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Indoor Residential Chemical Emissions as Risk Factors for Respiratory and Allergic Effects in Children: a Review

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Practical Implications – Composite wood materials that emit formaldehyde, flexible plastics that emit plasticizers, and new paint have all been associated with increased risks of respiratory and allergic health effects in children. Although causal links have not been documented, and other correlated indoor-related exposures may ultimately be implicated, these findings nevertheless point to a new class of little recognized indoor risk factors for allergic and respiratory disease, distinct from the current set of indoor risk factors. The available evidence thus raises initial questions about many common residential practices: for instance, using pressed wood furnishings in children's bedrooms, repainting infant nurseries, and encasing mattresses and pillows with vinyl for asthmatic children. The findings summarized here suggest a need for substantially increased research to replicate these findings, identify causal factors, and validate preventive strategies.

Abstract

Most research into effects of residential exposures on respiratory health has focused on allergens, moisture/mold, endotoxin, or combustion products. A growing body of research from outside the U.S., however, has associated chemical emissions from common indoor materials with risk of asthma, allergies, and pulmonary infections. This review summarizes 21 studies in the epidemiologic literature on associations between indoor residential chemical emissions, or emission-related materials or activities, and respiratory health or allergy in infants or children. Associations, some strong, were reported between many risk factors and respiratory or allergic effects. Risk factors identified most frequently included formaldehyde or particleboard, phthalates or plastic materials, and recent painting. Findings for other risk factors, such as aromatic and aliphatic chemical compounds, were limited but suggestive. Elevated risks were also reported for renovation and cleaning activities, new furniture, and carpets or textile wallpaper. Reviewed studies were entirely observational, limited in size, and variable in quality,

and specific risk factors identified may only be indicators for correlated, truly causal exposures. Nevertheless, overall evidence suggests a new class of residential risk factors for adverse respiratory effects, ubiquitous in modern residences and distinct from those currently recognized. It is important to confirm and quantify any risks, to motivate and guide necessary preventive actions.

Key Words: *indoor air quality; formaldehyde; phthalates; volatile organic compounds; asthma; allergy*

Introduction

Concerns about recent increases in the incidence of asthma and allergies worldwide have stimulated much research on potential environmental causes (Chan-Yeung and Becker, 2006). Most of this research has focused on exposures in residences, where children spend the majority of their time. The indoor residential risk factors of primary interest for asthma, allergies, and respiratory health have included allergens such as dust mites, cockroaches, and pet dander; moisture, mold, and endotoxin; and combustion byproducts from appliances, tobacco, or other indoor combustion sources (Johnson et al., 2002).

A growing body of epidemiologic research from outside the U.S., however, has shown associations between common indoor materials or their emissions in residences, and a variety of adverse respiratory and allergic health effects, including increased risk of asthma, pulmonary infections, and allergy. The identified risk factors include specific organic compounds such as formaldehyde, benzene, and phthalate esters, indoor materials or finishes such as carpet, flexible flooring, paint, and plastics, and indoor activities related to these materials.

Although many recent review articles have considered aspects of this overall picture (Becher et al., 1996; Andersson et al., 1997; Institute of Medicine, 2000; Delfino, 2002; Johnson et al., 2002; Weisel, 2002; Brunekreef, 2004; Dales and Raizenne, 2004; Viegi et al., 2004; Richardson et al., 2005), none includes the full range of current epidemiologic evidence linking indoor chemical emissions and these health effects. This article reviews and summarizes current findings from studies in the scientific literature on associations between indoor residential chemical emissions, or materials or activities associated with such emissions, and respiratory or allergic effects in infants or children.

Methods

The online site Entrez PubMed (www.pubmed.gov) was used to identify relevant epidemiologic studies in the published literature through mid-2006. Additional publications were selected from reference lists in identified articles. From the identified papers, studies meeting the following eligibility criteria were selected:

- publication in peer-reviewed scientific journals;
- investigation of associations between respiratory or allergic effects in human infants or children (up to age 16) and either indoor residential chemical exposures or residential materials or activities considered to be risk factors for chemical exposures; and
- a cross-sectional, case-control, cohort, panel, or quasi-experimental design.

Findings were excluded on adult populations, school or ambient exposures, risks from byproducts of combustion including tobacco smoke (e.g., Rolle-Kampczyk (2002)) and risks

from synthetic bedding materials (e.g., Ponsonby (2003)). Findings were also excluded if not controlled for key potential confounding factors (e.g., Lehmann (2002c)), or if risk factors were determined for time periods not relevant to the health effect measured (e.g., Tavernier (2006)).

Eligible studies were organized in two broad (potentially overlapping) categories of health outcomes: asthma and lower respiratory effects (e.g., diagnosed asthma, asthma symptoms, lower respiratory symptoms, obstructive or chronic bronchitis, bronchial obstruction, adverse changes in lung function assessed by spirometry, airway inflammation assessed by exhaled nitric oxide, house dust mite sensitization, and pulmonary infections) and allergic effects (e.g., atopy by skin prick tests, allergic symptoms, diagnosed rhinitis, diagnosed eczema, increased total or specific IgE as indicators of allergy, and altered subpopulations of T lymphocyte cells that may influence immune response and allergy).

Reported risk factors, health outcomes, subjects, and designs were abstracted and summarized. Reported associations between the studied risk factors and health outcomes were also abstracted, generally expressed as odds ratios (ORs), which estimate the relative odds of an outcome occurring in association with a specific risk factor. Specific associations reported in multiple studies most frequently and consistently were highlighted. Detailed critique of the study design, measurements, analyses, and potential biases in the reviewed studies, and detailed synthesis of findings for all risk factors reviewed are not provided, although these issues are discussed. Findings on associations between respiratory health and outdoor air ventilation of residences were also summarized, as ventilation influences indoor concentrations and exposures related to indoor sources present. To help in interpretation of the associations reported, example sources of specific indoor chemical emissions were provided. To facilitate comparisons, air concentrations of formaldehyde were converted to common units of $\mu g/m^3$ where necessary, from mg/m^3, parts per million, or parts per billion.

Results

Twenty-one identified studies met the selection criteria: 11 studies investigating health effects associated with indoor residential chemical *concentrations*, including formaldehyde, aromatic compounds, aliphatic compounds, and other volatile organic compounds (VOCs) in air as well as phthalate esters in dust; and 12 studies (with some overlap) investigating health effects associated with indoor residential chemical *sources*, including recent painting or renovation, new furniture or particleboard, new synthetic carpets, plastic surfaces, and cleaning activity. Study designs included cohort, case-control, and cross-sectional, with many studies including multiple approaches. The 19 most recent papers, published between 1996 and 2005, all reported studies conducted in Western Europe, Australia, or Russia. The two earliest papers, published in 1989 and 1990, reported studies of formaldehyde and were the only reports from the U.S.

Higher concentrations of chemical compounds measured in air (or dust) in residences were associated in numerous studies with health effects related to respiratory, allergic, or immune effects in infants or children. (See Appendix 1 for information on risk factors, health outcomes, subjects, and study designs. See Table 1 for reported associations.)

Types of indoor residential materials and coatings, as well as renovation or cleaning activities, were associated with health effects related to asthma or allergy in infants or children. (See Appendix 2 for information on risk factors, health outcomes, subjects, and study designs. See Table 2 for reported associations.) The following summary combines findings for some chemical compounds with those of their primary indoor sources: formaldehyde and particleboard

(a composite wood material bonded with urea-formaldehyde resin), and phthalates and plastic surface materials.

Associations with multiple findings

The most frequently identified risk factors related to indoor residential chemical emissions include formaldehyde or (formaldehyde-emitting) particleboard, plasticizers or plastic materials, and recent painting. Findings for each of these risk factors are summarized below by type of health effect.

Higher indoor concentrations of formaldehyde or presence of particleboard were associated with the following outcomes:

- diagnosed asthma, in three studies: with concentrations over 60 $\mu g/m^3$ (Rumchev et al., 2002), with concentrations over 73 $\mu g/m^3$ (but only in houses with ETS) (Krzyzanowski et al., 1990), and (nonsignificantly) with particleboard (Jaakkola et al., 2004);
- diagnosed chronic bronchitis in one study, with concentrations over 73 $\mu g/m^3$ (Krzyzanowski et al., 1990);
- increased exhaled nitric oxide in one study (a marker of lower airway inflammation elevated among asthmatics), with concentrations > 61$\mu g/m^3$ (Franklin et al., 2000);
- increased wheeze in one study, with particleboard (Jaakkola et al., 2004); increased frequency of nighttime and daytime wheeze among wheezing subjects in one study, especially with concentrations >22-32$\mu g/m^3$, but not presence of wheeze (Venn et al., 2003);
- respiratory symptoms in one study, with concentrations >20$\mu g/m^3$ (Garrett et al., 1999), but not in two studies with the concentrations observed (Quackenboss et al., 1989; Krzyzanowski et al., 1990);
- adverse effects on lung function in two studies, with concentrations over 36 $\mu g/m^3$ (30 ppb) (Krzyzanowski et al., 1990) and over 30 $\mu g/m^3$ (Quackenboss et al., 1989), but not in one study with concentrations over 61$\mu g/m^3$ (Franklin et al., 2000);
- atopy and increasing severity of sensitization in one study, with concentrations above 20$\mu g/m^3$ (Garrett et al., 1999) and allergy in one study, with particleboard (Jaakkola et al., 2004).

