible (Senerat et al., 2021). Secondly, to achieve source attribution of pollutants, studies must combine biomonitoring with environmental sampling of specific media, including active or passive air sampling to capture the inhalation of gas-phase pollutants, and settled dust collection to capture the ingestion of particle-bound pollutants. Relying solely on a single environmental measurement is no longer sufficient. Lastly, research must shift towards longitudinal cohort studies to account for seasonal and intra-individual variability. Crucially, these efforts must prioritise school settings and low- and middle-income countries, where

the combined burdens of indoor heating, poor infrastructure, and high population density pose the greatest undetermined risk to child health (Bruce et al., 2000), (Chen et al., 1990), (Kalisa et al., 2023).

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CRediT authorship contribution statement

Wai Kei Chu: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **Thomas Celis:** Investigation, Methodology, Validation, Visualization, Writing – review & editing. **Lama Said:** Investigation, Validation. **Peter H.M. Hoet:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Jeroen A.J. Vanoirbeek:** Conceptualization, Methodology, Project administration, Supervision, Writing – review & editing.

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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Appendix A. Supplementary data

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Abbreviations

1-OHN, 1-hydroxynaphthalene; **1-OHP**, 1-hydroxypyrene; **1-OHPG**, 1-hydroxypyrene glucuronide; **1-OHPhe**, 1-hydroxyphenanthrene; **2cx-MMHTP**, 1-mono-(2-carboxyl-methylhexyl) Benzene-1,4-dicarboxylate; **2-OHF**, 2-hydroxyfluorene; **2-OHFlu**, 2-hydroxyfluorene; **2-OHN**, 2-hydroxynaphthalene; **3-HO-TBOEP**, Bis(2-butoxyethyl) 3-hydroxy-2-butoxyethyl phosphate; **3-HO-TPHP**, 3-hydroxyphenyl Diphenyl Phosphate; **3-PBA**, 3-phenoxybenzoic Acid; **4,4'-DDE**, p,p'-dichlorodiphenyldichloroethylene; **4-HO-DPHP**, 4-hydroxyphenyl phenyl phosphate; **4-HO-TPHP**, 4-hydroxyphenyl diphenyl phosphate; **53BP1**, P53 Binding Protein 1; **5cx-MEPA**, Mono-5-carboxy-2-ethylpentyl Adipate; **5cx-MEPTP**, Mono(2-ethyl-5-carboxypentyl) Terephthalate; **5-HO-EHDPHP**, 2-ethyl-5-hydroxyhexyl Diphenyl Phosphate; **5OH-MEHA**, Mono-2-ethyl-5-hydroxyhexyl Adipate; **5OH-MEHTP**, Mono(2-ethyl-5-hydroxyhexyl) Terephthalate; **5oxo-MEHA**, Mono-(2-ethyl-5-oxohexyl) Adipate; **5oxo-MEHTP**, Mono(2-ethyl-5-oxohexyl) Terephthalate; **6-OHChr**, 6-hydroxychrysene; **8-OHdG**, 8-hydroxydeoxyguanosine; **ALT**, Alanine Aminotransferase; **AM**, Arithmetic Mean; **AST**, Aspartate Aminotransferase; **BaA**, Benzo[a]anthracene; **BaP**, Benzo[a]pyrene; **BB153**, 2,2',4,4',5,5'-hexabromobiphenyl; **BbF**, Benzo

