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GUIDELINES

EAACI Guidelines on Environmental Science for Allergy and Asthma—Recommendations on the Impact of Indoor Air Pollutants on the Risk of New-Onset Asthma and on Asthma-Related Outcomes

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Abbreviations: ACQ, asthma control questionnaire; ACT, asthma control test; AHR, airway hyperreactivity; AQG, air quality guideline; AQI, air quality index; AQLQ, asthma-related quality of life; AR, allergic rhinitis; BTEX, (ambient) benzene, toluene, ethylbenzene, and xylene; CI, confidence interval; CO, carbon monoxide; COI, conflict of Interest; COPD, chronic obstructive pulmonary disease; EAACI, European Academy of Allergy and Clinical Immunology; ED, emergency department; EPA, United States Environment Protection Agency; EtD, evidence to decision; EU, European Union; FEV1, forced expiratory volume in 1; GDG, guideline development group; GRADE, grading of recommendations, assessment, development, and evaluation; HCP, health care professional; HVAC, central heater, ventilation, and air-conditioner; IAQ, indoor air quality; IL, interleukin; ILC, innate lymphoid cells; LRTI, lower respiratory tract infection; MP, microplastic; NO_2, nitrogen dioxide; OR, odds ratio; OSRC, oil spill response and clean-up; PECO, population exposure comparator outcome; PEF, peak expiratory flow; PG, propylene glycol; PM, particulate matter; QoL, quality of life; Rn, radon; ROB, risk of bias; RR, risk ratio; SoF, summary of findings; SR, systematic review; T2, type 2 immune response; US, United States of America; VOC, volatile organic compound; WHO, World Health Organisation.

Ioana Agache, Isabella Annesi-Maesano, and Lorenzo Cecchi are co-first equal contribution.

Marek Jutel and Cezmi A. Akdis are co-last equal contribution.

ABSTRACT

The EAACI Guidelines used the GRADE approach to evaluate the impact of major indoor air pollutants (dampness and mould, cleaning agents, volatile organic compounds and pesticides) on the risk of new-onset asthma and on asthma-related outcomes. The guideline also acknowledges the synergies among indoor air pollutants and other components of the indoor exposome (allergens, viruses, endotoxins). Very low to low certainty of evidence was found for the association between exposure to indoor pollutants and increased risk of new-onset asthma and asthma worsening. Only for mould exposure there was moderate certainty of evidence for new-onset asthma. Due to the quality of evidence, conditional recommendations were formulated on the risk of exposure to all indoor pollutants. Recommendations are provided for prevention, patient care and mitigation in a framework supporting rational decisions for healthcare professionals and patients to individualize and improve asthma management. For policymakers and regulators this evidence-informed guideline supports setting legally binding standards and goals for indoor air quality at international, national and local levels. Asthma management counselled by the current EAACI guidelines can improve asthma-related outcomes but community and governmental measures for improved indoor air quality are needed to achieve significant impact.

1 | Introduction

1.1 | Indoor Air Pollutants, New-Onset Asthma, and Asthma-Related Outcomes

Asthma inception and natural evolution follow a complex interplay between the individual genetic background and environmental exposures, such as indoor and outdoor air pollutants, infectious agents, allergens, irritants, occupational factors, diet and lifestyle, currently known as the exposome [1–14]. Several thousands of new chemicals have been introduced in modern life without our full understanding of their toxic health effects and ways to mitigate these effects [10, 11, 15]. The overwhelming aggression of the environment challenges significantly the resilience mechanisms and overcomes the allostatic process favoring the development of chronic inflammatory diseases and driving their severity [1, 4, 12, 16]. Supported by extensive previous research on the role of respiratory epithelium in asthma, the recently introduced *'epithelial barrier hypothesis'* proposes that exposure to the urban environment and significant changes in the urban exposome by modernization and industrialization damages and initiates inflammation of the epithelium [15, 17–25].

Among the environmental asthma triggers, indoor exposure is of particular interest because people spend more than 80 to 90% of their time indoors. Increasing prices for oil, gas, and other primary energy sources led to better insulation and reduced drafts of the buildings to reduce energy costs. In the quest for energy-efficient homes, insulation stands as a formidable champion but the decreased air exchange rates between the outdoor and indoor air, while preventing the entry of outdoor pollutants or allergens, decreases the amount of fresh, clean air in the indoor environment [26]. The "hand-in-glove" relationship between insulation and ventilation thus becomes an important risk factor for patients with asthma if not properly handled. For children, the school environment is of paramount importance and potentially amenable to intervention [27].

Major indoor air pollutants include cleaning and disinfecting products, dampness/mould, pesticides, and volatile organic compounds (VOCs). Health effects following exposure to indoor air pollutants may be experienced immediately after exposure or years later [1, 2, 4, 5]. There is a clear impact of indoor air pollutants on the risk of new-onset asthma and on numerous asthma-related outcomes, such as exacerbations and deterioration of asthma control, lung function decline, increased use of asthma medication and of healthcare resources, including visits to emergency department and hospital admissions, and increased mortality [8, 9, 28–33].

The mechanisms through which indoor pollutants induce or aggravate asthma are multiple, and include damage to the epithelial barrier, perturbation of the respiratory tract microbiome, immune dysregulation, increased oxidative stress, neurogenic dysfunction and inflammation, and epigenetic and metabolic reprogramming [15, 17–20, 34–40] (Figure 1).

Around 2.4 billion people, especially in low- and middle-income countries, are exposed to dangerous levels of indoor air pollutants. The combined effects of outdoor and indoor air pollutants were associated with 7 million premature deaths annually [41, 42]. Many reports and studies indicate that vulnerable populations (e.g., children, pregnant women, elderly, individuals with chronic diseases, disabled or with low-income) are disproportionately impacted by indoor pollutants [41, 42].

Household wood-heating, extensively used in low- and middle-income countries, has regained popularity in Europe and Northern America due to policies encouraging wood and other biomass burning for energy security and climate change mitigation. Whether these policies are truly low-carbon has been questioned, and they also have important implications for indoor air quality (IAQ). Ambient wood-smoke exposure was associated with childhood respiratory diseases and has been shown to breech the epithelial barrier [28, 41, 43–46].

Cleaning agents (e.g., disinfectants, bleach, detergents, etc.) become an indispensable part of modern life, as they are used on daily basis in nearly all workplaces and homes. Detergent residues are components of the house dust and are presumably inhaled into the airways in daily life. Most cleaning agents breech the epithelial barriers at very low concentrations and thus can initiate epithelitis and local and systemic inflammation, and have a sensitizing potential [15, 21, 47, 48]. In a mouse model, laundry detergents and surfactants induced eosinophilic airway inflammation through epithelial cell and type 2 (T2) innate lymphoid cells (ILCs) activation. They also induced IL-33 expression in human airway epithelial cells through oxidative stress [49]. Neutrophilic inflammation can also occur [50]. At

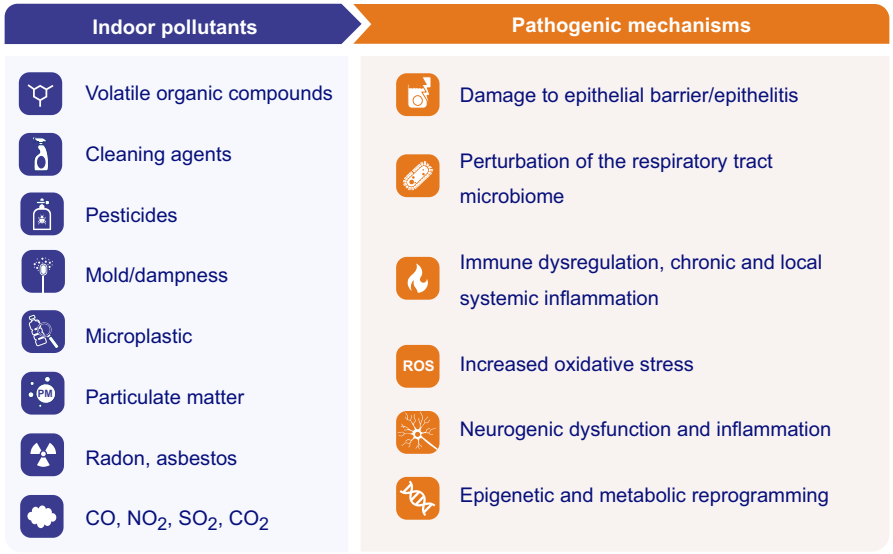

FIGURE 1 | Indoor air pollutants with their pathogenetic mechanisms. CO, carbon monoxide; CO_2, carbon dioxide; NO_2, nitrogen dioxide; SO_2, sulphur dioxide.

higher concentrations irritant-induced mechanisms prevail [51]. The main culprits contained in cleaning products are quaternary ammonium compounds (such as benzalkonium chloride), amine compounds, and fragrances. The strongest airway irritants are bleach (sodium hypochlorite), hydrochloric acid, and alkaline agents (ammonia and sodium hydroxide), which are commonly mixed together [52]. Cleaning agents may elicit new-onset asthma or exacerbate asthma symptoms in individuals with pre-existing asthma [53]. Weekly use of irritants, scented, green and homemade products, as well as sprays, perfumes and other cosmetic products, softeners, haircare products, baby products and disinfecting wipes were significantly associated with asthma symptoms and lung function decline, with significant trends according to the frequency of use [8, 54]. Further, weekly use of common cleaning irritants was associated with an increased risk of current asthma, irrespective of the allergic status [54].