Higher concentration of specific phthalate plasticizers (measured in dust rather than air due to relatively low volatility), or the presence of plasticizer-containing surface materials such as polyvinyl chloride (PVC) or vinyl, were associated with:

- increased asthma diagnosis in two studies, with DEHP >1.3 mg/g dust (and with an apparent dose-response relation beginning with the category of 0.05-0.13 mg/g dust), and (nonsignificantly) with BBzP >0.25 mg/g dust (Bornehag et al., 2004);
- bronchial obstruction in one study, with PVC flooring (dose-response relationship) (Jaakkola et al., 1999), and in another paper on the same study, more strongly associated with PVC flooring combined with low ventilation rate (Oie et al., 1999);
- wheeze in two studies, with new "linoleum" floor (indicating "unspecified flexible flooring," including various synthetic floorings such as PVC and possibly true linoleum) (Jaakkola et al., 2004) and with plastic wall materials (Jaakkola et al., 2000), but in one study not with new PVC flooring (Emenius et al., 2004a);
- both cough and phlegm in one study, with plastic wall materials (Jaakkola et al., 2000);

- allergy in two studies, with new "linoleum" (i.e., unspecified flexible) flooring (Jaakkola et al., 2004), with BBzP >0.25 mg/g dust, and with PVC flooring (Bornehag et al., 2004);
- both rhinitis and eczema in one study, with BBzp >0.25 mg/g dust (Bornehag et al., 2004);
- not upper respiratory symptoms in one study, with plastic wall materials (Jaakkola et al., 2000).

Painting or renovation was associated with the following outcomes:

- wheeze in four studies (Diez et al., 2000; Diez et al., 2003; Emenius et al., 2004a; Jaakkola et al., 2004), but not in one study (Trevillian et al., 2005);
- wheeze (synergistic increase in observed risk associated with use of synthetic bedding), in one study (Trevillian et al., 2005);
- history of asthma (synergistic increase in observed risk associated with use of synthetic bedding) (Trevillian et al., 2005);
- obstructive bronchitis in one study (Diez et al., 2003);
- pulmonary infection in one study (Diez et al., 2000);
- allergy in two studies (Aberg et al., 1996; Jaakkola et al., 2004).

Associations with limited reported findings

Available findings on other risk factors for indoor residential chemical emissions were sparse. These risk factors include indoor air concentrations (of aromatics, aliphatics, and "other" VOCs), indoor materials (textile wall coverings, new wall covering, new furniture, new synthetic carpets), and use of chemical products for cleaning.

Some of these studies included, as outcomes, altered cytokine secretion profiles among T-cells in blood. Early programming of the T-cell system toward Th2 reactivity (e.g., the cytokines interleukin-4 (IL-4), IL-5, and IL-13) is considered to increase allergic responsiveness, while programming toward Th1 reactivity (e.g., the cytokines interferon-gamma (IFN-□) and tumor necrosis factor-alpha (TNF-□) is considered to inhibit allergic responsiveness (Lehmann et al., 2002b). Georas (2005) provides additional detail on this topic. The clinical significance of specific changes in cytokine secretion profiles has not been established.

Regarding increased concentrations of aromatic organic compounds: toluene, benzene, and dichlorobenzene were associated with increases in diagnosed asthma (Rumchev et al., 2004), benzene and styrene with increased pulmonary infections (Diez et al., 2000), toluene, m-p-xylene, 4-ethyltoluene, and cholorobenzene with increased IgE sensitization to foods or total IgE (Lehmann et al., 2001), naphthalene with elevated proportions of IL-4-producing type 2 T cells in cord blood (Lehmann et al., 2002b), and styrene with reduced proportions (contrary to hypotheses) of CD8+ IL-4-producing T cells (Lehmann et al., 2001). Aliphatic hydrocarbons such as hexane, nonane, and decane, which may be at higher concentrations with recent painting but come from many sources, were associated with increased IgE sensitization to foods and with reduced proportions of IFN-□-producing T cells (Lehmann et al., 2001). Limonene and trichloroethylene were associated with reduced proportions (contrary to hypotheses) of IL-4-producing T cells (Lehmann et al., 2001; Lehmann et al., 2002b), whereas methylcyclopentane and delta-3-carene were associated with increased proportions (Lehmann et al., 2002b) Tetrachloroethylene was associated with reduced proportions of IFN-□-producing T cells (Lehmann et al., 2002b). Higher total VOC concentration was not associated with persistent wheezing (Venn et al., 2003).

New synthetic carpet was associated with increases in current asthma, wheezing, and allergy (Jaakkola et al., 2004). New furniture and new wall covering were both associated with increased allergy (Jaakkola et al., 2004). Textile wall covering was associated with increased bronchial obstruction (Jaakkola et al., 1999; Oie et al., 1999).

Use of many chemical-based cleaning products by mothers was associated with a significant dose-response increase in persistent wheeze in young children and, for comparison of the highest to lowest chemical use scores, a doubling of odds for both persistent wheeze and (nonsignificantly) for late-onset wheeze (Sherriff et al., 2005).

Outdoor air ventilation

Lower outdoor air ventilation rates in homes in one study were associated directly with increased prevalence of asthma and allergic symptoms in children, with a dose-response trend (Bornehag et al., 2005b), and in another study with a nonsignificant *decrease* in recurrent wheezing in infants (Emenius et al., 2004b). This last study reported (in a separate publication) no influence of ventilation rate on risk estimates related to indoor painting or moisture (Emenius et al., 2004a). A third study, however, found that lower outdoor air ventilation rates, although not directly associated with risk of bronchial obstruction in infants, *synergistically increased* the risk of bronchial obstruction associated with indoor sources present (Oie et al., 1999). For instance, for risk of bronchial obstruction among infants living in homes with plasticizer-containing surfaces compared to those in homes without, the OR over all study homes was 2.9, while in analyses restricted to homes with low ventilation rates the OR was 12.6 (Oie et al., 1999). Similar but less strong "effect modification" by ventilation rate were observed with risks from other indoor sources, including textile wallpaper, environmental tobacco smoke, and dampness.

Typical indoor conditions relative to conditions associated with health risks

Increased health risks have been reported at indoor formaldehyde concentrations above 16, 20, 22, 30, 36, 50, 60, 62, 73, and 75 $\mu g/m^3$, and with the presence of particleboard. Indoor concentrations of formaldehyde reported in the reviewed studies include: mean 35 $\mu g/m^3$ (Quackenboss et al., 1989); mean 32 $\mu g/m^3$, 4% over 75 $\mu g/m^3$, maximum 175 $\mu g/m^3$ (Krzyzanowski et al., 1990); median 16 $\mu g/m^3$, maximum 139 $\mu g/m^3$ (Garrett et al., 1999); mean 30 $\mu g/m^3$, maximum 224 $\mu g/m^3$ (Rumchev et al., 2002); median 22 $\mu g/m^3$, 75th percentile 32 $\mu g/m^3$ (Venn et al., 2003). Installation of new particleboard was reported in 25% of residences (Jaakkola et al., 2004). Magnitudes of associated effects were large. For instance, in an Australian cross-sectional study, proportions of diagnosed asthmatic children were 16%, 39%, and 44% in categories for peak indoor formaldehyde concentrations of less than 20, 20-50, and greater than 50 $\mu g/m^3$ (Garrett et al., 1999). In an Australian case-control study, risk of emergency treatment for asthma increased by 39% at concentrations over 60 $\mu g/m^3$ (Rumchev et al., 2002). The authors report an estimated 3% increased risk per 10 $\mu g/m^3$ increase in indoor formaldehyde concentrations over the observed range starting below 10 $\mu g/m^3$, if the formaldehyde concentration is treated as a continuous variable; however, the published figure shows risk increasing only above 50 $\mu g/m^3$, at a much steeper rate (Rumchev et al., 2002).

For phthalates, increased health risks have been reported at BBzP dust concentrations >0.25 mg/g dust, relative to reported measured U.S. concentrations of median 0.04, 90th percentile 0.28, and maximum 1.3 mg/g dust (Rudel et al., 2003); at DEHP dust concentrations >1.3 mg/g dust (but with a nonsignificant dose-related increase beginning above 0.05 mg/g dust)

relative to reported measured U.S. concentrations of median 0.34, 90th percentile 0.85, and maximum 7.7 mg/g dust (Rudel et al., 2003); and with the presence of PVC flooring and other plastic surface materials. Reported frequencies of plastic surfaces include: PVC flooring in 54% and vinyl wallpaper in 10% of children's bedrooms (Bornehag et al., 2005a) and PVC flooring in 65% and PVC wallpaper in 33% of children's bedrooms (Jaakkola et al., 1999). For plastic surfaces, ORs as high as 3.4 and 3.3 were reported for persistent wheeze and bronchial obstruction, and for phthalates, ORs as high as 2.9 and 3.0 for diagnosed asthma and diagnosed rhinitis.