[b]fluoranthene; **BBOEHP**, Bis(2-butoxyethyl) 2-hydroxyethyl Phosphate; **BBOEP**, Bis (2-butoxyethyl) Phosphate; **BBzP**, Butyl Benzyl Phthalate; **BCIPHIPP**, Bis(1-chloro-2-propyl) 1-hydroxy-2-propyl Phosphate; **BCIPP**, Bis(1-chloro-2-propyl) Phosphate; **BDCIPP**, Bis(1,3-dichloro-2-propyl) Phosphate; **BDCM**, Bromodichloromethane; **BDE-100**, 2,2',4,4',6-pentabromodiphenyl Ether; **BDE-153**, 2,2',4,4',5,5'-hexabromodiphenyl Ether; **BDE-154**, 2,2',4,4',6,6'-hexabromodiphenyl Ether; **BDE-183**, 2,2',3,4,4',5,6-heptabromodiphenyl Ether; **BDE-196**, 2,2',3,3',4,4',5,6,6'-nonabromodiphenyl Ether; **BDE-204**, 2,2',3,3',4,4',5,5',6-nonabromodiphenyl Ether; **BDE-206**, 2,2',3,3',4,4',5,6,6'-nonabromodiphenyl Ether; **BDE-207**, 2,2',3,3',4,5,5',6,6'-nonabromodiphenyl Ether; **BDE-209**, Decabromodiphenyl Ether; **BDE-28**, 2,4,4'-tribromodiphenyl Ether; **BDE-47**, 2,2',4,4'-tetrabromodiphenyl Ether; **BDE-85**, 2,2',3,4,4'-pentabromodiphenyl Ether; **BDE-99**, 2,2',4,4',5-pentabromodiphenyl Ether; **BFRs**, Brominated Flame Retardants; **BghiP**, Benzo[ghi]perylene; **BkF**, Benzo[k]fluoranthene; **BoEF**, Biomarkers of Effect; **BoEX**, Biomarkers of Exposure; **BPA**, Bisphenol A; **BPAF**, Bisphenol AF; **BPAP**, Bisphenol AP; **BPB**, Bisphenol B; **BPF**, Bisphenol F; **BPS**, Bisphenol S; **BPZ**, Bisphenol Z; **BTBPE**, 1,2-bis-(2,4,6-tribromophenoxy)ethane; **BTEX**, Benzene, Toluene, Ethylbenzene, and Xylenes; **CI**, Confidence Intervals; **Cis-/Trans-DCCA**, Cis- and Trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane Carboxylic Acid; **CK-18**, Cytokeratin-18; **CMHC**, 3-chloro-4-methyl-7-hydroxycoumarin; **CTFCA**, Cis-3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylic Acid; **cx-MINCH**, Cyclohexane-1,2-dicarboxylic Acid-monocarboxy Isooctyl Ester; **DahA**, Dibenzo[a,h]anthracene; **DALYs**, Disability-adjusted Life Year; **DAP**, Dialkyl Phosphate; **DBCA**, Cis-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropane Carboxylic Acid; **DBCM**, Dibromochloromethane; **DBDPE**, Decabromodiphenyl Ethane; **DBP**, Dibutyl Phthalate; **DcHP**, Di-cyclohexyl Phthalate; **DDE**, Dichlorodiphenyldichloroethylene; **DDT**, Dichlorodiphenyltrichloroethane; **DEDTP**, Diethyldithiophosphate; **DEHA**, Di(2-ethylhexyl) Adipate; **DEHP**, Di(2-ethylhexyl) Phthalate; **DEHTP**, Di-2-ethylhexyl