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Indoor Air Quality and Asthma: Has Unrecognized Exposure to Acrolein Confounded Results of Previous Studies?

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Abstract

Numerous contaminants in indoor air and their potential to cause or exacerbate asthma continue to be a subject of public health concern. Many agents are causally associated with or can exacerbate asthma, particularly in children. For formaldehyde, an established respiratory irritant based on numerous studies, the evidence for an association with asthma is still considered only limited or suggestive. However, there is no evidence that indicates increased sensitivity to sensory irritation to formaldehyde in people often regarded as susceptible such as asthmatics. Acrolein, but not formaldehyde, was significantly associated with asthma in a large cohort of children. This prompted an evaluation of this highly irritating chemical that had never previously been considered in the context of the indoor air/childhood asthma issue. Because acrolein is more potent than formaldehyde as a respiratory irritant and ubiquitous in indoor air, it is plausible that previous studies on potential risk factors and childhood asthma may be confounded by formaldehyde acting as an unrecognized proxy for acrolein.

Keywords

formaldehyde, acrolein, asthma, children, indoor air, confounding

Introduction

Exposure to numerous substances in indoor air, each with varying degrees of scientific certainty(note 1) have been associated with or can exacerbate existing asthma, particularly in children. With childhood asthma an issue of growing public health concern, it is important to focus on indoor air factors with the strongest evidence of being causally related to this disease. As noted in an authoritative review,[1] studies of asthma can be divided into those dealing with factors leading to the development of asthma and those dealing with factors that exacerbate the illness in known asthma group. Most of the research on this topic address "asthma exacerbation," the onset or worsening of symptoms—some combination of shortness of breath, cough, wheezing, and chest tightness—in someone who already has developed asthma. In assessing potential exposures that might exacerbate asthma in children,[1] there was (1) sufficient evidence to conclude that there is a causal relationship between exposure to the allergens produced by cats, cockroaches, and house-dust mites and exacerbations of asthma in sensitized individuals; and environmental tobacco smoke (ETS) exposure and exacerbations of asthma in preschool-aged children and (2) sufficient evidence of an association between dog allergen exposure and fungal exposure with exacerbation of asthma in individuals specifically sensitized to these allergens. In addition, damp conditions or indicators of dampness (eg, dust mite and fungal allergens) are associated with the presence of symptoms considered to reflect asthma;(3) for nonacute, nonoccupational formaldehyde (FA) exposure, there was limited or suggestive evidence for an association with wheezing and other respiratory symptoms as well as inadequate or insufficient evidence to determine whether an association exists between FA exposure and asthma development; and (4) inadequate or insufficient evidence to determine an association between indoor residential VOC exposures and the development or the exacerbation of asthma. Unlike allergens, for chemical constituents in indoor air such as FA and as discussed in this review acrolein, the dose–response aspects of their potential irritant properties must be accounted for with respect to biological plausibility. In a comprehensive update to

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the first authoritative review[1] involving 69 additional studies,[2] there was a causal association between mold (ie, indoor dampness and dampness-related agents) and exacerbation of asthma in children, while still only limited or suggestive evidence of an association between FA exposure and exacerbations of asthma, in particular through enhanced response to other allergens.

The above noted substances potentially present in indoor air that can exacerbate childhood asthma, many with different levels of certainty, present a substantial challenge with respect to designing and interpreting studies. The discovery that acrolein, an aldehyde 200 times more potent than FA[3] and ubiquitous in indoor air, was significantly associated with asthma, whereas FA was not[4] therefore prompted this review. Because a meta-analysis[5] is the principle basis for noncancer regulatory policy on FA,[6,7] the underlying studies are critically evaluated. Since it is plausible that FA has served as an unrecognized proxy for acrolein in studies conducted to date, the review then briefly summarizes the well-established dose–response aspects of FA-induced irritation and its potential to exacerbate asthma symptoms (note 2). This is followed by a review of the available data on acrolein in sufficient detail to document its likely role in exacerbating asthma due to its irritant properties. The implications of acrolein as a previously unrecognized confounder are that indoor air studies, which report associations between FA and childhood asthma, should be interpreted with caution unless/until potential contributions and/or associations with acrolein are also considered.