Dampness and moulds are common indoor exposures. Humidity problems in buildings may originate from leaks, condensation, or improper insulation. Excess humidity promotes the growth of micro-organisms such as moulds and bacteria [55]. Fungi represent one of the most diverse and abundant eukaryotes on earth and thus are central components of the exposome and key determinants of human health [56]. The interplay between mould exposure and the host immune system is still not fully elucidated. While the induction of allergic immune responses by moulds is generally acknowledged, other direct health effects like the toxic mould syndrome are controversially discussed. Recent observations indicate a particular importance of mould/mycotoxin exposure in individuals with pre-existing dysregulation of the immune system. Exposure to mycotoxins worsens the respiratory epithelium barrier impairment. Dendritic cells respond to mycotoxin-exposure with decreased production of IL-12, overactivation of the inflammasome and activation of oxidative stress pathways [57]. Fungal spores and fungal fragments are biologically active and contribute to asthma development and severity. Recent mechanistic studies have demonstrated that fungi are potent immunomodulators (through beta-glucans and chitin) and have powerful effects on asthma, independent of their potential to act as antigens [58]. Several studies have suggested that visible mould or residential fungal exposures are associated with new-onset asthma or asthma symptoms [59–65]. Exposure to mould or dampness during infancy increased the risk of asthma and rhinitis up to 16 years of age, particularly for nonallergic disease. Early exposure to mould or dampness appeared particularly associated with persistent asthma through adolescence [66]. A mouldy home environment in early life is associated with an increased risk of asthma particularly in young children and with allergic rhinitis (AR) symptoms in school-age children [67]. Being sensitized to any moulds was associated with a very high risk of current asthma, higher than being sensitized to other aeroallergens. Interestingly, the level of T2 cytokines was reduced, thus raising the hypothesis that underlying biological mechanisms driving allergic inflammatory responses in adults sensitized to moulds may differ from those sensitized to other aeroallergens [68].

VOCs include a variety of chemicals emitted as gases from solvents, floor adhesive, paint, cleaning products, furnishings, polishes, and room fresheners. Benzene, toluene, ethylbenzene, and xylene (BTEX) levels produced outdoors from various types of anthropogenic sources, mainly stationery and traffic emissions or emissions from the petrochemical industries can add to the indoor BTEX derived from smoking and/or building materials. Concentrations of many VOCs are consistently higher indoors than outdoors [69]. VOCs induce airway inflammation and airway obstruction [70, 71]. Benzene metabolites alter biochemical and functional activities of other immunocompetent cells and may impair immune responses in the lung [72]. Toluene diisocyanate was shown to induce neutrophilic inflammation and neutrophil extracellular traps (NETs), which further impacted the epithelial barrier and were linked to corticosteroid resistance [73]. Exposure to BTEX has been suggested to be a potential risk factor for asthma development and severity acting through increased oxidative stress and sphingolipid dysregulation [74]. Indoor VOCs may also act as endocrine-disrupting chemicals (EDCs). Increased

individual and combined EDCs levels were found in classrooms having more children with asthma and obesity [75]. The quality of diet (pro- or anti-inflammatory) might affect the association between indoor air pollutants and asthma in children, highlighting the relevance of children's diet as a potential protective factor to pollutant exposure in childhood asthma [76]. Indoor exposure to VOCs has been related to asthma symptoms, increased airway hyperreactivity (AHR), and decreased lung function [77–79]. The oil spill response and clean-up workers exposed to airborne total hydrocarbons, benzene, toluene, ethylbenzene, o-, m-, and p-xylenes, and n-hexane from crude oil and particulate matter (PM) (i.e., PM2.5) from burning/flaring oil and natural gas were shown to be at high risk of new-onset asthma [80].

Indoor pesticides damage the bronchial epithelium, stimulate irritant receptors in the airways with neurogenic inflammation and cholinergic dysregulation, eventually leading to chronic inflammation and increased AHR [81–84]. Pesticides may interact synergistically with allergen sensitisation rendering individuals more susceptible for developing asthma. Emerging data have linked household pesticide use to persistent wheezing among pre-schoolers and residential pesticide exposure to asthma in adolescents [85–87]. Children may be a particularly vulnerable population to indoor pesticides, as they are more likely to be exposed to household than occupational pesticides and to more pesticide per unit of body weight than adults, while their immune system and lung function are not fully developed [88–90].

1.2 | Purpose of the EAACI Guideline

Delivering high-quality clinical care is a central priority for allergists, pneumologists, paediatricians, epidemiologists and other specialties caring for patients with asthma. The European Academy of Allergy and Clinical Immunology (EAACI) develops and updates each year resources to help health care professionals (HCPs) and researchers to design the best interventions, deliver high standard care and to assess their actions and decisions for purposes of quality improvement and/or reporting. They also provide support to decisions of policy makers and regulators and engage patients, their caregivers and the overall society in driving adaptation and mitigation measures to prevent disease development and improve its management.

EAACI Guidelines include recommendations for the management of patients with particular conditions or diseases. Recognizing asthma as an environmental-driven disease both in its inception and its evolution, EAACI developed guidelines on the impact of indoor air pollutants on the risk of new-onset asthma and on asthma-related outcomes.

EAACI Guidelines are developed using the GRADE systematic process and are based on available evidence and the clinical experience and expertise of all interested stakeholders.

1.3 | Target Audience

The target audience includes HCPs and researchers involved in the management of asthma, patients and caregivers, regulatory authorities, and policymakers. The perspective of the guideline is of the HCPs.

1.4 | Rationale for the Indoor Pollutants' Exposure Evaluated

The current guidelines address the effects of major indoor pollutants on the risk of new-onset asthma and on asthma-related outcomes. Pollutants listed in the European Environment Agency (EEA) [91] and the United States Environmental Protection Agency (EPA) IAQ standards [92] with defined thresholds were included for the systematic review (SR) supporting the recommendations of the guidelines. Although we acknowledge the synergic interaction between indoor pollutants and other components of the exposome (allergens, viruses, endotoxins, etc.) the SRs were focused solely on major indoor pollutants.

The EAACI Guidelines on the impact of exposure to indoor pollutants on the risk of new-onset asthma and on asthma-related outcomes provide a framework for rational decisions for:

a. HCPs and patients to individualize and improve asthma prevention and management
b. For policymakers and regulators as an evidence-informed reference to help setting legally binding standards and goals for indoor air quality at international, national, and local levels.

Statements regarding the underlying values and preferences as well as qualifying remarks accompanying each recommendation are an integral part of the Guidelines and aim to facilitate more accurate interpretation. They should never be omitted or ignored when quoting Guidelines' recommendations.

2 | Methods

The EAACI Guidelines followed the GRADE methodology (available at www.gradeworkinggroup.org). Training was conducted with all members of the guidelines development group (GDG) to prepare them for their roles, including specific sessions on the GRADE methodology.

2.1 | The Guidelines Development Group

A Core Leadership Team supervised the project and was responsible together with the Voting Panel for defining the project scope, drafting the clinical questions (Q) to be addressed by the guideline, coordinating the literature search, and drafting the manuscript (Table S1; in alphabetical order). The GDG was led by three chairs with both content and methodologic expertise. The GDG received support from a methodologist team, who advised on the process and provide input on the GRADE summary of findings (SoF) tables and from experts in guideline development.

The methodologist team conducted the SR for each of the clinical questions, graded the quality of evidence, developed the SoF tables and provided the evidence reports. Narrative reviews were conducted by different content specialist subgroups for each topic to be covered to complement the SRs.

The Voting Panel, composed of content experts, decided which clinical questions are to be asked and which outcomes are critical, important, and of low importance, and voted for the final recommendations after reviewing the evidence provided by the methodology team and the narrative reviews. It included specialists with expertise and clinical experience in treating asthma, biologists, respiratory physicians, occupational physicians, clinical immunology experts, epidemiologists with a special focus on the exposome, as well as aerobiology, biometeorology, and climate change experts.

In accordance with EAACI policy, everyone who was intellectually involved in the project (i.e., considered for guideline authorship) disclosed all potential conflict of interest (COIs) in writing at the beginning, middle, and end of the project. The Guideline Oversight Committee lead by the EAACI Ethics Committee Chair was responsible for developing and implementing rules related to COIs.

2.2 | Definitions

The population was defined as children or adults with or without asthma.

The guideline focused mainly on the impact of indoor exposure to cleaning agents, dampness/mould, pesticides, and VOCs, as measured through direct sampling (proxies for exposure were excluded). Other components of the indoor exposome are also briefly discussed.

The outcomes were defined as new-onset asthma and as asthma-related outcomes. Asthma-related outcomes were prioritized according to GRADE into critical and important (Table 1). Comparisons were made between exposure and no exposure (Q1 to Q4).

2.3 | Task Force Questions and Prioritization of Outcomes

For this guideline, the following PECO (population, exposure, comparator, and outcomes) questions were identified:

1. Is indoor exposure to VOCs associated with new-onset asthma and/or unfavorable asthma-related outcomes?
2. Is indoor exposure to cleaning agents associated with new-onset asthma and/or unfavorable asthma-related outcomes?
3. Is indoor exposure to dampness/mould associated with new-onset asthma and/or unfavorable asthma-related outcomes?
4. Is indoor exposure to pesticides associated with new-onset asthma and/or unfavorable asthma-related outcomes?

As a fully developed framework for operationalizing the development of PECO questions does not exist, the GDG followed the recommendations issued by Morgan et al. in building the exposure scenarios [93]. As the cut-offs and the size of increments of exposure could be informed iteratively by the EPA thresholds the scenarios chosen were to evaluate the effect of an exposure cut-off on asthma development and asthma-related outcomes.

The outcomes evaluated in the SRs were prioritized by the GDG as per GRADE approach as critical or important (Table 1). Critical outcomes include new-onset doctor-diagnosed asthma, incident recurrent wheezing (more than three episodes of wheezing in the past year for infants or pre-school children), low lung function (as a proxy for new-onset asthma), severe asthma exacerbations and asthma control (asthma control questionnaire (ACQ), asthma control test (ACT)) as well as quality of life (QoL). Severe asthma exacerbations are defined as emergency department visits, hospital admissions and/or systemic use of corticosteroids for >3 consecutive days. Lung function parameters (FEV1 and PEF), asthma symptoms/asthma well days, and use of asthma rescue medication were scored as important outcomes.

TABLE 1 | Prioritization of the asthma-related outcomes as per the GRADE approach.

Outcome	Definition/parameters measured	Importance
Severe asthma exacerbations	Asthma-related emergency department visits Asthma-related hospital admissions Systemic corticosteroid use	Critical
Asthma control	Asthma control test; asthma control questionnaire	Critical
Asthma-related quality of life	AQLQ	Critical
Lung function	FEV1, PEF	Important
Asthma symptoms/asthma well days	Symptom scores	Important
Use of rescue medication	Average number of uses per individual per time period	Important

Abbreviations: AQLQ, asthma-related quality of life; FEV1, forced expiratory volume in the 1st second; GRADE, grading of recommendations, assessment, development, and evaluation; PEF, peak expiratory flow.

2.4 | The GRADE Approach

Key principles and provisions, key terms, descriptions, PECO questions, search methodology and evidence reporting used in the guideline development process were predefined.