Terephthalate; **DEP**, Diethyl Phthalate; **DETP**, Diethyl Thiophosphate; **DiBP**, Di-isobutyl Phthalate; **Di-DnHP**, Di-isononyl Phthalate; **DINCH**, 2-cyclohexane Dicarboxylic Acid Diisononyl Ester; **DiNP**, Di-isononyl Phthalate; **DMDTP**, Dimethyl- Dithiophosphate; **DMP**, Dimethyl Phthalate; **DMTP**, Dimethyl Thiophosphate; **DNBP**, Di-n-butyl Phosphate; **DnBP**, Di-n-butyl Phthalate; **DnHP**, Di-n-hexyl Phthalate; **DP**, Dechlorane Plus; **DPa**, Dechlorane Plus Anti; **DPDBE**, Decabromodiphenyl Ethane; **DPHP**, Diphenyl Phosphate; **DPs**, Dechlorane Plus Syn; **DSBs**, Double-strand Breaks; **EBC**, Exhaled Breath Condensate; **ECD**, Electron Capture Detector; **ECLIA**, Electrochemiluminescence Immunoassays; **EHDHP**, 2-ethylhexyl Diphenyl Phosphate; **EHPHP**, 2-ethylhexyl Phenyl Phosphate; **ELISA**, Enzyme-linked Immunosorbent Assay; **eNO**, Exhaled Nitric Oxide; **EPA**, Environmental Protection Agency; **EPHP**, Effective Public Health Practice Project Quality Assessment Tool; **ETBE-A**, Ethyl Tert-butyl Ether; **ETS**, Environmental Tobacco Smoke; **ETU**, Ethylene Thiourea; **EU**, European Union; **FID**, Flame Ionization Detector; **FLD**, Fluorescence Detector; **F-PBA**, 4-fluoro-3-phenoxybenzoic Acid; **FPD**, Flame Photometric Detector; **FSH**, Follicle-stimulating Hormone; **FT3**, Free Triiodothyronine; **FT4**, Free Thyroxine; **GC**, Gas Chromatography; **GC-HRMS**, Gas Chromatography-high-resolution Mass Spectrometry; **GC-ID-HRMS**, Gas Chromatography-isotope Dilution-high Resolution Mass Spectrometry; **GGT**, Gamma-glutamyl Transferase; **GGT**, Gamma-glutamyltransferase; **HB2GV**, Human Biomonitoring Health-based Guidance Value; **HBM**, Human Biomonitoring; **HCDBCO**, Hexachlorocyclopentadienyl-dibromocyclooctane; **HEL**, Hexanoyllysine; **HESI**, Heated Electrospray Ionization; **HIV**, Human Immunodeficiency Virus; **HNE**, 4-hydroxynonenal; **HPLC**, High-performance Liquid Chromatography; **HPLC-UV**, High-performance Liquid Chromatography With Ultraviolet Detection; **HS-SPME**, Headspace Solid-Phase Microextraction; **IAP**, Indoor Air Pollution; **IAQ**, Indoor Air Quality; **IcdP**, Indeno[1,2,3-cd]pyrene; **IgA**, Immunoglobulin A; **IgE**, Immunoglobulin E; **IgG**, Immunoglobulin G; **IgM**, Immunoglobulin M; **i-HBM**, International Human Biomonitoring; **IMPy**, 2-isopropyl-4-methyl-6-