Formaldehyde and Childhood Asthma

Despite the conclusions[1,2] concerning the strength of evidence for FA and asthma, regulatory policy[6,7] heavily relies on a single meta-analysis.[5] Because this serves as a primary basis for conclusions about FA and its putative relationship to childhood asthma, the rigor and relevance of this study is critically assessed. This analysis of indoor air/childhood asthma studies concluded there was a significant positive association between FA exposure and childhood asthma. However, a key authoritative review[2] was skeptical about this conclusion noting, "Although epidemiologic studies have shown associations of indoor FA exposures with asthma development and prevalent asthma in children (as reviewed by McGwin et al[5] [p. 32]), evidence on exacerbation of asthma was not available." Although this conclusion fails to meet the evidentiary burden for other agents in indoor air (ie, causal relationship or sufficient evidence of an association), it does generate a perplexing paradox. There are at least a hundred studies in which various indoor air factors and asthma (particularly in children) have been investigated. Consequently, it seems reasonable to consider why this large body of data on FA, an extensively investigated respiratory irritant with well-established dose–response characteristics for sensory irritation, still remains in the category of "limited or suggestive" with respect to its potential role in childhood asthma. As discussed in Acrolein section, a plausible explanation for this conundrum is that unrecognized confounding by acrolein may be responsible for this phenomenon in indoor air studies conducted to date.

The meta-analysis[5] relied on 8 studies as the basis for the systematic review, with[8] accounting for 99% of the weight in a fixed-effects model and[8-10] accounting for 72% of the weight in a random-effects model. The data from one of the studies[8] appeared to have been manipulated (note 3), whereas the data from another[10] was misrepresented (note 4). Germane to this review is that mean indoor air concentration of FA in these 3 studies was 18 ppb, which is approximately 20% of the World Health Organization (WHO)[12] FA value of 80 ppb for indoor air. As discussed in section on Upper Respiratory Tract Irritant Effects of FA in Adults and Children, with a clear threshold of 300 ppb for sensory irritation, and no differences between children and adults for such effects, it is unlikely that FA exposures of 18 ppb would play a causal role in exacerbation of asthmatic symptoms in children.

Given the central importance of the above noted 3 studies to the overall conclusions of the meta-analysis,[5] it is reasonable to assume that all relevant data pertaining to these studies would have been considered. However, not mentioned (or cited) was that 2 of the cohorts had also been studied by the same authors for other factors in indoor air and their potential associations with childhood asthma. In one of the cohorts, indoor air fungal spores and house dampness were studied[13] as potential risk factors for respiratory symptoms in children (odds ratio [OR] = 1.43 95% confidence interval [CI]: 1.03-2.0), concluding that asthma, atopy, and respiratory symptoms were all significantly associated with exposure to 1 or more genera of fungal spores. Given these findings in the same cohort, the extent that the presence of fungal spores and mold confounded the findings in the study relied upon in the meta-analysis[8] is unknown. It should also be noted that with respect to strength of evidence, mold is considered causal, fungal spores have significant evidence of an association, whereas FA is in the category of inadequate/insufficient.

In the other cohort,[14] associations of indoor air exposures to VOCs with asthma were studied on the same cohort of children who were investigated for potential effects of exposure to FA[8]. Recent painting in the house was significantly associated ($P < .05$) with more asthma cases than for children without asthma. The results of this study[14] showed that asthma cases were exposed to significantly higher VOC concentrations than controls ($P < .01$). Also determined was whether the presence of FA confounded the effect of total VOCs on asthma by fitting a model adjusted for FA, house-dust mites, atopy, family history of asthma, and the presence of gas appliances (nitrogen dioxide [NO_2]). As noted by the authors, the results showed that exposure to total VOCs still had a highly significant effect on asthma. Again, at the very least, the meta-analysis[5] should have acknowledged and discussed the results of this study and attempted to reconcile these findings.

There are 9 indoor air factors either causally (ie, dust mites, cats, cockroaches, dampness/mold) or significantly associated (ETS, dogs, fungi, NO_2, endotoxins) with childhood asthma. The average number of these factors accounted for in the 8

studies comprising the meta-analysis was slightly more than 2. Consequently, none of these studies were capable of providing evidence of the true relationships between indoor air factors and childhood asthma. As discussed in the Discussion section, the only way to ensure the accuracy of conclusions concerning indoor air factors as putative causes of childhood asthma exacerbations is to account for the majority of factors known to be either causally or significantly associated with this condition. None of the studies comprising the meta-analysis[5] were conducted with sufficient rigor to provide the data required to make this possible.