Increased health risks have been reported with painting during pregnancy or during the first years of an infant's life. Reported frequencies of painting include: 44% during pregnancy (Diez et al., 2003), and over 50% during the year before or year after a child's birth (Emenius et al., 2004a). For recent painting, ORs were reported as high as 5.6 for pulmonary infections and 1.9 for wheezing. For redecoration that may include painting, ORs up to 4.1 were reported for obstructive bronchitis. For hexane, nonane, and decane, the top quartile of bedroom exposures had ORs of 9.6, 5.7, and 8.1 for increased food-specific IgE, with median concentrations of 2.5, 1.2, and 2.7 $\mu g/m^3$ (Lehmann et al., 2001).

Brown (1994) has provided perhaps the most comprehensive available summary of reported indoor concentrations of VOCs, based on multiple studies published between 1978 and 1990. Other publications summarize more recent studies of indoor residential VOC concentrations; e.g., Zhu (2005), Brown (2002). Brown (1994) provides geometric mean indoor concentrations in new residences and ratios of new vs. established residences; e.g., m&p-xylene (18 ug/m^3, 16:1) and n-decane (5 ug/m^3, 80:1). Reitzig (1998) shows that renovation is associated with high indoor concentrations of both common and uncommon chemical compounds. Data from Brown and Retzig document that new constuction and renovation can be a source for many chemical compounds in indoor air.

Sources of indoor chemical emissions

Table 3 provides example sources for the chemical compounds investigated in the reviewed studies.

Discussion

The reviewed studies have reported many associations, some strong, between risk factors for indoor residential chemical emissions and respiratory or allergic effects in infants or children. Reported statistically significant ORs ranged to high levels (even without considering the ORs up to 22.3 related to changes in cytokine expression profile in T-cell subpopulations): for formaldehyde, to 8.2; for aromatic chemicals, to 11.2; for aliphatic chemicals, to 8.1; for plastics and plasticizers, to 3.4 (and with low ventilation, to 12.6); and for painting, to 5.6. Elevated risks were also reported for renovation and cleaning activities, new furniture or particleboard, and carpets or textile wallpaper. Effects were evident with conditions very common in the studied populations of children for some risk factors such as formaldehyde, particleboard, DEHP, PVC surfaces, and recently painted surfaces.

Limitations

Persuasiveness of this body of findings is limited by the small total number of available studies involving a wide range of risk factors, health outcomes, populations, study designs, and

analysis strategies. The available studies include only one or two findings on each of many specific associations of risk factors and health outcomes, although multiple findings are available for several relationships. Discussion of the findings will emphasize those relationships with multiple findings.

This review does not provide a detailed critique of the design, measurements, analyses, and potential biases of all reviewed studies. Nor does it provide detailed synthesis or discussion of findings for the many specific risk factors or health outcomes studied. For instance, this paper does not distinguish exposures at different ages, separate findings for outcomes of causation and exacerbation of asthma, or interpret reported effects on subpopulations of T lymphocyte cells.

Alternate explanations for the findings reviewed here include: bias from inaccurate measurement of risk factors or health outcomes (such bias in these studies would generally be random or nondifferential, and thus would tend to diminish estimated associations toward the null); biased selection of study participants (not likely to be a substantial issue in most of the reviewed studies); confounding by true but unmeasured causes, if correlated with the studied risk factors (very likely in all reviewed studies); confounding by other indoor risk factors studied but not simultaneously adjusted for in multivariate analyses (an issue in several studies – see below); recall bias from participants' responses (a possible source of exaggerated estimates for popularly suspected risk factors, in cross-sectional or retrospective studies using parental report of renovation activities); chance but spurious associations resulting from large numbers of statistical comparisons (possible in studies investigating many risk factors and outcomes); and overall bias of the review toward positive findings because of publication bias (likely). Some of these issues are discussed further below.

All the reviewed studies used observational designs, with the limitations and biases inherent in such studies; however, research on these risks in humans, especially in children, will of necessity be largely observational. Although many studies used subjects from prospective cohort studies, which are the strongest type of observational study, few (Diez et al., 2000; Diez et al., 2003; Emenius et al., 2004a) (Trevillian et al., 2005) used a true prospective design, in which information on risk factors is collected and a cohort followed over time to examine associations between prior risk factors and later disease developing during follow-up. Most of the reviewed studies used cross-sectional methods, even if working with a prospective cohort population or with case and control subjects selected from a cohort or cross-sectional base. Most, that is, collected risk factor information at the same time as, or after, disease ascertainment. Of these studies with cross-sectional analyses, only a few collected information to *retrospectively* characterize risk factors in the relevant period prior to ascertainment of disease status (Aberg et al., 1996; Lehmann et al., 2002b; Sherriff et al., 2005). For instance, Lehmann (2002b) collected information after childbirth, asking parents about prior renovations and measuring indoor chemical concentrations. Because the study outcomes were measured in cord blood, a valid retrospective analysis was possible for risk factors of prenatal maternal exposure separate from postnatal exposure to the infant.

The validity of associations estimated in studies without either prior or retrospective information would depend on how well presence of sources (or contaminants) in houses after disease has developed correlates with their presence during the relevant period before disease development. The current *presence* of source materials in houses may be a more stable indicator of past conditions than the current indoor *concentration* of contaminants. However, later incorporation of a studied risk factor (e.g., replacement of carpet with PVC flooring for an asthmatic child) or exaggerated reporting of the risk factor that is systematically correlated with

past health outcomes ("recall bias") may produce spurious risk relationships (see Dales (2004)). In contrast, random changes in or random misreporting of risk factors are likely to diminish the ability to find even true associations in these studies.

Measurements of both health effects and risk factors/exposures in all reviewed studies have varying limitations, and possibilities for measurement bias. For example, symptoms assessed by questionnaire are susceptible to a variety of inaccuracies; asthma diagnosed in children under three years of age is not reliable; "linoleum floors" identified in a study from Russia may include any type of flexible synthetic flooring, but are assumed in this review to indicate probable PVC flooring; and even accurate measurements of indoor concentrations will inaccurately estimate personal exposures. This review did not systematically assess quality of measurements. In general, this type of error, if random, is most likely to diminish ability to detect true associations.

Regarding potential confounding, most reviewed studies adjusted for key potential confounding variables in multivariate models. A few studies adjusted in models for many but not all key confounders, omitting socioeconomic status (SES) or environmental tobacco smoke (ETS) (Diez et al., 2000; Diez et al., 2003; Bornehag et al., 2004). One study stratified analyses by age, gender, and ETS (Quackenboss et al., 1989). Studies with no control for confounding were excluded from the review.

Many of the risk factors investigated in these observational studies are highly correlated with each other and probably also with other true causes not studied. This source of confounding can produce spurious reported risk estimates for investigated compounds. Adjusting in statistical models simultaneously for the multiple risk factors investigated will at least reduce confounding bias *among* these risk factors, although confounding by other unmeasured risks can persist. (For example, Rumchev (2004) reported nine specific VOCs significantly associated with asthma in nine separate multivariate models, each adjusted for confounding; however, with all VOCs then included simultaneously in one model, only three were independently associated with asthma.) Most reviewed studies with multiple risk factors included such adjustment (Jaakkola et al., 1999; Oie et al., 1999; Lehmann et al., 2002b; Bornehag et al., 2004; Emenius et al., 2004a; Jaakkola et al., 2004; Rumchev et al., 2004; Trevillian et al., 2005). One study reported risk estimates for multiple risk factors, each adjusted only for confounding variables, but not for other risk factors (Lehmann et al., 2001); some other studies did not specify (Aberg et al., 1996; Diez et al., 2000). Thus, some of the elevated risks reported by Lehmann (2001), and possibly by Diez (2000) and Aberg (1996), are especially likely to be biased for some of the studied risk factors.

The simultaneous investigation of multiple risk factors increases the likelihood of "significant" findings (p-values <0.05) occurring by chance. This should be considered in interpreting the reported findings. Also, because positive findings are more likely to be published than negative findings, this review based on the published literature may provide a picture biased toward the positive, relative to the true findings of all studies performed (Copas and Shi, 2000). Furthermore, this review did not summarize all negative findings implied but not specifically reported in reviewed studies. Although the small numbers of studies available for each association of interest made it impossible to use available techniques to check for this publication bias, such bias seems likely for all relationships reviewed here.