Separate SRs on the impact of indoor exposure to cleaning products, dampness/mould, pesticides, and VOCs on the incidence of asthma as well as on the impact on asthma-related outcomes were conducted to inform the recommendations [84]. A GRADE SoF table was provided for each PECO question.

The quality of evidence was evaluated based on GRADE quality assessment criteria by two independent reviewers and discordance was resolved by consensus. Quality assessment includes the risk of bias (ROB) of included trials, the likelihood of publication bias, inconsistency between trial results, indirectness of the evidence (e.g., differences between populations, interventions or outcomes of interest in the group to whom the recommendation applies versus those who were included in the studies referenced) and imprecision (wide confidence intervals, usually due to a small number of patients or events, or those situations where clinical decision-making would differ at the extremes of the confidence interval).

The quality of evidence for each outcome was rated as moderate, low, or very low. Grading started from high certainty in randomized controlled trials and low certainty in observational studies, and quality was downgraded or upgraded according to the standard GRADE domains (ROB, imprecision, inconsistency, indirectness, and publication bias). Search results were pooled in an evidence report as SoF tables and accompanied by a qualitative summary of the evidence for each PECO question. The Core Leadership Team reviewed the drafted evidence report to address evidence gaps prior to presentation to the Voting Panel.

2.5 | Consensus Building and Formulating Recommendations

After reviewing the evidence report and the additional evidence, the Voting Panel decided in an online plenary meeting followed by subsequent emails regarding the final recommendations. For each PECO question, the Voting Panel heard an oral summary of the evidence and provided votes on the direction and strength of the related recommendation. A 70% consensus threshold was reached for all recommendation presented below. The recommendations follow the data included in the evidence-to-decision (EtD) tables and take into consideration the balance of desirable and undesirable consequences, quality of evidence, patients' values and preferences, feasibility, and acceptability of various interventions, use of resources paid for by third parties, equity considerations, impacts on those who care for patients and public health impact. A conditional recommendation was provided if there were reasons for uncertainty on the benefit–risk profile, especially for low or very low quality of evidence. The underlying values and preferences played a key role in formulating recommendations. As the key target audience of the EAACI Guidelines are HCPs involved in the management of asthma patients and the patients with asthma themselves the perspective chosen when formulating recommendation was mainly that of HCPs and patients, although the policymakers and the health system perspective was also considered.

Guidance and recommendations are provided *per* exposure and *per* outcome. They should be used following the GRADE interpretation (Table 2).

These recommendations will be reconsidered when new evidence becomes available, and an update of these guidelines is planned for 2029.

The Guidelines were available on the EAACI website for 2 weeks (12 November–29 November, 2024) for public comments and were external peer-reviewed. All comments received were carefully revised by the GDG and incorporated where applicable.

2.5.1 | Final Review and Approval of the Guideline by EAACI

In addition to journal and external peer review, the EAACI Executive Committee reviewed the manuscript. These EAACI oversight group did not mandate those certain recommendations be made within the guideline, but rather serve as peer reviewers.

3 | Key Guidance and Recommendations

3.1 | PECO 1: Is Indoor Exposure to VOCs Associated With New-Onset Asthma and/or Unfavorable Asthma-Related Outcomes?

In a recent SR, there was strong evidence suggesting that exposure to VOCs, especially aromatic and aliphatic compounds, was associated with worsening of asthma symptoms [94]. Further,

TABLE 2 | Interpretation of GRADE recommendations.

Implications	Conditional recommendation
For healthcare professionals	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful helping individuals making decisions consistent with their values and preferences
For patients	The majority of individuals in this situation would want the suggested course of action but many would not
For policy makers	Policy making will require substantial debate and involvement of various stakeholders. Documentation of appropriate (e.g., shared) decision-making processes can serve as performance measure

Abbreviation: GRADE, grading of recommendations, assessment, development, and evaluation.

VOCs' exposure was associated with higher risk for wheeze between colds and with new-onset asthma [95].

Consumer products and building materials including paints emit VOCs, such as propylene glycol, which was shown to dehydrate the respiratory mucus gel layer, leading to an overproduction of mucus due to goblet cell metaplasia, a mechanism similar to exercise-induced bronchoconstriction. The basement membrane also thickens as a result of dehydration. The thickened mucus layer also results in the compression of cilia causing decreased muco-ciliary clearance [96–98]. High levels of VOCs persist indoors for many weeks after painting. Paint exposure was shown to increase the risk of asthma attacks among children [98].

For farmers' exposure, studies showed that VOCs concentrations were higher in dwellings than in workplaces. Asthma was positively associated with elevated exposure to benzene, trichloroethylene, and halogenated hydrocarbons score. Early airway obstruction was related to elevated exposure to 2-butoxyetylacetate and glycol ethers score [99].

3.1.1 | Does Indoor Exposure to VOCs Increase the Risk of New-Onset Asthma?

3.1.1.1 | Summary of Supportive Evidence. For physician diagnosed new-onset asthma, the SR showed only inconsistent significant associations for benzene, formaldehyde, toluene, and xylenes, with very low certainty of evidence [84].

No association between VOCs exposure and persistent wheezing was observed (very low certainty of evidence), except in one study showing a protective association between total VOCs and persistent wheezing [84]. Only exposure to formaldehyde was found to be potentially associated with a higher risk of new-onset of wheeze, however with low certainty of evidence [84].

For lung function, the SR reported no association with exposure to total VOCs (very low certainty of evidence) [84].

Full evidence profiles are presented in Tables S2.1.

3.1.2 | Does Indoor Exposure to VOCs Impact Asthma-Related Outcomes?

3.1.2.1 | Summary of Supportive Evidence. For asthma symptoms, the SR found very low certainty of evidence for exposure to VOCs being associated with more self-reported episodes of nocturnal breathlessness or chest tightness in the previous 12 months, either considering total VOCs (OR = 9.9; 95% CI: 1.7; 58.8), formaldehyde (OR = 12.5; 95% CI: 2.0; 77.9), and toluene (OR = 4.9; 95% CI: 1.1; 22.8). No significant association was found between high exposure to benzene and self-reported episodes of wheezing, wheezing after effort, dry cough, and at least four wheezing crises in the previous 12 months (wheezing: OR = 1.89, 95% CI: 0.39; 9.23; dry cough: OR = 1.25, 95% CI: 0.19; 7.88; wheezing after effort: OR = 10.38, 95% CI: 0.63; 170.44; at least four wheezing crises per year: OR = 2.95, 95% CI: 0.46; 18.64) [84].

For lung function, the SR found very low certainty of evidence for decrease in FEV1 values upon exposure to formaldehyde [84].

Full evidence profiles are presented in Tables S2.2.

3.1.2.2 | Recommendations. The EtD Tables are presented in Tables 3A–3C for the risk of new-onset asthma and in Tables 4A and 4B for the impact on asthma-related outcomes (Boxes 1 and 2).

BOX 1 | Guidance on the Impact of Indoor Exposure to VOCs on the Risk of New-Onset Asthma.

Indoor exposure to VOC may increase the risk of new-onset asthma and/or persistent low lung function	Conditional recommendation
Exposure to benzene or formaldehyde may increase the risk of new-onset asthma	Conditional recommendation
Indoor exposure to tetrachloroethylene, toluene, or xylenes increases the risk of new-onset asthma	Conditional recommendation

BOX 2 | Guidance on the Impact of Indoor Exposure to VOCs on Asthma-Related Outcomes.

Indoor exposure to VOC may increase the risk of worsening asthma symptoms	Conditional recommendation
Exposure to benzene, toluene, or formaldehyde may increase the risk of worsening asthma symptoms	Conditional recommendation

3.1.2.3 | Justification and Additional Considerations. Very low to low certainty evidence was found for indoor exposure to VOCs in relation to increased risk of new-onset asthma. Moreover, very low certainty of evidence exists for the association between exposure to VOCs and unfavorable asthma-related outcomes. Although the importance of VOCs on their impact on new-onset and/or asthma-related outcomes is widely acknowledged, due to the quality of available evidence the GDG formulated a conditional recommendation.

3.1.2.4 | Age Subgroups. Children and adults were equally affected [84].

TABLE 3A | Evidence to decision table supporting guidance on the impact of VOCs (volatile organic compound) exposure on the increased risk of developing asthma or of persistent low lung function.

	JUDGEMENT						
PROBLEM (IMPORTANCE)	No	Probably no	Probably yes	Yes		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No studies included

TABLE 3B | Evidence to decision table supporting guidance on the impact of exposure to benzene or formaldehyde on the increased risk of developing asthma.

	JUDGEMENT						
PROBLEM (IMPORTANCE)	No	Probably no	Probably yes	Yes		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No studies included

TABLE 3C | Evidence to decision tables supporting guidance for the impact of exposure to tetrachloroethylene, toluene, xylenes on the increase risk of developing asthma.

	JUDGEMENT						
PROBLEM (IMPORTANCE)	No	Probably no	Probably yes	Yes		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No studies included

TABLE 4A | Evidence to decision table supporting guidance on the impact of VOCs exposure on the increased risk of developing asthma symptoms.

	JUDGEMENT						
PROBLEM (IMPORTANCE)	No	Probably no	Probably yes	Yes		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No studies included

TABLE 4B | Evidence to decision table supporting guidance on the impact of exposure to benzene, toluene, formaldehyde on the increased risk of developing asthma symptoms.

	JUDGEMENT						
PROBLEM (IMPORTANCE)	No	Probably no	Probably yes	Yes		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No studies included

3.2 | PECO 2: Is Indoor Exposure to Cleaning Agents Associated With New-Onset Asthma and/or Unfavorable Asthma-Related Outcomes?

Numerous studies suggest that workers (including healthcare workers) exposed to cleaning agents are at increased risk for the development or exacerbation of asthma or other respiratory conditions [51–54, 100]. According to the European Agency for Safety and Health at Work (EU-OSHA) respiratory diseases, including asthma are the most common work-related health effects found in cleaners [101]. Accessing information on occupational diseases remains challenging as cleaning workers are spread over different sectors and it is therefore difficult to put monitoring systems in place. In addition, a significant part of the cleaning workforce is undeclared, especially in private households, which also complicates data collection [101]. While industrial and domestic cleaning workers may perform similar tasks, domestic cleaners are likely to be more exposed because they often receive little to no training in the safe use of chemical cleaning products and they lack organized control measures and legislative protections [102].