Upper Respiratory Tract Irritant Effects of FA in Adults and Children

The dose–response characteristics of FA-induced upper respiratory tract irritation demonstrate an unequivocal threshold of 0.3 ppm.[15-22] Consequently, there is no controversy concerning air concentrations required to reliably (ie, in the absence of false-positives) elicit symptoms of sensory irritation (ie, eyes, nose, or throat). This conclusion for false-positives is well supported by at least 4 controlled human studies[23-26] that report positive sensory irritation response rates between 5% and 39% at 0 ppm FA exposure. Furthermore, following exposure to FA at concentrations sufficient to elicit symptoms of sensory irritation (ie, >0.3 ppm), and subsequently might also trigger asthma symptoms, there is no evidence suggesting that children and adults would respond differently. It has therefore been concluded[15]:

> Whereas there are numerous studies of adults occupationally exposed to formaldehyde and exposed under acute controlled conditions, data regarding the toxicological properties of formaldehyde in children are limited. Nevertheless, the same type of effects that occur in adults are expected to occur in children . . . . Symptoms expected to occur in children include eye, nose, and throat irritation from exposure to airborne concentrations between 0.4 and 3 ppm (p. 227).

This suggests that FA indoor air concentrations below the WHO guidance level of 80 ppb would be incapable of triggering asthma exacerbations in children. Consequently, there is no evidence indicating an increased sensitivity to sensory irritation to FA among people often regarded as susceptible (asthma group, children, and older people).[12]

Acrolein

A possible resolution of why so many studies have failed to demonstrate more than limited or suggestive evidence of an association between FA exposure and exacerbations of asthma is that unaddressed exposure factors in indoor air may be confounding the reported findings. This is especially the case at the low FA air concentrations (ie, <80 ppb) in most studies conducted in homes. A plausible explanation for this exposure–response dilemma may be found in a relevant study[4] that evaluated relationships between indoor air quality and asthma in 401 randomly selected classrooms from 108 primary schools attended by 6590 children (mean age 10.4 years). Air concentrations of $PM_{2.5}$, NO_2, and 3 aldehydes (acrolein, FA, and acetaldehyde) were measured (note 5), and health status variables, including skin prick testing to 10 common allergens, and exercise-induced asthma (EIA) assessed for each participant. Potential confounders considered included age, gender, passive smoking, paternal/maternal history of asthma or allergic disease, dampness, gas appliance, ethnicity, and socioeconomic status. An increased prevalence of asthma in the past year was reported in children using classrooms with elevated levels of $PM_{2.5}$, NO_2, and acrolein. Rhinoconjunctivitis was the most common condition observed followed by EIA and asthma, with allergic asthma more frequent than nonallergic asthma. Acrolein was the only exposure significantly associated with both asthma (OR: 1.37, 95% CI: 1.14-1.66) and allergic asthma (OR: 1.41, 95% CI: 1.16-1.73) whereas NO_2 was significantly associated with asthma (OR: 1.18, 95% CI: 1.01-1.39). Formaldehyde was significantly associated only with rhinoconjunctivitis (OR: 1.41, 95% CI: 1.08-1.85) but not with asthma. When the total population was stratified based on a positive skin prick test to 10 common allergens, which is a measure of atopy, $PM_{2.5}$, acrolein, and NO_2 were significantly related to allergic asthma. The only significant positive correlation in this study was between EIA and levels of $PM_{2.5}$ and acrolein in the same week.

Median reported FA levels (21 ppb)[4] at which rhinoconjunctivitis (ie, eye/nose irritation) occurred appear inconsistent with substantial data on dose–response aspects of FA-induced sensory irritation. Nevertheless, these are the only data that have (1) separately documented irritant, but not asthma, symptoms from FA and (2) accounted for the potential contribution of acrolein, a potent upper and lower respiratory tract irritant. As discussed below, acrolein is mechanistically and etiologically associated with asthma but has never previously been considered in any of the numerous indoor air studies investigating potential associations between FA and asthma.