Perhaps the most important source of bias in this body of research, even in the well-designed studies, is confounding. Confounding by causal exposures that are unmeasured, or measured but not adjusted for, may result in elevated risk estimates for a risk factor that is not causal but is correlated with a true cause. For instance, benzene may be an indicator for the

many other toxic constituents of tobacco smoke. The aliphatic hydrocarbons, such as hexane, nonane, and decane, although not generally considered high-risk exposures, had highly elevated risk estimates, including ORs for elevated food-specific IgE ranging from 5.7-9.6. These risks may be due to other exposures emitted from the same sources, whether paint, carpet padding, or adhesives or from other renovation-associated sources. Yet with such highly elevated risks, it is not clear what confounding factor could produce these estimates in the absence of a strongly causal indoor exposure emitted by renovation-related materials. For, instance, significant correlations (r) in bedroom air concentrations reported for decane include nonane (0.87), undecane (0.69), dodecane (0.52), styrene (0.58), chlorobenzene (0.66), and o-xylene (0.49), and for hexane, methylcyclopentane (0.58) (Lehmann et al., 2001).

Considering the types of limitations and strengths of the studies reviewed here, the findings (with the exception of those for aromatic chemicals) seem unlikely to be due to confounding by currently recognized indoor risk factors for asthma or respiratory disease; e.g., allergens, moisture/mold, endotoxin, or combustion products from indoor or outdoor sources. It seems more likely that these findings point to an additional class of important but little recognized risk factors for these outcomes, although with specific causal factors not yet identified.

Related findings

Controlled exposure studies with children are understandably rare, but can provide clear findings. A recent study reported significantly increased bronchial responsiveness in asthmatic children sensitized to dust mites after a 30-minute exposure to a low level of formaldehyde – 100 $\mu g/m^3$, the World Health Organization's recommended maximum value for indoor environments. A single pre-exposure to formaldehyde caused significantly increased immediate sensitivity to bronchial challenge with dust mite antigen (response at a 24% lower dose than with placebo), and also a significantly increased late-phase reaction (a 36% greater fall in FEV1) [Casset, 2006].

After homes, children spend most time in schools, but little research is available on the effects of chemical exposures in schools on children's health. One study reported an OR of 2.9 for asthma and exposure to formaldehyde in schools (Smedje and Norbäck, 2001). Wantke (1996) found that formaldehyde exposure in schoolchildren led to increased risk of IgE-mediated sensitization to formaldehyde, and to various symptoms, but the sensitization was not related to symptoms. Numerous studies in adults have reported associations of indoor chemical emissions or emission sources with respiratory and allergic effects (Pazdrak et al., 1993; Jaakkola et al., 1994; Norbäck et al., 1995; Wieslander et al., 1997a; Norbäck et al., 2000a; Hoppin et al., 2004; Lagercrantz et al., 2005; Jaakkola et al., 2006), including one study with controlled exposures (Pappas et al., 2000). Observational studies in adults have shown increased irritant symptoms associated with exposure to formaldehyde or VOCs in residences (Liu et al., 1991; Saijo et al., 2004). Dales (2004) has reviewed and contrasted findings from observational and experimental studies on asthma and exposures to VOCs and formaldehyde. Occupational asthma from high-level formaldehyde exposures is well recognized (Burge et al., 1985). Increased risk of asthma associated with exposures to domestic cleaning products has been documented (Zock et al., 2001; Medina-Ramon et al., 2003; Jaakkola and Jaakkola, 2006). Research has also shown that, for some chemicals identified as risk factors in indoor air, higher concentrations in *outdoor* air from heavy traffic or industry are respiratory health risks. Reported ORs for asthma severity in children related to outdoor concentrations were, for formaldehyde, 1.4 (Delfino et al., 2003a); for

benzene, 5.9; for toluene, 5.0; and for m-p-xylene, 3.6 (Delfino et al., 2003b). Ware (1993) reported an increase in diagnosed asthma and chronic lower respiratory symptoms with high levels of ambient VOCs.

A substantial body of research has associated the use of synthetic bedding materials with consistently increased risk of asthma, wheeze, reduced FEV1, and nasal symptoms in children (Strachan and Carey, 1995; Frosh et al., 1999; Zacharasiewicz et al., 2000; Ponsonby et al., 2002; Ponsonby et al., 2003; Ponsonby et al., 2004; Trevillian et al., 2004; Trevillian et al., 2005). Although a role of chemical emissions from synthetic bedding materials is possible, this increased risk, also found for sheepskin bedding, seems more likely to be due to the much higher concentration of dust mites found in these materials. For instance, Mills (2002) found significantly higher content of house dust mite allergen (Der p 1) in pillows and comforters filled with synthetics rather than feathers (7- and 15-fold, respectively). Rains (Rains et al., 1999) reported that new synthetic pillows accumulated three times as much Der p 1 as feather pillows within one year.

Plausibility of findings and possible mechanisms

Long term low-level chemical exposures in the home, where infants and children spend most of their time, may result in appreciable cumulative exposures during a period of relatively high susceptibility. Still, it is not yet clear through what mechanisms inhalation of relatively low levels of chemicals such as formaldehyde, plasticizers, and emissions from paint could increase asthma or allergies. The reviewed studies have associated indoor chemical emissions with increased airway inflammation, allergic sensitization, and potentially altered immune system development in infants and children, all processes involved in the genesis and exacerbation of asthma. Many of the effects reported in children have also been reported in adults, although fewer studies are available. Leikauf (2002) has developed a list of chemical compounds predicted to have a strong impact on the induction or exacerbation of asthma, based on available evidence. This list includes formaldehyde, styrene, benzene, and dibutyl phthalate. Although a prior critical review found limited evidence of an association between formaldehyde and asthma exacerbation, and inadequate evidence for an association between VOCs with asthma (Institute of Medicine, 2000), most studies reviewed here were not available for that report.

Regarding formaldehyde: particleboard, medium density fiberboard, interior plywood, and interior hardwood paneling are ubiquitous pressed wood products used in construction and furnishings. These materials contain large amounts of urea-formaldehyde resin, which releases formaldehyde over extended periods of time, especially in conditions of moisture and heat. A period of concern during the 1980s about irritation symptoms from formaldehyde-emitting products such as insulation and particleboard resulted in public concern, changes in product formulation, and lowered emissions of formaldehyde. Although indoor levels since then have popularly been considered sufficiently low to allay health concerns, findings reviewed here suggest otherwise.

In the studies reviewed, long-term formaldehyde exposures, from concentrations above levels as low as 20 $\mu g/m^3$ or from increased but unmeasured levels caused by particleboard, were associated with a variety of asthma-related and allergy-related health effects, although only levels above 60 $\mu g/m^3$ were associated with diagnosed asthma. Findings from shorter-term controlled human exposures have not been fully consistent. Most studies of *short-term* respiratory exposures to formaldehyde in adults have not seen changes in lower airway function or bronchial hyperreactivity ; e.g., in asthmatics, to 3,750 $\mu g/m^3$ for ten minutes (Sheppard et al.,

1984) or to 850 $\mu g/m^3$ for 90 minutes in subjects with substantial bronchial hyper-reactivity (Harving et al., 1986), and in nonasthmatics, to 3,750 $\mu g/m^3$ for 3 hours (Sauder et al., 1987)). However, Green et al. (1987), found clinically significant decrements in pulmonary function in both asthmatic and nonasthmatic adults exposed to 3,750 $\mu g/m^3$ formaldehyde for 1 hour. These findings on short-term exposures seem mostly inconsistent with a role of inhaled formaldehyde as an acute, nonspecific lower respiratory irritant, even in asthmatics, and consistent with the fact that inhaled formaldehyde is mostly absorbed in the upper respiratory tract (Harving et al., 1986). A marked exception to this pattern is the increased bronchial reactivity in sensitized asthmatic children caused by short-term, low-dose formaldehyde exposure (Casset et al., 2006).

Kriebel et al. (1993) found reductions in pulmonary function in students from 3-hour exposures to formaldehyde (mean 910 $\mu g/m^3$), repeated weekly for 10 weeks; reductions were found weekly and over 10 weeks, but resolved later. In a later study of pulmonary function in students with 2.5 hour exposures over 14 weeks to formaldehyde at mean levels of 1,380 $\mu g/m^3$, Kriebel (2001) found a short-term decrement in pulmonary function that decreased each week and disappeared, as well as a small decrement (0.5%) associated with each ppm of average exposure during all preceding study weeks, up to 14 weeks. These two studies had the advantages of using subjects not previously exposed or sensitized and settings with only one predominant exposure, doing detailed exposure assessments, including longer term exposures, and analyzing separately the effects of short- and long-term exposures. Several other studies have shown asthmatic responses to controlled formaldehyde vapor challenge in asthmatic workers who have had prior extended occupational exposure (e.g., (Nordman et al., 1985)). The positive studies tend to involve somewhat longer exposure periods during the studies or before, although the exposures involved are substantially higher than in most residences.