Frequent use of cleaning sprays, especially scented air-refresheners, was associated with increased incidence of asthma symptoms or use of asthma medications [103]. Moreover, exposure to domestic cleaning agents early in life was associated with increased risk of new-onset wheeze in young children [104].

3.2.1 | Does Indoor Exposure to Cleaning Agents Increase the Risk of New-Onset Asthma?

3.2.1.1 | Summary of Supportive Evidence. The SR reported that occupational exposure to cleaning products may be associated with risk of new-onset asthma in: (a) nurses (adjusted RR = 1.38; 95% CI = 1.03; 1.85); (b) cleaning workers following 5 years of exposure (adjusted RR = 1.71; 95% CI = 0.92; 3.17); (c) cleaning workers following over 10 years of exposure (adjusted RR = 1.50; 95% CI = 1.43; 1.57) (low certainty of evidence) [84]. Low certainty of evidence was also found in the SR for the increased risk of physician-diagnosed new-onset asthma following exposure to cleaning sprays in residential settings (adjusted RR = 2.11; 95% CI = 1.15; 3.89) [84].

Full evidence profiles are presented in Tables S3.1.

3.2.2 | Does Indoor Exposure to Cleaning Agents Impact Asthma-Related Outcomes?

3.2.2.1 | Summary of Supportive Evidence. Household use of cleaning products may increase the risk of severe asthma exacerbation (OR = 2.20; 95% CI = 1.20; 4.04, low certainty of evidence). The SR also showed low certainty of evidence for the association between poor asthma control and: (a) occupational exposure to cleaning products (OR = 2.30; 95% CI = 1.40; 3.60); (b) residential exposure to cleaning products (OR = 2.05 95% CI = 1.25; 3.35) [84].

Occupational and residential exposure to cleaning products may worsen asthma symptoms (low certainty of evidence) (OR = 2.19; 95% CI = 0.87; 5.49, respective OR = 2.50; 95% CI = 1.54; 4.03). The SR reported low certainty of evidence for the association between occupational exposure to cleaning agents and asthma severity in women (OR = 5.10; 95% CI = 1.70; 15.30) and in professional cleaning workers (OR = 7.20; 95% CI = 2.40; 23.50) [84].

There was very low certainty of evidence for the impact on lung function measured by FEV1 (95% CI: 34 mL; 314 mL) and PEF (95% CI: 4 L/min; 70 L/min), both for occupational and residential exposures to cleaning products [84].

Full evidence profiles are presented in Tables S3.2.

3.2.2.2 | Recommendations. The EtD Tables are presented in Tables 5A–5D (Boxes 3 and 4).

BOX 3 | Guidance on the Impact of Exposure to Cleaning Agents on the Risk of New-Onset Asthma in Adults.

Occupational exposure to cleaning agents may increase the risk of new-onset asthma	Conditional recommendation
Residential exposure to cleaning agents may increase the risk of new-onset asthma	Conditional recommendation

BOX 4 | Guidance on the Impact of Exposure to Cleaning Agents on Asthma-Related Outcomes in Adults.

Occupational exposure to cleaning agents may increase asthma severity and may decrease lung function	Conditional recommendation
Residential exposure to cleaning agents may increase asthma severity and may decrease lung function	Conditional recommendation

3.2.2.3 | Justification. There was low certainty evidence for the association between exposure to cleaning products and increased risk of new-onset asthma development, increased risk of asthma exacerbations, or with decreased asthma control and/or severe asthma. The evidence on the impact of indoor exposure to cleaning products on lung function had very low certainty. Although the risk of exposure to cleaning products in patients with asthma is highly acknowledged, due to low quality of available evidence the GDG formulated conditional recommendations.

3.2.2.4 | Subgroups.

a. Age subgroups

Only adults were evaluated [84].

b. Gender subgroups

In occupational settings, men and women were equally impacted following exposure to cleaning agents, both having increased risk of new-onset asthma and of unfavorable asthma-related outcomes. In residential settings, women were more prone to increased risk of developing asthma as well as severe asthma following exposure to cleaning. This might be explained by the bias of exposure with women handling more frequent domestic cleaning.

3.3 | PECO. 3: Is Indoor Exposure to Dampness/Mould Associated With Increased Risk of New-Onset Asthma and/or With Unfavorable Asthma-Related Outcomes?

Damp indoor environments put inhabitants at risk for new-onset asthma, allergic rhinitis, eczema, or hypersensitivity pneumonitis, and favour asthma exacerbations or respiratory infections [60, 61, 105–108]. In children, exposure to visible mould and mould odor was associated with new-onset asthma and asthma exacerbations, providing sufficient evidence of a causal relationship [59]. However, a recent birth-cohort study suggested that neither fungal diversity nor load was associated with asthma within the population, but higher fungal richness was a risk factor among children on farms. Moreover, higher fungal loads in house dust were associated with the risk of inhalant atopy [109]. Elderly population, especially women, living in social welfare

TABLE 5A | Evidence to decision table supporting guidance on the impact of occupational exposure to cleaning agents on the increased risk of developing asthma.

	JUDGEMENT						
PROBLEM (IMPORTANCE)	No	Probably no	Probably yes	Yes		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No studies included

TABLE 5B | Evidence to decision table supporting guidance on the impact of residential exposure to cleaning agents on the increased risk of developing asthma in adults.

	JUDGEMENT						
PROBLEM (IMPORTANCE)	No	Probably no	Probably yes	Yes		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No studies included

TABLE 5C | Evidence to decision table supporting guidance on the impact of occupational exposure to cleaning agents on the increased risk of asthma severity and decreased lung function.

	JUDGEMENT						
PROBLEM (IMPORTANCE)	No	Probably no	Probably yes	Yes		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No studies included

TABLE 5D | Evidence to decision table supporting guidance on the impact of residential exposure to cleaning agents on the increased risk of asthma severity in adults.

	JUDGEMENT						
PROBLEM (IMPORTANCE)	No	Probably no	Probably yes	Yes		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No studies included

housings and exposed to visible mould growth were proved to be at higher risk for developing asthma [110].

3.3.1 | Does Indoor Exposure to Dampness/ Mould Increase the Risk of New-Onset Asthma?

3.3.1.1 | Summary of Supportive Evidence. The SR showed with moderate certainty of evidence that exposure to any dampness indicator, mould moisture, and visible mould were associated with increased risk of new-onset asthma (OR 1.43, 95% CI: 1.22; 1.67; OR = 1.48, 95% CI: 1.19 with moderate heterogeneity; 1.84; and OR = 1.34, 95% CI: 1.12; 1.61 with substantial heterogeneity) [84]. Exposure to water damage was linked with increased risk of new-onset asthma with low certainty of evidence (OR = 1.13; 95% CI: 0.98; 1.30) [84].

Full evidence profiles are presented in Tables S4.1.1—S4.1.4.

3.3.2 | Does Indoor Exposure to Dampness/ Mould Impact Asthma-Related Outcomes?

3.3.2.1 | Summary of Supportive Evidence. The SR showed very low certainty of evidence for the association between exposure to dampness and increased risk of moderate asthma exacerbation (adjusted OR = 7.60, 95% CI: 2.00; 28.60 and unadjusted OR = 1.63, 95% CI: 0.78; 3.39), with increased risk for recurrent exacerbation in children (adjusted OR = 3.80, 95% CI:1.10; 12.80). Exposure to mould may also be associated with asthma exacerbations, however the results were not consistent. The evidence on the impact of dampness and mould on asthma control and on asthma-related QoL had very low certainty [84].

For asthma symptoms, the SR reported very low certainty of evidence for the exposure to being associated with shortness of breath in children (unadjusted OR = 1.77, 95% CI: 1.22; 2.55). No association was found with speech limiting (unadjusted OR = 2.20, 95% CI: 0.70; 6.70) or asthma symptom days (unadjusted OR = 0.91, 95% CI: 0.63; 1.30). For the increased use of asthma medication, the SR did not show a significant association either for dampness (OR = 1.35, 95% CI: 0.84; 2.19) or mould exposure (OR = 0.82, 95% CI: 0.37; 1.79), with very low certainty of evidence [84]. Similarly, there was no association between dampness and decrease in FEV1 in adults (adjusted regression coefficient = −0.04; 95% CI: −0.27; 0.18) or FVC (adjusted regression coefficient = 0.09; 95% CI: −0.06; 0.24) (very low certainty of evidence). However, mould exposure may increase the risk of persistent airway obstruction (OR = 2.25, 95% CI:1.00; 5.05).

TABLE 6A | Evidence to decision table supporting guidance on the impact of exposure to water damage on the risk of developing asthma.

	JUDGEMENT						
PROBLEM (IMPORTANCE)	No	Probably no	Probably yes	Yes		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No studies included

TABLE 6B | Evidence to decision table supporting guidance on the impact of exposure to dampness on the risk of developing asthma.

	JUDGEMENT						
PROBLEM (IMPORTANCE)	No	Probably no	Probably yes	Yes		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No studies included

TABLE 6C | Evidence to decision table supporting guidance on the impact of exposure to mould on the risk of developing asthma.

	JUDGEMENT						
PROBLEM (IMPORTANCE)	No	Probably no	Probably yes	Yes		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No studies included

TABLE 6D | Evidence to decision table supporting guidance on the impact of exposure to dampness and mould on the risk of developing asthma.

	JUDGEMENT						
PROBLEM (IMPORTANCE)	No	Probably no	Probably yes	Yes		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No studies included

TABLE 6E | Evidence to decision table supporting guidance on the impact of exposure to dampness on the risk of moderate or severe asthma exacerbations.

	JUDGEMENT						
PROBLEM (IMPORTANCE)	No	Probably no	Probably yes	Yes		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No studies included

TABLE 6F | Evidence to decision table supporting guidance on the impact of exposure to dampness on asthma control and lung function.

	JUDGEMENT						
PROBLEM (IMPORTANCE)	No	Probably no	Probably yes	Yes		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No studies included

TABLE 6G | Evidence to decision table supporting guidance on the impact of exposure to moulds on the risk of severe asthma exacerbations or decreased lung function.

	JUDGEMENT						
PROBLEM (IMPORTANCE)	No	Probably no	Probably yes	Yes		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No studies included

Full evidence profiles are presented in Tables S4.2.1 and S4.2.2.

3.3.2.2 | Recommendations. The EtD Table is presented in Tables 6A–6I (Boxes 5–9).