Due to the fact that acrolein, but not FA, was significantly associated with asthma in children, it is necessary to explore this heretofore unrecognized potential confounder in studies of asthma and indoor air. A predominant source of acrolein exposure is from the atmosphere. Ambient air concentrations are around 8.2 to 24.6 $\mu g/m^3$ (mean 14.3 $\mu g/m^3$) and, as discussed further below, concentrations in indoor air, particularly in conjunction with ETS, are much higher.[27] With human air intake of approximately 16 m^3/24h, acrolein exposure through indoor air would amount to 228 µg/d, an amount roughly equal to that generated by smoking 2.5 cigarettes. This would explain the relatively high levels of 3-hydroxypropyl mercapturic acid, an acrolein metabolite found in the urine of nonsmokers.[28]

As further described below, indoor cooking with various oils at temperatures of 180°C generates substantial amounts of acrolein (ie, 5-250 mg/kg oil) subsequently released into indoor air. For example, as reported in Ho et al,[29] total emissions of acrolein from commercial kitchens in Hong Kong was

estimated at 7.7 tons/year, far exceeding the annual vehicle emissions of acrolein in that city (1.8 tons/year). As noted by Leikauf,[30] due to ever-increasing acrolein emissions into the environment, acrolein as a direct irritant may increasingly become a health hazard in individuals with respiratory diseases such as asthma. With the above brief preamble, it is clear that acrolein deserves consideration as a previously unrecognized confounder in indoor air studies.

Although acrolein is well established as a potent eye and respiratory irritant, its potential to exacerbate asthma symptoms was not considered in any of the individual studies in the meta-analysis,[5] systematic review, or in other studies in which indoor air factors have been investigated in conjunction with childhood asthma. For example, an elaborate screening procedure was developed[31] to identify those chemicals of most concern with respect to indoor air. Following a critical assessment and evaluation involving consideration of odor thresholds and potential exposure, the initial list of 40 chemicals was reduced to FA, carbon monoxide, NO_2, benzene, and naphthalene. Of these, for potential associations with asthma, NO_2 is considered to have significant evidence and FA limited/suggestive evidence, while for benzene (ie, VOCs) the evidence is considered inadequate/insufficient. Acrolein was presumably omitted due to its presence in cigarette smoke (evaluated separately in the European Union (note 6). This is but one illustration of how this chemical, despite its well-established potency as a respiratory tract irritant, has escaped notice regarding its potential involvement in the asthma/indoor air issue.

However, there is substantial evidence that acrolein, which is present in ETS as well as in ambient and indoor air, is likely to play an etiological role particularly in exacerbating asthma symptoms. Acrolein can affect the entire respiratory tract, from the nasal epithelium to the alveolar spaces, and individuals with emphysema or allergic conditions such as asthma are at a higher risk of developing adverse respiratory responses.[16] Also noteworthy is that it is estimated that acrolein is responsible for a substantial contribution, that is, 75% of noncancer respiratory health effects attributable to air toxics in the United States, based on the National-Scale Air Toxics Assessment for 2005.[32] In addition, using the above estimate, a provocative assessment was conducted[33] based on data from 271 348 adults compiled in the National Health Interview Survey (2000-2009). In the highest quintile of outdoor acrolein exposure (0.05-0.46 $\mu g/m^3$), there was a "marginally significant" increase in the asthma attack prevalence odds ratio (pOR) of 1.08 (95% CI: 0.98-1.19) relative to the lowest quintile. The pOR in the same quintile was also associated with a marginally significant increase (pOR: 1.13; 95% CI: 0.98-1.29) in never smokers ($n = 153\ 820$). Because indoor air concentrations of acrolein are higher than outdoor air concentrations, it supports a conclusion that this reactive chemical should be accounted for in the indoor air/asthma debate.