Analagous findings are available from animal models. Swiecichowski et al. (1993) found increases in both pulmonary resistance and airway reactivity in guinea pigs after controlled exposure to inhaled formaldehyde, with effects occurring at much lower concentrations with 8 hour exposures (>380 $\mu g/m^3$) than with 2 hour exposures (>11,200 $\mu g/m^3$). The authors, in reporting these effects from low concentrations that approach an environmentally relevant range, suggested that "the duration of exposure is important to the induction of airway hyperreactivity and that prolonged, low-level exposures may generate abnormal physiological responses in the airways not detectable after acute exposures (Swiecichowski et al., 1993)." Riedel et al. (1996) found that guinea pigs, after 5-day inhalation exposure to 310 $\mu g/m^3$ formaldehyde, had substantial increases in both sensitization (specific antibodies) and specific bronchial provocation to inhaled ovalbumin. Little airway inflammation was seen. Other animal studies have shown increased response to antigens after repeated exposure to formaldehyde (Sadakane et al., 2002; Kita et al., 2003). Franklin (2000) and Oie (1997) discuss possible mechanisms for human respiratory response to formaldehyde. Overall, available evidence suggests that long-term exposures to formaldehyde may have effects on respiratory sensitization at lower formaldehyde concentrations than would short-term exposures. Thus, the effects found in epidemiologic studies at the relatively low formaldehyde levels common in residences seem plausible, although sufficiently long-term controlled studies have not been performed. These effects may involve inflammation, or increased sensitization without inflammation.

The current evidence for health effects of low levels of indoor formaldehyde or the presence of formaldehyde-emitting materials, although incomplete, is the strongest among all the risk factors reviewed here. Interpretation of the elevated health risks reported for formaldehyde and particleboard, however, need to consider the complexity of indoor chemical emissions.

Formaldehyde is emitted indoors primarily from composite wood products, but also from a variety of indoor sources, including tobacco smoking and other combustion processes, varnishes, paints, carpets, and fabrics. Therefore other compounds emitted from these sources, to the extent that they are correlated with formaldehyde, may play a part in the elevated risks estimated for formaldehyde. Composite wood products also emit compounds other than formaldehyde, including high levels of other irritant aldehydes such as hexanal not included in the original product (Baumann et al., 2000), and terpene hydrocarbons, demonstrated to react with ozone to produce irritant compounds including aldehydes (Hodgson et al., 2002).

Phthalate plasticizers in dust or plastic surface materials were associated with a variety of asthma-related and allergy-related effects. Oie (1997) has proposed that phthalates may cause lung inflammation through their chemical similarity to prostaglandins, naturally occurring inflammatory agents. Lagercrantz (2005) has shown that controlled inhalation exposures to low levels of phthalates increased levels of exhaled nitric oxide, indicating lower airway inflammation. Indoor dust concentrations of phthalates have seemed useful for estimating ingestion exposures among small children, but not necessarily inhalation exposures among other building occupants. Weschler (2005), however, suggests that indoor phthalate dust concentrations may usefully estimate total airborne concentrations of phthalates (either in the gas-phase or sorbed on airborne particles), and thus may appropriately estimate inhalation exposure to phthalates in health studies. If, as is commonly believed, dietary intake of phthalates were the primary means of human exposure, with only a small portion of human intake occurring via air and dust (Wensing et al., 2005), and effects were systemic, then the reported associations of health effects with increased inhalation might seem implausible. Otake (2004), however, suggests that phthalates may have different effects when inhaled than when ingested, as inhaled phthalate esters may reach target organs in intact form, whereas ingested phthalates are metabolized and detoxified in several stages. Furthermore, Otake estimates that inhalation intake of phthalates from indoor environments is as important as dietary intake (Otake et al., 2004).

With respect to both composite wood products and flexible plastics: moisture is a well-documented risk factor for respiratory health effects (Institute of Medicine Committee on Damp Indoor Spaces and Health, 2004), and is usually assumed to be an indicator of microbiologic contamination and exposures. Directly measured microbiologic exposures, however, have generally not been as strongly related to health outcomes as have crude indices of moisture (Institute of Medicine Committee on Damp Indoor Spaces and Health, 2004). Often mentioned, but not often studied, is the fact that moisture in buildings increases nonbiologic types of emissions as well, including formaldehyde emissions from composite wood products (Matthews et al., 1986) and chemical byproducts from moisture-related degradation of DEHP in PVC flooring (Norbäck et al., 2000b).

Recent painting was associated with various respiratory outcomes, including pulmonary infections and allergic outcomes. Aliphatic compounds correlated with painting but emitted from other source as well were associated with various immunologic changes, such as increased food-specific sensitization and T cell activity modified toward an asthma phenotype. Wieslander et al. (1997a) reported that blood eosinophils and the prevalence of asthma were significantly increased among adults with newly painted indoor surfaces at home; recent painting was also associated with higher levels of VOCs and, when wood details were newly painted, with formaldehyde. Occupational exposure, to water-based and especially to solvent-based paints, have been associated with adverse effects on the lower airway (Wieslander et al., 1994; Wieslander et al., 1997b). Plausible mechanisms for these effects are unclear. Lehmann (2001)

(2002b) discusses possible mechanisms for the reported immunologic effects. Interior water-based paints emit a wide range of chemicals, including formaldehyde, glycol ethers, and 2,2,4-trimethyl-1,3-pentanediol monoisobutyrate. Solvent-based paints emit organic solvents including aromatic organic compounds. Type of paint used was not specified in the reviewed residential studies.

Aromatic chemical compounds were associated with diagnosed asthma, pulmonary infections, and increased IgE levels. Benzene in residential indoor air is introduced primarily from sources not in the intended scope of this review: ETS, vehicle emissions or stored fuel from attached garages, and vehicle exhaust from roadways. ETS in particular includes a large number of toxic compounds, only partially identified, that have been shown to increase asthma and respiratory disease in exposed children. Diez (2000) reported that indoor smoking increased average indoor benzene levels by 28%. Ideally, studies of benzene in air within residences would exclude homes with indoor smoking, or stratify analyses for these homes separately. The reviewed studies of indoor benzene concentrations did neither, but simply included a covariate to adjust for ETS in statistical models (Diez et al., 2000; Lehmann et al., 2001; Rumchev et al., 2004). This analysis strategy estimates risks from indoor benzene in a way that would also include risks from the other highly correlated chemical compounds in ETS. Thus, although benzene was reported to be associated with large increases in diagnosed asthma (up to 8-fold) and pulmonary infections (more than doubled) (Diez et al., 2000; Rumchev et al., 2004), this may reflect effects from the many constituents of ETS. Toluene, associated with diagnosed asthma (Rumchev et al., 2004) and increased specific and total IgE (Lehmann et al., 2001), has common indoor sources such as adhesives and solvent-based consumer products, but is also a component of tobacco smoke, so the ultimate causes here are unclear. Wichmann (2005) has shown that controlled exposure to toluene has a dose-related effect on the cytokine secretion of human mononuclear cells, unexpectedly in a direction considered to *inhibit* allergic reactivity; e.g., inhibiting IL-4 and increasing TNF-□.

Although styrene, another aromatic compound, is a component of tobacco smoke, Diez (2000) found indoor levels correlated not with ETS but with new wall-to-wall carpeting, a plausible styrene source. Thus the association found in this study between styrene levels >2.0 $\mu g/m^3$ and pulmonary infections is less likely to be explained by ETS. Because dichlorobenzene is emitted in residences primarily by household products made almost entirely of dichlorobenzene (e.g., moth balls, bathroom deodorizers), its one reported association with increased risk of diagnosed asthma (Rumchev et al., 2004) may indicate risk associated directly with that compound rather than with other correlated emissions. Chlorobenzene, 4-ethyltoluene, and m-p-xylene have each been associated with substantial increases in specific or total IgE, but in analyses not adjusted for other risk factors. Thus these associations may be due to effects from correlated exposures (i.e., emitted from the same sources, such as solvent-based paints). See Table 3 for example emission sources.

Reported risk estimates for aliphatics and "other" VOCs were not (except for methylcyclopentene, tetrachloroethylene, and trichloroethylene) adjusted for other chemical compounds studied (Lehmann et al., 2001). However, for a confounding factor to explain risks of the magnitude reported (e.g, ORs from 5-10 for aliphatic compounds and increased IgE), it must be at least as strong a risk and also highly correlated with the studied risk factor. Overall, these findings suggest that substantially increased specific and total IgE, along with changes in cytokine secretion profiles of T-cells, result from exposure to some substance(s) emitted from the same sources or processes as these compounds. See Table 3 for example sources. Neither

potential biologic mechanisms nor clinical significance of these outcomes is clear; however, further follow-up of this study cohort showed increased IgE to milk at age 3 to be associated with an OR of 30.1 for eczema at age 4 (Lehmann et al., 2002a).

New synthetic carpets have been associated in one study with current wheezing, allergy, and (nonsignificantly) with current asthma (Jaakkola et al., 2004). New furniture and new wall coverings have each been associated in one study with allergy (Jaakkola et al., 2004). Textile wall coverings have been associated in one study with bronchial obstruction in infants (Jaakkola et al., 1999). While these results are limited, these materials may all emit chemical compounds, especially when new, although any effects of these emissions are not yet understood. Also, carpets and textile wall coverings, as high surface area materials that are difficult to fully clean, may collect dust and microorganisms, but whether this results in increased or decreased adverse exposures is unknown. Some studies have found carpets associated with reduced prevalence of asthma (Zock et al., 2002), which may indicate a true benefit or a bias from the more frequent use of carpets with children not considered at risk of asthma.