BOX 5 | Guidance on the Impact of Exposure to Dampness on the Risk of New-Onset Asthma.

Exposure to any dampness indicator increases the risk of developing asthma	Conditional recommendation
Exposure to water damage may increase the risk of developing asthma	Conditional recommendation

BOX 6 | Guidance on the Impact of Exposure to Mould on the Risk of New-Onset Asthma.

Exposure to mould (visible/odor) increases the risk of developing asthma	Conditional recommendation

BOX 7 | Guidance on the Impact of Exposure to Both Dampness and Mould on the Risk of New-Onset Asthma.

Exposure to dampness and mould increases the risk of developing asthma	Conditional recommendation

BOX 8 | Guidance on the Impact of Exposure to Dampness on Asthma-Related Outcomes.

Exposure to dampness might increase the risk of moderate asthma exacerbations	Conditional recommendation
Exposure to dampness might decrease asthma control and lung function	Conditional recommendation

3.3.2.3 | Justification. The SR showed moderate certainty of evidence for the association between mould exposure and increased risk asthma development. However, due to the high ROB, a conditional recommendation was formulated.

Very low certainty of evidence showed that exposure to dampness and mould might be associated with increased risk of asthma exacerbations, worsened asthma control and/or asthma-related QoL and decreased lung function. Thus, although the impact of exposure to dampness/mould is acknowledged by the GDG, a conditional recommendation was formulated.

BOX 9 | Guidance on the Impact of Exposure to Moulds on Asthma-Related Outcomes.

Exposure to mould might increase the risk of asthma exacerbations and might decreases lung function	Conditional recommendation
Exposure to mould may increase the risk of moderate asthma exacerbations and may decrease asthma-related quality of life	Conditional recommendation
Exposure to mould decreases asthma control	Conditional recommendation

3.3.2.4 | Age Subgroups. The risk of new-onset asthma and/or asthma exacerbation following exposure to dampness/mould was more prominent in children [84]. Children and adults were at similar risk for decreased asthma-related QoL and lung function [84].

3.4 | PECO 4: Is Indoor Exposure to Pesticides Associated With Increased Risk of New-Onset Asthma and/ or With Unfavourable Asthma-Related Outcomes?

Indoor exposure to pesticides may occur through multiple pathways: food, water, indoor air, soil, house dust, surfaces, and depends on the proximity to areas treated with pesticides, domestic uses at home, in the garden, on pets (flies and ticks) and also on humans (lice and scabies) [111]. These pesticides may interact synergistically with indoor allergen sensitization rendering individuals more susceptible for new-onset asthma. The Infants' Environmental Health study showed that prenatal exposure during the first half of pregnancy may be associated with increased risk of increased respiratory infections and wheezing in the first year of life [112] and that current exposure may affect children's respiratory and allergic health at 5 years of age [113]. In a recent SR 79% of the studies included found positive associations with pesticide exposure and asthma, wheezing, acute respiratory infections, AR, eczema and lung function impairment [114].

3.4.1 | Does Indoor Exposure to Pesticides Increase the Risk of New-Onset Asthma?

3.4.1.1 | Summary of Supportive Evidence. The SR reported that exposure to fungicides did not significantly increase the risk of developing asthma (very low certainty of evidence).

However, exposure to insecticides and herbicides was associated with low certainty of evidence with increased risk of new-onset asthma (OR = 1.75; 95% CI: 0.78; 3.90 and OR = 2.12; 95% CI: 0.94; 4.75, respectively). There was no association between indoor pesticide exposure and low lung function (OR = 1.12; 95% CI: 0.88; 1.41, very low certainty of evidence) [84].

Full evidence profiles are presented in Tables S5.

3.4.2 | Does Indoor Exposure to Pesticides Impact Asthma-Related Outcomes?

3.4.2.1 | Summary of Supportive Evidence. The SR showed very low certainty of for the associations between indoor exposure to standard insecticides (older formulation), formulations B1, B2 and low-irritant aerosols and a decreased FEV1 [84].

3.4.2.2 | Recommendations. The EtD Tables are presented in Table 7 (Boxes 10 and 11).

BOX 10 | Guidance on the Impact of Indoor Exposure to Pesticides on the Risk of New-Onset Asthma.

Exposure to insecticides and herbicides may be associated with new-onset asthma	Conditional recommendation

BOX 11 | Guidance on the Impact of Indoor Exposure to Pesticides and Asthma-Related Outcomes.

Exposure to standard insecticide (older formulation), formulations B1, B2 and low-irritant aerosols may impact lung function	Conditional recommendation

3.4.2.3 | Justification. Although the importance of the exposure to pesticides is highly acknowledged by the GDG, as the certainty of evidence for the impact of indoor exposure to pesticides and increased risk of new-onset asthma and of unfavorable asthma-related outcomes was very low the GDG formulated a conditional recommendation.

4 | Exposures Not Covered by the Systematic Reviews

This Guideline formulated recommendations for the impact of exposure to cleaning agents, dampness/mould, indoor pesticides, and VOCs on the risk of new-onset asthma and on asthma-related outcomes. Nonetheless, the GDG acknowledges the risk conferred by other indoor exposures not covered by the SRs. These include indoor allergens and endotoxin and many indoor pollutants of emerging concern like asbestos, phthalates, adipates, terephthalates, microplastics (MPs), lead, radon (Rn), indoor PM, perfluorocarbons, UV-filters, synthetic musks, parabens, siloxanes, neonicotinoids and drug residues. Mixed sources of carbon monoxide (CO), sulphur dioxide (SO_2), nitrogen dioxide (NO_2), ozone (O_3) and PM emissions such as cooking stoves, indoor fireplaces, heaters, are also important indoor pollutants, especially in association with a low socio-economic status. Another exposure that was not included in the SR was exposure to chlorine subproducts in indoor swimming pools, a particular risk factor for allergy and asthma development.

The GDG also stresses the distinction of several types of exposure that can occur through lifetime: (a) early life exposure, with abundant literature demonstrating that environmental stressors in early life are major contributors to allergic diseases and asthma; (b) linear incremental exposure (e.g., ageing effect); (c) repetitive school, recreational and occupational exposure; (d) chronic low level exposure; (e) multiple-hit exposure reflecting a combination of intermittent and persistent exposure with variable dose and length of exposure (weight gain/loss, diet, exercise, pollution, microbiome, habitat change, etc) [13].

Furthermore, the GDG highlights the importance of integrating these individual exposures into the complex configuration of the indoor exposome [12, 13, 115–117], continuously shaped by the levels of outdoor pollution, human activities, and the building characteristics (Figure 2).

4.1 | Indoor Pollutants of Emerging Concern

Through an extensive literature review, 355 chemicals and their concentrations were documented and analysed for human exposure. Together with 81 compounds without concentration and 75 VOCs an indoor exposome database with 511 chemicals was established. Sixteen toxicological end points were selected for toxicity prioritization. Toxic equivalency factor-based toxicity, calculated from EPA's ToxCast database, revealed a comprehensive atlas of the chemicals that had a primary contribution. Many of the prioritized compounds are currently neglected or are not actively studied [115].

Exposure to phthalates may affect the respiratory microbiome, which may increase risk of development of allergy and asthma [118]. In vivo and in vitro studies have revealed the link between phthalate exposure oxidative stress, respiratory sensitization and unfavorable asthma-related outcomes [119, 120]. Overall, the evidence for association between phthalate exposure and respiratory disease is weak and inconsistent [121].

Microplastics (MPs) trigger local and systemic inflammation, oxidative stress, and epithelial barrier cytotoxicity with lung and systemic toxicity. Sources of MPs include indoor and outdoor dust, traffic, degradation of plastic [15, 21–23, 122–127]. Moreover, MPs can also serve as vectors for different pathogens [124, 127]. Most studies about MP effects have been conducted in isolated cell cultures or on animal models, while studies on the effects of MP on humans are lacking.

Painted window sashes and frames in homes built before 1978 may contain lead-based paint; this is a special concern because the friction of opening and closing windows can release lead

TABLE 6H | Evidence to decision table supporting guidance on the impact of exposure to moulds on the risk of moderate asthma exacerbations or decreased asthma-related QoL (quality of life).

	JUDGEMENT						
PROBLEM (IMPORTANCE)	No	Probably no	Probably yes	Yes		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No studies included

TABLE 6I | Evidence to decision table supporting guidance on the impact of exposure to moulds on the risk of decreased asthma control.

	JUDGEMENT						
PROBLEM (IMPORTANCE)	No	Probably no	Probably yes	Yes		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No studies included

TABLE 7 | Evidence to decision table supporting guidance on the impact of indoor exposure to pesticides (standard insecticide (older formulation), formulations B1, B2 and low-irritant aerosols) on lung function.

	JUDGEMENT						
PROBLEM (IMPORTANCE)	No	Probably no	Probably yes	Yes		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No studies included