The above logic is augmented in the comprehensive analysis[3] in which toxicological risk assessment principles were applied to the chemical constituents of cigarette smoke. A noncancer risk index was calculated for both acrolein and FA by dividing yield levels in cigarette smoke with the reference exposure levels (RELs) for each chemical. The RELs used were from US Environmental Protection Agency (EPA) or Cal/EPA for chronic respiratory effects due to chemical constituents of mainstream cigarette smoke based on a single cigarette/day. With RELs for acrolein and FA of 172 and 0.83, respectively, acrolein is >200 times more potent than FA as a respiratory irritant. This suggests that studies of indoor air factors and asthma which assess FA air concentrations, without accounting for acrolein may inadvertently (and erroneously) attribute associations with FA, when the more likely risk factor would be acrolein. This is supported by controlled human volunteer chamber studies, where acrolein was more potent than FA in eliciting acute symptoms of sensory irritation. As reported,[34] eye, nose, and throat irritation were elicited at exposures of 0.09 ppm (90 ppb), 0.26 ppm, and 0.43 ppm, respectively. Overall, eye irritation occurred at concentrations as low as 90 ppb for exposure durations as short as 5 minutes. In a more recent study,[35] 18 healthy volunteers were exposed 6 times over 2 hours to clean air and 0.05 ppm and 0.1 ppm acrolein (with and without 15 ppm ethyl acetate to mask the potential odor of acrolein). As concluded by the authors, the present study showed minor subjective eye irritation at short-term exposure to acrolein at 0.1 ppm with no such effect observed at 0.05 ppm. These results are consistent with the previous study[34] and demonstrate that acrolein is more potent as a respiratory irritant than FA.

In California[36] statewide average ambient concentrations of acrolein in 2004, 2005, and 2006 were 1.21, 1.37, and 1.35 $\mu g/m^3$, respectively, based on routine air monitoring. Others[37] have also reported somewhat higher indoor air concentrations of acrolein from 0.1 to 4.9 $\mu g/m^3$. As summarized by Agency for Toxic Substances and Disease Registry,[16] the average environmental concentrations of acrolein in outdoor air range from 0.5 to 3.19 ppb and in indoor air range from <0.02 to 12 ppb in residential homes. In an analysis of indoor/outdoor acrolein air concentrations in 15 homes in Los Angeles County, outdoor acrolein ranged from 0.09 to 1.7 $\mu g/m^3$, whereas indoor air concentrations were approximately 10 times higher (ie, 2.1-12.2 $\mu g/m^3$).[38] The primary emission sources were due to multiple factors including heated animal or vegetable oils that produce noticeable spikes in indoor air acrolein concentrations, which increase with cooking. It was noted[38] that the major finding of this study was that indoor concentrations of acrolein, one of the top hazardous air pollutants identified by the USEPA and a known pulmonary toxicant, were 3 to 40 times higher than outdoor concentrations. In another similar study,[39] acrolein emission rates were measured from various cooking oils (canola, soybean, corn, and olive) used for deep-frying foods. Although the food items made little contribution to air concentrations, cooking events resulted in acrolein air concentrations ranging from 26.4 to 64.5 $\mu g/m^3$. Therefore, it is reasonable to conclude that there is a sound exposure-based rationale for better understanding the potential health impacts of acrolein, particularly as they might relate to asthma.

Also noteworthy is that indoor air acrolein concentrations can exceed EPAs RfC for acrolein (based on rat nasal histopathology) of 0.02 μg/m^3 (0.01 ppm) or the slightly higher OEHHA chronic REL of 0.06 μg/m^3 (0.03 ppm). If RfCs are assumed to be reliable guidelines for protecting public health, it appears that the upper range of indoor air acrolein concentrations exceeding the RfC would be of concern. This conclusion was echoed,[39] regarding the above noted acrolein emissions from different cooking oils, that is, these concentrations exceed chronic regulatory exposure limits and many of the acute exposure limits.

Furthermore, 2 key chemical differences between FA and acrolein suggest that the fate and disposition of similar concentrations of each in the respiratory tract will be qualitatively and quantitatively different, that is, (1) the water solubility of acrolein is between 20% and 40% compared to >99% for FA and (2) FA is rapidly metabolized by aldehyde dehydrogenase to folate, whereas acrolein must be absorbed and metabolized in the liver by glutathione and excreted.[40] Consequently, any exposure to either chemical may result in greater penetration and/or deposition of acrolein in the respiratory tract, the primary target for exacerbation of asthma symptoms. This phenomenon would also appear to explain the findings of the study described above[4] where acrolein was associated with asthma symptoms while FA only with rhinoconjunctivitis. Since both FA and acrolein typically coexist in indoor air,[41] studies of potential risk factors related to asthma exacerbations suggest that each chemical should be quantified and their potential correlations established, before concluding that FA alone was responsible for any reported effects.