Maternal use of chemical-based products during pregnancy has been associated in one study with both persistent wheeze and late onset wheeze in infants (Sherriff et al., 2005). Findings in this study, which used a simple index for the total number of "suspect" chemicals used for housecleaning, are useful for generating hypotheses, and support a need for studies with more precise characterization of the type and frequency of products used.

Finally, several studies investigated associations between ventilation rate and health effects, with two also investigating whether lower ventilation rate increased the risk of health effects associated with presence of specific indoor chemical sources. Findings were inconsistent, but the processes being studied are complex. Outdoor air ventilation generally dilutes and reduces the indoor concentrations of pollutants emitted by indoor sources, but this is less true for semi-volatile compounds and some volatile compounds such as formaldehyde, for which lower air concentrations can lead to increased emissions. Higher ventilation rates would be predicted to reduce health effects among occupants only if sources of exposures causing that health effect were present, and if indoor concentrations were reduced by increased ventilation. Since indoor air concentrations and exposures are determined by both sources and removal processes, epidemiologic research on health effects from indoor sources should include not only assessment of sources and indoor exposures, but also measurement of ventilation rate and an understanding of how these factors interact for specific indoor pollutants.

Implications

Although the available studies are limited in number and quality, and although causal relationships have not been demonstrated, the findings overall suggest adverse respiratory and allergic effects associated with some common indoor materials in residences, including formaldehyde-emitting materials, flexible plastics, and recently painted surfaces. Formaldehyde is currently the most consistently identified risk factor, but substantial suggestive evidence is available for phthalate plasticizers and paint emissions. Findings of risks associated with other indoor sources or chemical compounds are more limited, although the magnitude of risks associated with some aliphatic compounds is high. It is difficult to postulate confounding factors unrelated to indoor material or product emissions that would provide alternate explanations for the associations reviewed here, particularly the most consistent associations and those of large magnitude. Thus, these findings seem to point to a new class of little recognized indoor risk factors for respiratory and allergic effects, distinct from the currently recognized indoor risk

factors; i.e., allergens, moisture/mold, endotoxin, or combustion products from indoor or outdoor sources. It would thus be prudent to increase research on this problem, and possibly take some precautionary actions.

If the associations reviewed here were causal, it would mean the large-scale occurrence of important yet preventable adverse respiratory and allergic effects in infants and children worldwide, related to modern residential building materials and coatings and possibly exacerbated by decreased ventilation. A contribution of these indoor sources to the recent increase in asthma and allergy in developed countries seems initially plausible. These indoor materials are nearly ubiquitous in modern homes, and their use seems likely to increase in both developed and developing countries, leading to increased emissions. Furthermore, as average ventilation rates continue to decrease in houses in the U.S. (Diamond, 2000) and other countries in order to increase energy efficiency, concentrations of and *exposures* to many indoor pollutants will tend to increase even if the presence of sources and emissions were not to increase.

For risk factors such as formaldehyde or particleboard, with the most documentation, research should quantify risk/response relations, estimate the magnitude of public health impacts, and evaluate potential preventive actions. Current recommended guideline levels for indoor formaldehyde concentrations intended to prevent acute sensory irritation (and also considered adequate to control cancer risks) vary, but some are as high as 1 ppm, or 1,250 ug/m^3; e.g., Arts et al. (2006). If the reported associations of residential formaldehyde concentrations ranging from 20 to 75 µg/m^3 with adverse health effects were corroborated as causal, indoor concentrations of formaldehyde considered acceptable would need to be substantially lower.

The body of evidence reviewed here suggests a need to better evaluate the risks of respiratory and allergic health effects from many common residential materials and practices. Additional research on formaldehyde and the other risk factors reviewed here should better quantify risks, in order to motivate and guide any necessary preventive actions.

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ABBREVIATIONS (for text and tables)

BBzP	*n*-butyl benzyl phthalate
BHR	bronchial hyperresponsiveness
©	controlled for key confounding variables
CD4+	T-cells binding to antigens related to class II histocompatibility molecules
CD8+	T-cells binding to antigens related to class I histocompatibility molecules
DEHP	di(2-ethylhexyl) phthalate
DEP	diethyl phthalate
DIBP	diisobutyl phthalate
DINP	diisononyl phthalate
DnBP	di-*n*-butyl phthalate
dx	diagnosis, diagnosed
E<D	risk factors assessed before health effects assessed
E=D	risk factors and health effects assessed simultaneously
E>D	risk factors assessed after health effects assessed
ETS	environmental tobacco smoke
FEF(25-75)	forced expiratory flow at the 25^{th} and 75^{th} percentile of the pulmonary volume
FEV1	forced expiratory volume in 1 second
IFN-□	interferon gamma
IgE	immunoglobulin E
IL-4 (-5, -13)	interleukin-4 (-5, -13)
max	maximum
mo	month
OR	odds ratio
PEF	peak expiratory flow (=PEFR)
PEFR	peak expiratory flow rate
PVC	polyvinyl chloride
Qx	questionnaire
SBMA	S-benzylmecapturic acid (toluene metabolite)
SES	socioeconomic status
SPT	skin prick tests for atopy
sx(s)	symptom(s)
TCE	tetrachloroethylene
TNF-□	tumor necrosis factor alpha
TVOC	total volatile organic compounds
VOC	volatile organic compounds
yr	year

Note: 1 $\mu g/m^3$ formaldehyde =~ 0.80 parts per billion (ppb);
1 ppm = 1,250 ug/m^3

Table 1. Reported associations between *indoor chemical concentrations* and respiratory or allergic effects in infants and children

Risk Factors	Health Outcomes	
Indoor Pollutant Concentrations**	**Asthma-Related or Lower Respiratory**	**Allergy/Atopy/ Eczema/ Altered Immune Parameters**
FORMALDEHYDE	Diagnosed asthma in past year, n-s increased trend with peak home concentrations above 20 µg/m^3 (Garrett et al., 1999); Respiratory symptoms, significant increase associated with peak home concentration >50 µg/m^3, and n-s increased trend with peak home concentrations above 20 µg/m^3 (Garrett et al., 1999) Diagnosed asthma, OR=1.4*; 39% increased odds of asthma with concentrations ≥60 vs. <10 µg/m^3, or 3% increase per 10 µg/m^3 (Rumchev et al., 2002) If concentration >75 µg/m^3 in kitchen, unadjusted prevalence ratio for dx chronic bronchitis, 8.2* ($p<0.001$) and for dx asthma, 2.0* ($p<0.03$); Peak expiratory flow, linear decrease of 22% per 75 µg/m^3, 10% decrease at 38 µg/m^3; Chronic respiratory symptoms, not related (Krzyzanowski et al., 1990) Exhaled nitric oxide (as marker for lower airway inflammation) = 15.5 vs. 8.7 ppb nitric oxide	Atopy (by skin prick tests), OR=1.4*per 20 µg/m^3 peak home formaldehyde; {estimated OR=4.1 for 100 vs. 20 µg/^{m3}}; severity of sensitization increased >20 µg/m^3 (Garrett et al., 1999)

Risk Factors	Health Outcomes	
Indoor Pollutant Concentrations**	**Asthma-Related or Lower Respiratory**	**Allergy/Atopy/ Eczema/ Altered Immune Parameters**
	(*estimated RR=1.8*) for concentration ≥62 μg/m^3 (p=0.002); spirometry, no effect (Franklin et al., 2000) Excess variability in PEFR, 28%* increased risk with concentration >30 μg/m^3; Symptoms of allergy/irritation and of acute respiratory illness, no increased risk (Quackenboss et al., 1989) Among wheezing subjects, per quartile of formaldehyde (above 1st quartile at 16 μg/m^3), increased frequency of nocturnal wheezing, 1.45* (2.06* in atopics), and of daytime wheezing, 1.40* (1.68* in atopics); presence of wheezing not associated (Venn et al., 2003)	
AROMATICS		
Toluene	Diagnosed asthma, OR=1.3* per 10 μg/m^3 over range of 0-154 μg/m^3 (Rumchev et al., 2004)	Increased IgE milk, OR=11.2*; elevated total IgE, OR=3.3* (Lehmann et al., 2001)
Benzene	Diagnosed asthma, OR=1.9 per 10μg/m^3 over range 0-82 (8-fold risk if benzene ≥ 20 μg/m^3) (Rumchev et al., 2004) Pulmonary infections, OR=2.4* for >5.6 μg/m^3 (Diez et al., 2000)	
M-p-xylene		Increased IgE milk, OR=8.0* for >11.4 μg/m^3 (Lehmann et al., 2001)