hydroxypyrimidine; **IQR**, Interquartile Range; **IRMA**, Immunoradiometric Assay; **LC**, Liquid Chromatography; **LC-API-MS/MS**, Liquid Chromatography Coupled With Atmospheric Pressure Ionization Mass Spectrometry; **LH**, Luteinising Hormone; **LOD**, Limit of Detection; **LOQ**, Limit of Quantitation; **MBzP**, Mono-benzyl Phthalate; **MDA**, Malondialdehyde; **MECPP**, Mono-2-ethyl-5-carboxypentyl Phthalate; **MEHHP**, Mono-2-ethyl-5-hydroxyhexyl Phthalate; **MEHP**, Mono-2-ethylhexyl Phthalate; **MEOHP**, Mono-2-ethyl-5-oxohexyl Phthalate; **MEP**, Mono-ethyl Phthalate; **MiBP**, Mono-isobutyl Phthalate; **MMP**, Mono-methyl Phthalate; **MMTFL**, 4-methoxymethyl-2,3,5,6-tetrafluorobenzyl Alcohol; **MnBP**, Mono-n-butyl Phthalate; **MPCA**, 2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropanecarboxylic Acid; **MS**, Mass Spectrometry; **MTBE-A**, Methyl Tert-butyl Ether; **MTBE-U**, Methyl-tert-butyl Ether; **MTFBL**, 4-methyl-2,3,5,6-tetrafluorobenzyl Alcohol; **NFR**, New Flame Retardant; **NO**, Nitric Oxide; **NPD**, Nitrogen Phosphorus Detector; **o,p'-DDE**, o,p'-dichlorodiphenyldichloroethylene; **o,p'-DDT**, o,p'-dichlorodiphenyltrichloroethane; **OH-MINCH**, Cyclohexane-1,2-dicarboxylic Acid Monohydroxy Isononyl Ester; **OH-MPHP**, Mono-(2-propyl-6-hydroxyheptyl) Phthalate; **OH-PAHs**, Hydroxy-polycyclic Aromatic Hydrocarbons; **OPFR**, Organophosphate Flame Retardant; **oxo-MINCH**, Cyclohexane-1,2-dicarboxylate-mono (oxo-isononyl) Ester; **oxo-MPHP**, Mono(propyl-6-oxo-heptyl) Phthalate; **p,p'-DDE**, 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene; **p,p'-DDT**, 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane; **PAH**, Polycyclic Aromatic Hydrocarbon; **PBB**, Polybrominated Biphenyl; **PBDEs**, Polybrominated Diphenyl Ethers; **PCB**, Polychlorinated Biphenyl; **PCP**, Pentachlorophenol; **PFAS**, Per- and Polyfluoroalkyl Substances; **PFRs**, Organophosphate Flame Retardants; **PM**, Particulate Matter; **PNP**, 4-nitrophenol; **PRISMA**, Preferred Reporting Items for Systematic reviews and Meta-Analysis; **RIA**, Radioimmunoassay; **SD**, Standard Deviation; **SG**, Specific Gravity; **SHBG**, Sex Hormone-binding Globulin; **SPMA**, S-phenylmercapturic Acid; **S-PMA**, S-phenylmercapturic Acid; **SVOC**, Semi-volatile Organic Compounds; **t,t-MA**, Trans-muconic Acid; **TAME-A**, Ter-amyl Methyl Ether; **TBB**, 2-ethylhexyl 2,3,4,5-tetrabromobenzoate; **TBECH**, Tetrabromoethylcyclohexane; **TBM**, Bromoform; **TBOEP**, Tris(2-butoxyethyl) Phosphate; **TBPH**, Bis(2-ethylhexyl) tetrabromophthalate; **TCEP**, Tris(2-carboxyethyl)phosphine; **TCIPP**, Tris(1,3-dichloroisopropyl)phosphate; **TCM**, Chloroform; **TCP**, Tricresyl-phosphate; **TCPY**, 3,5,6-trichloro-2-pyridinol; **TDCIPP**, Tris(1,3-dichloroisopropyl)phosphate; **TEB-OH**, Hydroxytebuconazole; **TEHP**, Tris (2-ethylhexyl) Phosphate; **TFBA**, 2,3,5,6-tetrafluorobenzoic Acid; **THMs**, Trihalomethanes; **TIBP**, Tri-iso-butyl Phosphate; **TMCA**, 3-Tetramethylcyclopropanecarboxylic Acid; **TNBP**, Tri-n-butyl Phosphate; **TOF**, Time of Flight Mass; **TPHP**, Triphenyl Phosphate; **TSH**, Thyroid-stimulating Hormone; **TVOCs**, Total Volatile Organic Compounds; **uLTE4**, Urinary Leukotriene E4; **UPLC**, Ultra-performance Liquid Chromatography; **VOC**, Volatile Organic Compound; **WHO**, World Health Organization; **α -HCH**, A-hexachlorocyclohexane; **β -HCH**, β -hexachlorocyclohexane; **γ -HCH**, γ -hexachlorocyclohexane; **Σ CMSs**, Total Concentration of Cyclic Methylsiloxanes; **Σ LMSs**, Total Concentration of Linear Methylsiloxanes; **Σ PAHs**, Total Concentration of Polycyclic Aromatic Hydrocarbons; **Σ PBDE**, Total Concentration of Polybrominated Diphenyl Ether.

Data availability

Data will be made available on request.

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