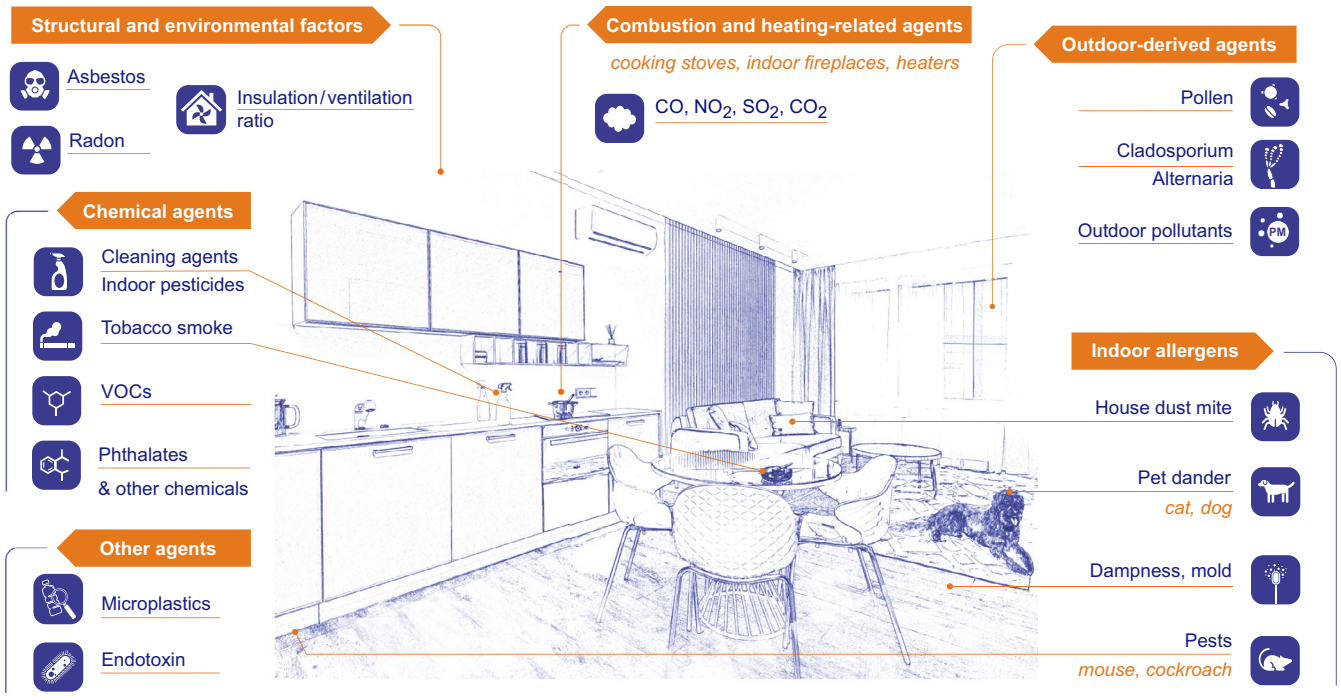

FIGURE 2 | Indoor exposures are part of the complex indoor exposome, which is continuously impacted by outdoor pollution and human activities. CO, carbon monoxide; CO_2, carbon dioxide; NO_2, nitrogen dioxide; PM, particular matter; SO_2, sulfur dioxide; VOC, volatile organic compound.

dust into the home. Young children are more susceptible to the toxic effects of lead exposure. In a cross-sectional evaluation lead exposure was associated with both high total serum IgE and asthma in boys [128].

Radon (Rn) is a naturally occurring radioactive gas formed from the radioactive decay of uranium in soil, rocks, and groundwater. It is well known for its carcinogenicity. Some evidence also reported that exposure to Rn may be also linked to other lung conditions, including asthma and COPD [129, 130]. In children with asthma exposure to Rn was associated with increased asthma morbidity [131].

PMs accumulate indoors from the outdoor environment, cooking, combustion activities (burning of candles, use of fireplaces, heaters, stoves, fireplaces and chimneys, cigarette smoking),

cleaning activities. They have been linked with deterioration of asthma control or decreased lung function [132, 133].

Asbestos is a mineral fibre that occurs in rock and soil. Because of its fiber strength and heat resistance it has been used in a variety of building construction materials for insulation and as a fire-retardant. Most of the evidence on asbestos exposure comes from the occupational settings where is has been shown to cause asbestosis (interstitial fibrosis), asbestos-related pleural disease and lung malignancies. There have been some isolated studies, which have demonstrated an association with small airways disease or reversible airway obstruction [134–136].

4.2 | Mixed Indoor Pollutants

Almost 3 billion of the world's poorest people still rely on solid fuels (wood, animal dung, charcoal, crop wastes, and coal) burned in inefficient and highly polluting stoves for cooking and heating, currently resulting in about 4 million premature deaths annually among children and adults from respiratory and cardiovascular diseases, and cancer [137]. According to the WHO these stoves are one of the major contributors to poor IAQ. Especially women of all age living in low- and -middle-income countries are at greater risk.

These indoor heating/cook sources are mixed sources of carbon monoxide (CO), sulphur dioxide (SO_2), nitrogen dioxide (NO_2), ozone (O_3) and PM emissions. CO is a gas produced by the incomplete combustion of carbonaceous fuels such as wood, petrol, charcoal, natural gas, and kerosene CO exposure was associated with increased risk of hospitalization for asthma, COPD, lower respiratory tract infection, and influenza-pneumonia. Women were more susceptible [138]. Together with ultrafine particles, CO exposure was associated with increases in the relative odds of ED visits for asthma in children [139]. NO_2 exposure was similarly associated with increased risks of ED visits and hospital admissions for asthma, especially in children and the elderly with asthma [140].

4.3 | Chlorine Products Exposure in Swimming Pools

Chemicals resulting from the interaction between chlorine and organic matter trigger airway epithelial damage and with nasal and lung permeability, with consequent airway inflammatory (reflected in a specific metabolomic profile in exhaled breath) and remodeling [141, 142]. Children, lifeguards, workers in swimming pools and elite swimmers are at increased risk. The prevalence of atopy, rhinitis, asthma and AHR was reported to be increased in elite swimmers compared with the general population [143].

5 | Recommendations for Healthcare Professionals and for Patients With Asthma

5.1 | Integration of Indoor Exposure Assessment and Mitigation in the Asthma Management Plan

Incorporating the assessment of indoor exposure (Table 8), together with a personalized adaptation and mitigation plan incorporated in the asthma management plan, is strongly recommended for all patients with asthma. A special attention should be given to the most vulnerable categories: children, pregnant women, and elderly with multiple co-morbidities, patients with disabilities or those socio-economically disadvantaged. Asthma environmental-driven endotypes could also benefit more from this approach.

TABLE 8 | Check-list for the HCP (healthcare professional) managing patients with asthma. All indoor settings are recommended to be evaluated: Home, school, work, indoor recreational areas.

Building characteristics	Temperature
	Humidity
	Ventilation system
	Humidification devices
	Insulation, carpet and cabinetry
	Central heating and cooling systems
	Flooring
Exposures	Combustion sources (oil, gas, kerosene, coal, and wood)
	Radon
	Indoor allergens
	Tobacco products
	Moisture
	Furniture made of certain pressed wood products
	Products for household cleaning and maintenance
	Products for personal care or hobbies
	Outdoor sources such as outdoor air pollutants, pesticides, and radon

Estimating exposure from inhalation requires information on the concentrations of contaminants in the air and the timeframe over which inhalation exposure occurs. To calculate an inhaled dose, inhalation rates and patient body weight might also be needed. The expertise necessary for applying exposure assessment methods can be found in a number of disciplines: biology, chemistry, toxicology, physiology, occupational hygiene, epidemiology and ventilation or building design engineering, thus a multidisciplinary approach is warranted. The panel recommends evaluating all indoor settings where the patient with asthma may be potentially exposed (Table 8).

The classical way of monitoring indoor pollutants is air and dust analysis and therefore, the spectrum of analytical techniques needs to be continuously broadened [144]. In addition, there is also a role for human biomarkers, preferably in saliva or urine [13]. A further important aspect is the post hoc analysis of house dust and urine samples, which are stored in environmental specimen banks. The identification and temporal tracking of new aggressors is thereby enabled. Combining classical interior analytics with human biomonitoring to promptly detect

indoor pollutants using the exposomic approach is highly recommended [13, 27].

Adaptation measures to reduce the impact of indoor air pollutants on asthma-related outcomes at an individual level include: (a) reduction or removal of the sources of pollutants; (b) ventilation with clean outdoor air; (c) use of air cleaners to filter the air; (d) use of personal monitors and alert systems [145]. These measures are all likely to come at a significant net cost. Conversely, mitigation protects those who do not or cannot adapt. Even with mitigation, however, policy to promote more adaptation can offer net benefits. Such policy could, for example, lower adaptation costs or improve indoor air quality [146]. The potential for adaptation should be individually evaluated in each patient with asthma and a personalised plan should be co-created using various methods: complying with alerts issued at high indoor pollutant concentration thresholds ("Threshold"), complying with alerts based on the behaviour of others ("Social Learning"), adapting on days for which the benefits of adaptation exceed their costs ("Rational Actor"), and adapting to offset their rising asthma-related risks ("Forced") [147].

WHO, the EC and EPA have all developed tools like the Air Quality Index (AQI), defined indoor pollutants concentrations thresholds, and provides information on major sources of indoor air pollutants (41, 56,117). In January 2019, the National Institute for Occupational Safety and Health (NIOSH) released the Dampness and Mould Assessment Tool for Schools and the Dampness and Mould Assessment Tool for General Buildings [148, 149]. The IDEAL cluster, focused on identifying the chemical and microbiological drivers contributing to indoor air pollution, identifying their main sources and assessing their health impacts, including asthma, has recently published its first joint policy brief to improve indoor air quality in Europe. These tools may help identify and determine the severity of known and unknown areas of dampness and mould, prioritize repair and remediation, and track past and present problems.

The use of personal monitors and/or warning systems is recommended, especially for vulnerable patients with asthma [27, 150–153]. Continuous indoor air quality (IAQ) monitoring is the best way to receive real-time data on the levels of indoor air pollutants. By using a multi-pollutant air quality sensor, one can track parameters such as VOCs, humidity, and more (92).

Using a portable air cleaner and/or upgrading the air filter in the furnace or central heating, ventilation, and air-conditioning (HVAC) system can help to improve IAQ. These appliances can reduce indoor air polluntants and thus improve asthma-related outcomes; however, they cannot remove all pollutants from the air [154–157]. Currently, air cleaning technologies lack an accepted test standard to evaluate their VOC removal performance. The activated carbon air cleaner device seems to outperform in VOC clean air delivery rate the hydroxyl radical generator device [158]. Interventions in schools to improve IAQ show potential [159], however the number of interventions that can be implemented are limited due to the high costs involved. Interventions are therefore mostly limited to awareness campaigns and ventilation strategies, which show moderate success and rely strongly on the participation and motivation of the occupants of the classrooms [160].

In occupational exposures (i.e., professional cleaners, health workers), possible preventive measures include substitution of cleaning sprays, bleach, and ammonia; minimising the use of disinfectants; limit use of disinfectants in spray form, avoidance of mixing products; use of respiratory protective devices; and worker education [100]. Moreover, the education of unions, consumer, and public interest groups to encourage safer product is recommended [52, 161].

5.2 | The Pursuit of Optimal Indoor Air Quality: The Balance Between Insulation and Ventilation

The American Society of Heating, Refrigerating and Air-Conditioning Engineers (ASHRAE) recommends that buildings maintain a rate of air changes per hour (ACH) to ensure health and comfort. ACH calculation is based on the volume of the building and the number of occupants. ASHRAE sets the standard for minimum ventilation rates for residential spaces at 0.35 ACH or 15 cubic feet per minute per person, whichever is greater [162].