Risk Factors	Health Outcomes	
Indoor Pollutant Concentrations**	**Asthma-Related or Lower Respiratory**	**Allergy/Atopy/ Eczema/ Altered Immune Parameters**
Styrene	Pulmonary infections, OR=2.1* for >2.0 µg/m^3 (Diez et al., 2000)	More subjects (66.6 vs. 0%) with reduced proportion of CD8+ IL-4 producing T cells (opposite of predicted), for >1.1 µg/m^3 (p<0.01) (Lehmann et al., 2001)
Dichlorobenzene	Diagnosed asthma, OR=1.2* per 10 µg/m^3 over range 0-202 µg/m^3 (Rumchev et al., 2004)	
4-ethyltoluene		**For concentration >1.6 µg/m^3, increased IgE milk, OR=9.3*; elevated total IgE, OR=3.0* (Lehmann et al., 2001)**
Chlorobenzene		Increased IgE milk, OR=5.9* for >0.6 µg/m^3 (Lehmann et al., 2001)
Naphthalene		Elevated proportion of IL-4-producing type 2 T cells in cord blood, OR=2.9* (Lehmann et al., 2002b)
Sum of 10 aromatics	Diagnosed asthma, OR=1.3* per 10µg/m^3 over range 0-622 µg/m^3 (4-fold risk if ≥ 60 µg/m^3, the median) (Rumchev et al., 2004)	
ALIPHATICS		
Nonane		Increased IgE milk, OR=5.7*; reduced # of IFN-g producing CD8+ peripheral T cells, OR=13.6* for >2.6 ug/m^3, (Lehmann et al., 2001)
Dodecane		Reduced # of IFN-□ producing CD8+ peripheral T cells, OR=20.3* for >2.6 µg/m3 (Lehmann et al., 2001)

Risk Factors	Health Outcomes	
Indoor Pollutant Concentrations**	**Asthma-Related or Lower Respiratory**	**Allergy/Atopy/ Eczema/ Altered Immune Parameters**
Decane		Increased IgE milk, OR=8.1*; reduced # of IFN-□ producing CD8+ peripheral T cells, OR=22.8*, for >5.7 µg/m3 (Lehmann et al., 2001)
Heptane		Higher proportion of children (75% vs. 22%) with increased CD8+ IL-4 producing T cells, (p=0.04) (Lehmann et al., 2001)
Hexane		Increased IgE milk, OR=9.6*; increased IgE egg, OR=6.4*, for >4.5 µg/m^3 (Lehmann et al., 2001)
OTHER VOCS		
Methylcyclopentane		Elevated proportion of IL-4-producing type 2 T cells in cord blood, OR=3.3* (Lehmann et al., 2002b)
Limonene		Reduced proportion of CD8+ IL-4 producing T cells, 60.0% vs. 5.9% for >44.3 µg/m^3; reduced proportion of CD4+ IL4-producing T cells, 80.0% vs. 14.3%, for >44.3 µg/m^3 (contrary to hypotheses) (p<0.01) (Lehmann et al., 2001)

Risk Factors	Health Outcomes	
Indoor Pollutant Concentrations**	**Asthma-Related or Lower Respiratory**	**Allergy/Atopy/ Eczema/ Altered Immune Parameters**
Δ^3-carene		Higher proportion of children (67% vs. 19%) with increased CD8+ IL-4 producing T cells, (p=0.03) (Lehmann et al., 2001)
Tetrachloroethylene		Reduced proportion of IFN-□-producing type 1 T cells in cord blood, OR=2.9* (Lehmann et al., 2002b)
Trichloroethylene		Reduced proportion of IL-4-producing type 2 T cells in cord blood, OR=4.4* (contrary to hypothesis) (Lehmann et al., 2002b)
Total VOCs	Persistent wheezing, no association (Venn et al., 2003)	
PHTHALATE ESTERS		
(concentrations in dust)		
BBzP	For 0.25-45.5 vs. <0.05 mg/g dust (quartile 4 vs. 1), asthma diagnosis, OR=1.9 (non-sig) (Bornehag et al., 2004)	For 0.25-45.5 vs. <0.05 mg/g dust, rhinitis diagnosis, OR= 3.0*; persistent allergic symptoms, OR= 2.0*; eczema diagnosis, OR= 2.6* (Bornehag et al., 2004)
DEHP	For 1.3-40.5 vs. <0.46 mg/g dust (quartile 4 vs. 1), asthma diagnosis, OR=2.9* (Bornehag et al., 2004)	
DEP, DIBP, DnBP, DINP	No associations	

* p-value ≤ 0.05

** all reported concentrations measured in indoor air unless concentrations in dust specified

Table 2. Reported associations between *indoor chemical source materials or activities* and respiratory or allergic effects in infants and children

Risk Factors	Health Outcomes	
Emission-Related Materials or Activities	**Asthma-Related and Lower Respiratory**	**Allergy/Atopy/ Eczema/ Altered Immune Parameters**
RENOVATION /NEW MATERIALS		
Painting, recent	Wheezing at 1 year, OR= 1.9*; (Diez et al., 2000) Recurrent wheezing OR=1.7* (Emenius et al., 2004a); current wheezing, OR=1.2 (n-s) (Jaakkola et al., 2004); Pulmonary infections at 6 weeks, OR=5.6* (Diez et al., 2000)	Any allergy, OR=1.2* (Jaakkola et al., 2004)
Recent painting of infant's room at age 4 wks	Wheezing at 7 years not related, OR=0.82, but synergistically increased risks of synthetic bedding in infancy on occurrence at age 7 of both recent wheezing (OR 1.65 → 5.39*) and history of asthma (OR 1.20 → 7.22*) (Trevillian et al., 2005)	

Risk Factors	Health Outcomes	
Emission-Related Materials or Activities	**Asthma-Related and Lower Respiratory**	**Allergy/Atopy/ Eczema/ Altered Immune Parameters**
Repainting or new wallpaper in child's bedroom after birth		Symptoms in the prior year of: allergic rhinitis with atopy by SPT, OR=1.7*; any of asthma, allergic rhinitis with atopy by SPT, or eczema, OR=1.2* (Aberg et al., 1996)
Redecoration (recent new painting, flooring, or furniture)	Obstructive bronchitis: risk in yr 1 from redecoration in yr 1, OR=4.1*; risk in yr 2 of redecoration in yr 2, OR=4.1*; no increased risk in yr 1 or yr 2 from redecoration during pregnancy (Diez et al., 2003) Wheeze: risk in yr 1 from redecoration in yr 1, OR=2.4 (non-sig); risk in yr 2 of redecoration in yr 2, OR=3.0* (Diez et al., 2003)	
New wall covering		Any allergy, OR=1.2* (Jaakkola et al., 2004)
New furniture, recent		Any allergy, OR=1.4* (Jaakkola et al., 2004)
New synthetic carpet, recent	Current asthma, OR=1.8 (ns); Current wheezing, OR=1.7* (Jaakkola et al., 2004)	Any allergy, OR=1.4* (Jaakkola et al., 2004)

Risk Factors	Health Outcomes	
Emission-Related Materials or Activities	**Asthma-Related and Lower Respiratory**	**Allergy/Atopy/ Eczema/ Altered Immune Parameters**
FORMALDEHYDE-EMITTING MATERIALS		
Particleboard older than 1 yr	Current asthma, OR=1.4 (ns); Current wheezing, OR=1.4* (Jaakkola et al., 2004)	Any allergy, OR=1.3* (Jaakkola et al., 2004)
PLASTIC-CONTAINING OR OTHER MATERIALS		
New linoleum floor	Current wheezing, OR=1.4* (Jaakkola et al., 2004)	Any allergy, OR=1.3* (Jaakkola et al., 2004)
PVC flooring	Bronchial obstruction, OR=1.9* (Jaakkola et al., 1999)	Persistent allergic symptoms, OR=1.6* (Bornehag et al., 2004)
New PVC flooring	Recurrent wheeze, no assoc (Emenius et al., 2004a)	
Plastic wall materials	Persistent wheeze, OR=3.4*; cough, OR=2.4*; phlegm, OR=2.8*; upper respiratory symptoms, no association (Jaakkola et al., 2000)	
Plastic-containing surfaces	Bronchial obstruction, OR=2.9 (with exposure-response); OR=12.6* with plastic surfaces and low ventilation; no increased risk for bronchial obstruction with PVC wall covering in >1 room	

Risk Factors	Health Outcomes	
Emission-Related Materials or Activities	**Asthma-Related and Lower Respiratory**	**Allergy/Atopy/ Eczema/ Altered Immune Parameters**
	(Oie et al., 1999) Bronchial obstruction, OR=3.3* for highest quartile of plasticizer exposure index vs. below median, or OR=1.8* per unit increase in plasticizer index over range 1-8 (Jaakkola et al., 1999)	
Plastic mattress cover in infancy	House dust mite sensitization at age 8, OR=2.1* (Trevillian et al., 2003)	
Textile wallcovering	Bronchial obstruction, OR=1.7; OR=3.7 for textile wallcovering with low ventilation (Oie et al., 1999) Bronchial obstruction, OR=1.6 (Jaakkola et al., 1999)	
CLEANING ACTIVITY		
Maternal use of chemical-based products during pregnancy (index for number used of 10 products)	Persistent wheeze, OR=2.3*, and late onset wheeze, OR=2.0 (ns) for top vs. bottom decile of exposure index (Sherriff et al., 2005)	