For new building construction, integrating ventilation into the design from the outset is the most efficient approach. This involves strategic planning such as location of the vents, incorporating ventilation in insulation plans or use of advanced framing technique such as incorporating channels for air flow that do not compromise the thermal envelope. Retrofitting existing building to optimize the insulation-ventilation balance requires a careful assessment of the existing structure to identify the best ways to improve ventilation without disrupting the home's thermal efficiency such as sealing leaks and adding vents, installing mechanical ventilation or adjusting insulation around ventilation. Humidity sensors and air quality monitors (e.g., carbon dioxide monitors) can guide adjusting ventilation as needed.

Advanced ventilation techniques have become increasingly important in modern homes as provide a continuous supply of fresh air but also enhance energy efficiency by recovering heat during the ventilation process (Table 9) [163, 164].

5.3 | Multifaceted Environmental Control Interventions Are Beneficial in Improving Asthma Symptoms and a Viable Prevention Strategy

Environmental control has an established role in asthma management. However, given the complexity of the indoor exposome an environmental intervention approach that targets multiple indoor aggressors is likely to be an appropriate strategy.

6 | Recommendations for Policy Makers and Regulators, Citizen Groups, ETC.

At the societal level policies that reduce indoor air pollutants are of great importance. The health risks of indoor air pollution have been addressed by several international working groups and projects (e.g., WHO, EPA 2005). In recent years, the WHO has been addressing this need through the development

TABLE 9 | Advanced ventilation techniques contributing to optimal indoor air quality.

Demand-controlled ventilation (DCV)	Smart technology that adjusts ventilation based on the occupancy and the quality of indoor air. Uses sensors for indoor pollutants and humidity levels
Smart ventilation systems	Take the capabilities of DCV a step further by integrating with home automation systems. Can be programmed and controlled via smartphones or other devices, allowing for precise management of indoor air quality. Work in tandem with smart thermostats to adjust heating or cooling when ventilating
Energy recovery ventilators and heat recovery ventilators	Recover energy from the outgoing stream of exhaust air to precondition the incoming fresh air

of a series of guidelines for IAQ, including three indoor AQG volumes: (1) dampness and mould (published in 2009), (2) selected pollutants (published in 2010), and (3) household fuel combustion [137]. Moreover, generally IAQ is covered in the recent WHO Air Quality Guideline (AQG) from 2021 (41). In 2003, the European Commission adopted a new Strategy on Environment and Health with the overall aim to reduce diseases caused by environmental factors in Europe. Moreover, the EU Action Plan on Environment and Health from 2004 intends to develop work on improving IAQ. In 2023, the WHO/Europe developed a tool to support the protection of children's health from chemical pollution of indoor air in settings where children spend substantial amounts of time, such as schools, kindergartens, and day-care centers (IAQ Risk Calculator). The IAQ Risk Calculator estimates the health risks for children from combined exposure to multiple hazardous chemicals in indoor air, which are often higher than the sum of risks posed by single chemicals due to synergistic effects. To assess IAQ in public and private buildings, several national agencies (e.g., EPA) have set health-based guide values and standards that enable a health-related assessment of substance concentrations in indoor air.

Based on the current research evidence the EAACI guidelines recommend decrease being exposed to indoor pollutants by frequent monitoring and use of smart ventilation systems and be prepared for adverse asthma-related outcomes (loss of control, exacerbations, lung function decline) in settings with heavy indoor pollution. For clinicians, the evidence informs incorporating environmental measures into their clinical advice to patients with asthma.

The EAACI guidelines recommendations aim to support the decisions of policy makers on the indoor pollution mitigation and adaptation plan, highlighting the benefits of preserving children's and adults' health and of minimising the impact on patients suffering from chronic diseases. Scientific societies and patient associations, along with other stakeholders in the health sector, should increase their engagement and advocacy to raise awareness on the importance of clean air policies and on the implementation of the latest WHO AQG and the EPA IAQ.

A list of policies implemented by different governments and organizations is presented in Table 10.

7 | Recommendations for Future Research/Gaps in Knowledge

Although a significant amount of research on indoor air pollutants impact on asthma has been done, major gaps in our knowledge remain to be further explored (Table 11).

A critical step resides in understanding the mechanisms by which exposure to indoor air pollutants contributes to the onset of asthma, from the individual risk (e.g., genetic or epigenetic factors) to the synergistic effects of multiple exposures. Improved mechanistic understanding of how asthma exacerbations occur following exposure to indoor pollutants is needed to develop prevention strategies. Another key question is the difference between short-term exposures versus time-weighted averages over longer time periods in increasing the risk of adverse asthma-related outcomes. Moreover, the impact of exposure to indoor air pollutants might vary over the life course with future research directed toward differential effects at different stages of development [13, 165]. Cumulative impacts of pollutant exposures in combination with other environmental stressors is another challenging concept for which innovative strategies are needed [166].

Effective strategies to address these gaps include epidemiological, toxicological and mechanistic studies. Longitudinal cohort studies that can capture time-varying outcome and exposure information have long been recommended for gene–environment interactions. A stratified sampling based on summaries of individual exposures and outcome trajectories coupled with a full conditional likelihood approach for estimation that adjusts for the biased sample was proposed [167]. By providing risk profiles and models of causality the exposomic approach is the best tool helping to understand and influence the bidirectional effect between human beings and the environment, as detailed in the subchapter of these the EAACI guidelines on environmental science [168]. Together with exposome studies, better population studies are required to understand population health and its determinants [169].

The demand for smart real-time monitoring and alert systems is rapidly growing. The ability of individual sensor-based time-resolved exposures to VOCs was tested in support of identifying potential sources informing exposure mitigation strategies [170]. Challenges still remain in terms of maturing technologies, or data mining and their interpretation [171].

TABLE 10 | Comparison of policies for improved IAQ.

Region	Policy/Guidance for regulating IAQ	Aim	Asthma-specific interventions and programs
EU	Strategy on Environment and Health EU Action Plan on Environment and Health National Emission reduction Commitments Directive Energy Performance of Buildings Directive Zero Pollution Action Plan Construction Products Regulation	Improved IAQ and reduced diseases caused by environmental factors in Europe	
USA	US EPA Indoor Air Quality Standards	Deliver information on IAQ and set exposure limits	Asthma Community Network Model State Indoor Air Quality Act
WHO	WHO AQG 2021 WHO indoor AQG—dampness and mould WHO indoor AQG—specific pollutants WHO indoor AQG—household fuel combustion	Protection of public health from adverse effects of indoor exposure to air pollution	IAQ Risk Calculator

Abbreviations: AQG, air quality guideline; EPA, the United States Environment Protection Agency; EU, European Union; IAQ, indoor air quality.

Most importantly, awareness of IAQ risks and availability of appropriate regulation are lagging behind the technologies. Regulatory acceptable concentration thresholds, monitoring methods and definitions of air quality vary across countries and thus what constitutes legally actionable evidence is difficult to implement further.

Last but not least, assuring public health has to undergo dramatic changes to adapt to the new understanding the ecology of health and the interconnectedness of the biological, behavioural, physical domains [172]. Thus, it becomes imperative to transform national health policies by incorporating the precepts of environmental health [6, 11, 14, 145, 146, 165]. Approaching health from a population perspective commits the nation to understanding and acting on the full array of factors that affect health. What is needed is the creation of an effective intersectoral public health system. One approach based on the assumption that the greatest benefit is achieved by shifting the entire distribution of risk to a lower level of risk, thus advocates prevention strategies applicable to a broad population. Because most people are in categories of moderately elevated risk, this strategy offers the greatest benefit in terms of population-attributable risk. Another approach focuses on differences in exposure risk combined with disparities in health outcomes, and thus tailor preventive measures to most vulnerable or most responsive groups (e.g., environmental endotypes). To create an efficient intersectoral model of the public health system the governmental sector needs to work in partnership with academia, media, business, community-based organizations and communities.

8 | Discussion

The EAACI Guideline recommendations on the impact of indoor air pollutants on the risk of new-onset asthma and on asthma-related outcomes summarizes the available evidence included into SR and rates their certainty based on the GRADE approach. Recommendations were formulated for exposure to different indoor air pollutants contributing to either residential or occupational exposure. Unfortunately, the evidence provided by the SRs was low- to very low quality and thus only conditional recommendations could be formulated. Only observational studies were available, so the quality of the evidence was moderate at its best. In addition, cross -sectional and case–control studies were used to assess the association between pesticide indoor exposure and asthma incidence, which is of course not ideal. Another inherent limitation is the difficulty of quantifying chronic exposure, particularly at the personal level. Measurements suffer from their own imprecision, often cross-sectional nature and a wide variability depending on external characteristics (e.g., the room, vertical dispersion, rhythm of ventilation and more). Taking into account that the pathophysiological effects may depend upon different models (e.g., thresholds or persistence), we can only expect a very rough estimation of true exposure at a personal level. Another important gap stems from the fact that pollutants are more often evaluated individually, while the possibility of between-pollutant interactions has been neglected [84]. The gaps in evidence (Table 11) need to be quickly solved in order to provide solid evidence as a basis for individual management plans and for pollution regulation policies.

Compared to the WHO AQG 2021, the WHO Guidelines on specific indoor pollutants, and the WHO Guidelines on dampness and mould, the evidence focused on the impact of different indoor pollutants on asthma development as well as on asthma exacerbations as defined as ED visits, hospital admissions, lung function, use of asthma medication, and QoL due to asthma. In addition, the EAACI Guideline provides recommendations about mixed exposures, which are not covered by the WHO Guidelines.

In general, poor IAQ can have adverse health effects, especially on the cardiovascular and respiratory system. However, health

TABLE 11 | Gaps in evidence for the impact of indoor air pollutants on asthma development and asthma-related outcomes and plans to address.