* p-value ≤ 0.05

Table 3. Example indoor sources for organic chemical pollutants[+]

Compounds	Example Sources
ALDEHYDES	
Formaldehyde	Composite wood and other products with urea formaldehyde resin, some architectural finishes, tobacco smoke and other combustion processes, (carpet, paint)
AROMATICS	
Benzene, toluene, xylenes, styrene, ethylbenzene, ethyltoluenes, and naphthalene	Motor vehicle exhaust, gsoline/fuel, tobacco smoke, solvent based paints, floor adhesives, PVC flooring, carpeting, printed material, solvent-based consumer products
Dichlorobenzene	Moth balls, bathroom deodorizers
Chlorobenzene	Possibly solvent based paints
ALIPHATIC HYDROCARBONS	
Hexane, nonane, decane, undecane, and dodecane	Some architectural finishes, floor adhesives, PVC flooring, consumer products (waxes, aerosol air fresheners)
Aliphatics (general)	Carpet padding, adhesives, calks, consumer products, (paint)
VOCS, OTHER	
Methylcyclopentane	Motor vehicle exhaust and evaporative emissions, (carpets)
Butanol	Some architectural finishes
Limonene	Cleaning products, air fresheners, many consumer products
Tetrachloroethylene	Dry-cleaning solvent and dry-cleaned clothing, (renovation)
Trichloroethylene	Aerosol paints, adhesives, lubricating oils, paint removers
PHTHALATE ESTERS	
BBZP	Vinyl flooring, carpet tile, adhesives
DEHP	Vinyl flooring, PVC plastics

[+] information in this table taken from a variety of sources

Appendix 1. Description of studies on associations between *indoor chemical concentrations* in air or dust and respiratory or immune health in infants and children

Risk Factor – Indoor Pollutant Concentrations**	Observed Range of Indoor Concentrations**	Effect	Subjects	Study Design and Analysis**	Reference
Formaldehyde concentration in bedroom and in home	median, 15.8 µg/m^3; maximum, 139 µg/m^3	Atopy (by skin prick tests); Asthma dx and respiratory symptoms in past yr	Age 7-14 yr	Cohort/C-S © E>D	(Garrett et al., 1999)
Formaldehyde concentration in bedrooms	median, 30 µg/m^3; range, <10 - 200 µg/m^3	Asthma emergency treatment	Age 6 mo-3 yr	C-S (CC) © E>D	(Rumchev et al., 2002)
Formaldehyde concentration in homes (mean of bedroom + living room)	not reported; high/low cut-off at 62.5 µg/m^3	Exhaled nitric oxide (indicator of lower airway inflammation); Spirometry	Age 6-13 yr, with no current or past respiratory disease	C-S © E=D	(Franklin et al., 2000)
Formaldehyde concentration in: kitchens	Mean, 32 µg/m^3; maximum, 175 µg/m^3; 4% of houses over 75 µg/m^3	Diagnosed chronic bronchitis; diagnosed asthma; peak expiratory flow; respiratory symptoms	Age 6-15 yr	C-S © E=D	(Krzyzanowski et al., 1990)
Indoor residential concentration of formaldehyde	median, 30 µg/m^3	Excess variability in PEFR; Symptoms – allergic, irritant, and acute respiratory	Age less than 16 yr	C-S analysis stratified by age, sex, ETS; E=D	(Quackenboss et al., 1989)
Indoor concentrations of Formaldehyde, Total VOCs	Formaldehyde median, 22 µg/m^3; Total VOCs median 393 µg/m^3	Persistent wheezing; frequent night sxs and day sxs among wheezing subjects	Age 9-11 yr	CC/C-S © E>D and =D	(Venn et al., 2003)
Benzene Toluene Dichlorobenzene Sum of 10 VOCs	Median and max (µg/m^3) 20 and 82; 17 and 154; 17 and 202; 55 and 622	Asthma, emergency treatment	Age 6 mo–3 yr	CC © E>D	(Rumchev et al., 2004)

Risk Factor – Indoor Pollutant Concentrations**	Observed Range of Indoor Concentrations**	Effect	Subjects	Study Design and Analysis**	Reference
Conc. in bedroom: 26 VOCs	Alkanes and aromatics, 0-180 µg/m^3; Terpenes 0-1300 µg/m^3; medians (µg/m^3): limonene, 19.1 benzene 1.7 toluene 13.3	Increased IgE sensitization to foods; Elevated total IgE; Reduced proportion of IFN-□ producing CD8+ T cells; Reduced proportion of CD8+ IL-4 producing T cells	Age 3 yr and at risk for atopy	Cohort/CS © not adjusted for all risks; E=D	(Lehmann et al., 2001)
Concentration of 28 VOCs in residence during 4 weeks after child's birth	Alkanes 0-24 ug/m^3; Aromatics 0-154 µg/m^3; Terpenes 0-198 µg/m^3	Reduced proportion of IFN-□ producing type 1 T cells in cord blood; Elevated proportion of IL-4-producing type 2 T cells in cord blood	Newborn infants	Cohort © E<=D	(Lehmann et al., 2002b)
25 VOCs in infant's bedroom in month after birth	not reported	Pulmonary infections on medical exam at age 6 wks; Sxs from parental Qx	Birth cohort at risk for atopy– at birth, 6 wks, and 1 yr	Cohort, CC © not SES; adjusted for all risks?? E<D	(Diez et al., 2000)
Phthalates in bedroom dust: BBzP DEHP 4 other phthalates	Median concentrations: 0.135 mg/g dust 0.770 mg/g dust 0.0-0.15 mg/g dust	Persistent allergic sxs; Asthma dx;. Rhinitis dx; Eczema dx	Age 1-6 yr	Cohort/C-S © not SES; E>D	(Bornehag et al., 2004)

* all concentrations measured in indoor air unless specified as measured in indoor dust

** all studies report estimates adjusted in multivariate models for potential confounding. All studies with multiple risk factors adjusted for all risk factors simultaneously, unless specified in table.

Appendix 2. Description of studies on associations between *indoor chemical sources* and respiratory or immune health in infants and children

Risk/Exposure	Effect	Subjects	Study Design**	Ref
Activities				
Renovation with painting	Pulmonary infections on medical exam at age 6 wks; sxs from parental Qx	Birth cohort at risk for atopy, at birth, 6 wks, 1 yr	Cohort, CC © not SES; (adjusted for all risks?) E<D	(Diez et al., 2000)
Redecoration of apartment (painting, new carpet, or new furniture) during first 2 years of infant's life	Obstructive bronchitis; from Qx at end of yr 1 and yr 2	Age 0-2 yr and at risk for atopy	Cohort, CC © not SES; E<D	(Diez et al., 2003)
Painting of surfaces in house in year before or year after birth; New PVC floor	3+ wheezing episodes >3 mo of age, and either use of inhaled steroids or BHR sxs at yr 2	Age 0-2 yr	Cohort, CC © E<D	(Emenius et al., 2004a); (Emenius et al., 2004b)
Repainting or new wallpaper in child's bedroom after birth	Prevalence in the prior year of asthma, allergic rhinitis with atopy by SPT, and eczema, or "allergic disease" (= any of the prior 3)	Age 7-9 yr	Cohort, retrospective © (adjusted for all risks?) E<=D	(Aberg et al., 1996)
Recent painting of infant's bedroom at age 1 month	recent wheezing and history or asthma at age 7	Age 0-7 yr	Cohort © E<D	(Trevillian et al., 2005)
Recent renovation in residence of: linoleum flooring, synthetic carpet, wall coverings, particleboard, furniture, painting	Current asthma; Current wheezing; Any allergy	Age 8-12 yr	C-S © E<=D	(Jaakkola et al., 2004)
Maternal use of chemical-based products during pregnancy	Transient early wheeze; Persistent wheeze (birth – 3.5 years); Late-onset wheeze	Age 0-3.5 years	Cohort, retrospective © E<=D	(Sherriff et al., 2005)
Surface materials				
Plastic wall materials in residence	Lower respiratory symptoms, including persistent wheeze, cough, phlegm; Asthma; Pneumonia	Age 1-7 yr	C-S © E>=D	(Jaakkola et al., 2000)

Risk/Exposure	Effect	Subjects	Study Design**	Ref
Plasticizer-containing surfaces in residence; ventilation rate; Textile wallpaper in residence	Bronchial obstruction	Age 0-2 yrs	CC/C-S/cohort © E>D	(Oie et al., 1999)
PVC flooring in bedroom	Persistent allergic symptoms	Age 1-6 yr	Cohort/C-S © not SES; E>D	(Bornehag et al., 2004)
PVC flooring in residence (vs. wood); Textile wall materials in residence (vs. painted walls)	Bronchial obstruction	Age 0-2 yr	CC/C-S/cohort © E>D	(Jaakkola et al., 1999)

** all studies report estimates adjusted in multivariate models for potential confounding. All studies with multiple risk factors adjusted for all risk factors simultaneously, unless specified in table