Gaps in evidence	Plan to address	Priority
Understanding of the biological mechanisms of exposure aggravating asthma pathogenetic mechanisms (inflammation, airway hyperreactivity, and remodeling)	Mechanistic studies on individual exposure followed by the exposomic approach for building risk profiles Confirmation of risk profiles in population-based studies	High
Which indoor pollutant is specifically associated with which specific asthma outcome	Identify mode-of-action of specific pollutants—mechanistic studies	High
Timing of exposure associated with asthma-related outcomes	Compare short- and long-term effects of exposure to indoor pollutants	High
Concentration of specific indoor pollutants associated with asthma-related health aspects (onset and outcomes)	Identify the minimum concentration needed to induce pathological changes within cells and tissues	High
Additive effects of indoor air pollutants and other environmental stressors (e.g., outdoor air pollution, climate change, allergens)	Exposomics and population-based studies	High
Effects of indoor pollutants exposure on different age groups, different gender, pregnant women	Studies on health aspects of indoor pollution on different developmental stages	High
Individual versus population risk profiles	Population-based studies to identify individual and population risks. Personalized risk assessment Integrate behavioral research	Medium
Expand focus on vulnerable populations	Priorities studies examining the impacts of indoor air pollutants on disadvantaged groups, including those in low-resource settings, to inform equitable interventions Enhance technology accessibility Explore cost-effective strategies for implementing sensor-based monitoring and real-time alert systems, ensuring accessibility for low-income populations. Encourage research on the differential impacts of indoor pollutants across regions and socioeconomic strata, focusing on high-burden areas like low- and middle-income countries	High
Investigate long-term impacts	Emphasize longitudinal cohort studies to capture the cumulative effects of indoor	High

effects of indoor air pollutants vary depending on the timing, duration and type of exposure (continuous, intermittent), exposure threshold, co-exposures, as well as the resilient response of the individual (Figure 3). The effects on the lung include direct toxicity and oxidative stress of epithelial cells, altered microbiome, acute and chronic inflammation, maladaptive immune response, impaired lung development and remodeling. These leads to exacerbation of pre-existing conditions such as asthma leading to increased morbidity and mortality.

Exposure to a mixture of VOCs or to single components (e.g., aldehydes, toluene) is possibly linked to new-onset asthma and worsening of asthma. Another recent metanalysis reported a medium-sized effect on the risk for onset of asthma and wheezing, but with the effect size variable by country, age and disease type [173]. Moreover, in atopic patients, exposure to VOCs was associated with a decreased lung function supporting that vulnerable population is at increased risk upon exposure to VOCs [174].

Exposure to cleaning agents either in occupational or in residential settings is possibly associated with asthma development and the exacerbation of asthma-related symptoms. Similar findings were reported by Vizcaya et al., who showed that the prevalence of current asthma was non-significantly higher among current and former cleaners compared to never-cleaners [175]. Additional evidence suggests that the risk for asthma is higher for domestic and industrial cleaners compared to professional employees [176], women are at greater risk for decreased lung function [177, 178] and children have higher odds of recurrent wheeze and asthma diagnosis if living in homes with a higher frequency of use of cleaning products during their infancy [104].

Exposure to dampness and mould increases the risk of new-onset asthma. Our recommendations on the increased risk are supported by several studies that showed that indoor exposure to dampness and mould raises the risk for asthma development, ever diagnosed asthma, and current asthma [60, 61, 179, 180].

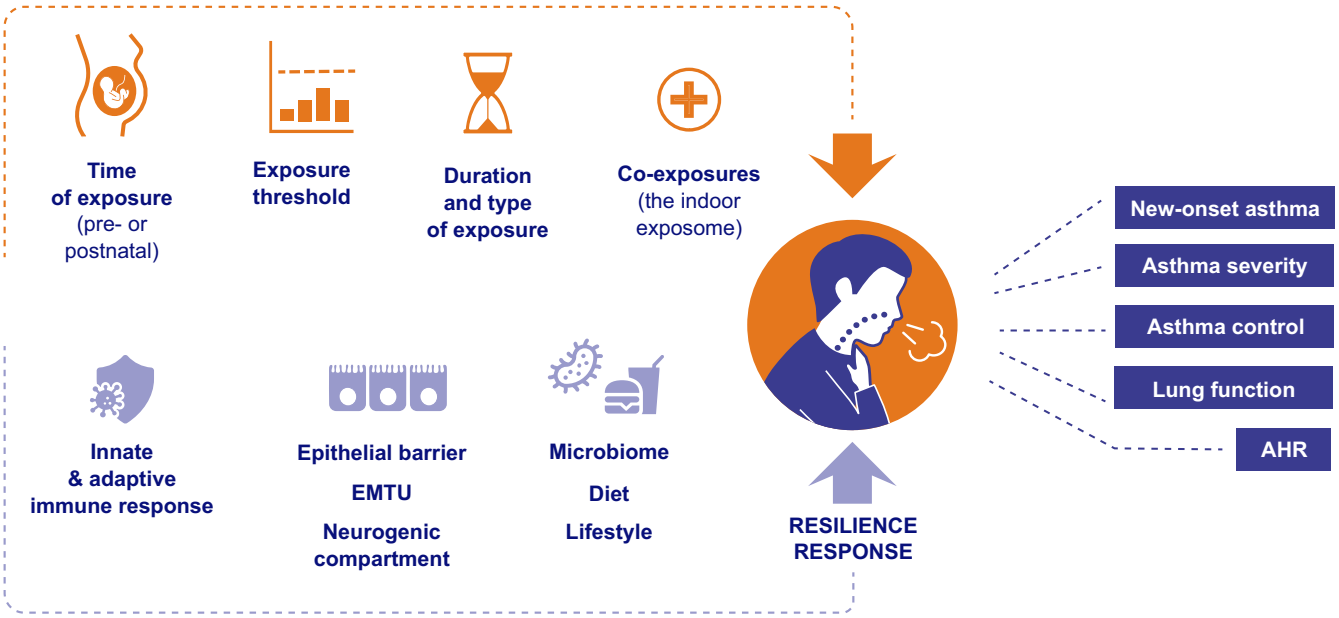

FIGURE 3 | Various aspects of indoor air pollutants impact health outcomes, including asthma onset, control, and severity. AHR, airway hyperreactivity; EMTU, epithelial-mesenchymal trophic unit.

Exposure to indoor pesticides may be associated with decreased lung function. Xu et al. reported that overall indoor pesticide use was not associated with respiratory symptoms in children, with the exception of use of insecticides in special rooms [87]. Moreover, among subjects exposed to over-the-counter insecticide sprays and powders, respiratory symptoms (i.e., cough, dyspnoea, wheezing, lower respiratory pain, and irritation) were the most frequently reported health effects [181]. The decrease in FEV1 and increased AHR were more pronounced in asthmatic patients exposed to low levels of insecticide aerosols compared to not-exposed patients, irrespective of whether the patients had mild or severe asthma [182]. Our recommendations are aligned with the general body of evidence showing that data are insufficient to draw firm conclusions on the impact of pesticide use on asthma development or worsening [183].

Overall, education, awareness campaigns, and community-based interventions in reducing exposure and improving IAQ, addressing global disparities, development of harmonized regulatory standards and international collaboration to establish unified thresholds for indoor pollutants and best practices for IAQ monitoring and intervention are urgently needed to protect against the negative impact of indoor air pollutants. Many of the indoor air pollutants come from daily indoor activities, thus individuals need to know how to adopt specific measures to improve the quality of the indoor air. Several tailored educational programs teaching on signs of unhealthy air and providing advice on construction, remodeling, ventilation and avoidance of indoor air pollutants, infographics on lung friendly workspaces and programs for corporate wellness are already in place [184]. EPA's IAQ Tools for Schools Action Kit helps ensuring good indoor air quality schools [185]. Every May, EPA hosts Air Quality Awareness Week. Similar educational and awareness activities are provided by the European Commission [186]. However, more needs to be done: a survey conducted in 2022 showed that only a minority of respondents (27%) have heard of EU's air quality standards [187]. Furthermore, low- and middle income countries and low-resource communities need increased educational and financial support to fight pollution.

9 | Conclusion

The current EAACI Guideline on the impact of indoor air pollutants on the risk of new-onset asthma and on asthma-related outcomes evaluated exposure to specific and mixed air indoor pollutants, including pesticides. Recommendations were formulated according to the GRADE approach. Exposure to all indoor pollutants is probably associated with an increased risk of new-onset asthma and asthma worsening, with lung function being especially impacted. Moderate certainty of evidence was found only for exposure to dampness and mould.

Due to the overall quality of evidence and the high risk of bias, conditional recommendations were formulated for all exposures. However, the GDG acknowledges the overall risk and burden of indoor pollutants and their association with asthma development and exacerbations. Interventions to reduce indoor air pollution and increase IAQ are certainly of paramount importance to prevent asthma and to improve its management.

The EAACI Guideline on the impact of indoor air pollutants on the risk of developing asthma and on asthma-related outcomes is meant to be a desk-reference tool for decision making by all involved parties. HCPs should include in their asthma management plan personalized approached to evaluate indoor exposures and reduce its impact on asthma. Patients are encouraged to take advantage of this information to prevent increased hospitalization rates and reduced quality of life. Policy makers should act upon the recommendations provided with proper mitigation and adaptation strategies.

Author Contributions

I.A., M.J., and C.A.A. conceptualized the outline of the guideline and wrote the manuscript. All the other authors revised and approved final manuscript.

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Conflicts of Interest

I.A. reports Deputy Editor of Allergy journal. K.N. reports grants from National Institute of Allergy and Infectious Diseases (NIAID), National Heart, Lung and Blood Institute (NHLBI), National Institute of Environmental Health Sciences (NIEHS) and Food Allergy Research & Education (FARE); Stock options from IgGenix, Seed Health, ClostraBio, Cour, Alladapt; Advisor at Cour Pharma; Consultant for Excellergy, Red tree ventures, Before Brands, Alladapt, Cour, Latitude, Regeneron, and IgGenix; Co-founder of Before Brands, Alladapt, Latitude and IgGenix; National Scientific Committee member at Immune Tolerance Network (ITN), and National Institutes of Health (NIH) clinical research centres; patents include 'Mixed allergen composition and methods for using the same', 'Granulocyte-based methods for detecting and monitoring immune system disorders' and 'Methods and Assays for Detecting and Quantifying Pure Subpopulations of White Blood Cells in Immune System Disorders'. J.S. works for Centro Cochrane Iberoamericano; the centre received funding for conducting the systematic reviews of the evidence. Marek Jutel reports personal fees outside of submitted work from Allergopharma, ALK-Abello, Stallergenes, Anergis, Allergy Therapeutics, Leti, HAL, GSK, Novartis, Teva, Takeda, Chiesi, Pfizer, Regeneron, AstraZeneka, Lallemand, Shire, Celltrion Inc., Genentech, Roche, Verona, Lek Pharmaceuticals, Arcutis Biotherapeutics and FAES FARMA. All other authors report no conflicts of interest in relation to this manuscript.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.