In addition to cooking, ETS is a major source of acrolein in indoor air. In order to assess its contribution to exposure, 2 acrolein metabolites in urine, *N*-scetyl-*S*-(3-hydroxypropyl)-L-cysteine (3HPMA) and *N*-acetyl-*S*-(2-carboxyethyl)-L-cysteine (CEMA), were evaluated as biomarkers of acrolein exposure for the US population.[42] This analysis, based on data from the National Health and Nutrition Examination Survey (2005-2006) that accounted for age, sex, race, and smoking status, was designed to assess tobacco smoke as a predictor of acrolein exposure. The results were dramatically higher in tobacco users (cigarettes, cigars, pipes) compared to nonsmokers with median 3HPMA levels in smokers and nonsmokers of 1089 and 219 μg/g creatinine, respectively. Median CEMA urine levels of 203 μg/g compared to 78.8 μg/g creatinine were found for smokers and nonsmokers. These data demonstrate the substantial differences between smokers and nonsmokers with respect to acrolein exposure. In addition, when considering asthma, the importance of knowing the smoking status and ambient acrolein concentrations in studies attempting to discern relationships between indoor air factors and asthma exacerbations should be evaluated.

Potential Relationship of Acrolein to Asthma

Given the striking exposure–response implications of the above data, it is incumbent to briefly summarize some relevant data on acrolein as it pertains to asthma. Other than in a single study,[4] acrolein has never been addressed in conjunction with childhood asthma. However, as summarized below, there are substantial data suggesting that acrolein can play a causal role in exacerbating asthma symptoms. It is clear that acrolein is far more potent than FA with respect to its irritant-inducing properties.[3] Consequently, until/unless the contribution of acrolein to whatever effects are now attributed solely to FA are addressed, FA would have to be considered as a proxy for acrolein.

In a comprehensive assessment of acrolein,[43] it was noted that based on case histories, clinical studies, or epidemiology studies, an increased susceptibility of children to acrolein toxicity is specific for those who have respiratory conditions such as bronchitis or asthma. This is supported by animal studies showing bronchial hyperresponsiveness and increases in inflammatory mediators following acrolein exposure.[44,45] Because one of the hallmarks of inflammatory airway disorders such as asthma is mucus hypersecretion in the upper airways, the effect of acrolein on mucus glycoprotein (mucin) gene expression was examined in airway epithelial cells.[46] Cultured cells were treated for 4 hours with 0.01 to 100 nM acrolein that acted either directly on such cells to increase mucin mRNA levels or indirectly through inflammatory mediators released following exposure. A signature feature of asthma is bronchial hyperreactivity in which low doses of inhaled irritants, such as acrolein, can induce broncoconstriction. Acrolein has long been known to induce apnea, shortness of breath, cough, airway obstruction, and mucous secretion.[47] As demonstrated in an in vitro study with human isolated airway tissues passively sensitized by incubation in sera from patients with asthma, preexposure to 0.3 μM acrolein for 10 or 20 minutes significantly increased the maximal contractile response to a specific antigen from house-dust mites.[48] In this regard, it has been noted[49] that acrolein exposure and passive sensitization interact (possibly in synergy) with human bronchial smooth muscle reactivity in response to both specific antigen and nonspecific agonists. Indoor air contains a number of potential allergens in addition to dust mites (eg, cats, dogs, mold, cockroach, etc) in the causal and/or associated with asthma categories. Consequently, consideration of acrolein as an unaddressed confounder in studies relied upon in assessing FA and asthma exacerbation should be part of the evaluation process.

To mitigate airway responses due to irritants, the airways have developed specialized mechanisms to protect alveoli from damage. This involves peripheral sensory neurons that express specific transient receptor potential (TRP) ion channels that are directly activated by reactive chemicals. Substantial research data are available on TRP channels which, when activated by reactive chemicals such as acrolein, triggers signaling to the brain. This initiates involuntary reflexes in the airways and lungs leading to respiratory depression, cough, glandular secretions, and other protective responses. A specific receptor, TRPA1 expressed by capsaicin-sensitive neurons in the respiratory tract, is well known for triggering attacks in individuals with asthma (ie, irritant-induced asthma).[50-53]

Noteworthy is that responses from cigarette smoke can be reproduced by acrolein alone in these test systems.[54,55] This demonstrates that acrolein is an active component in cigarette smoke responsible for irritant properties. These experimental data would appear to confirm the analysis[3] that reported acrolein to be 200 times more potent than FA as a respiratory irritant. Furthermore, given that acrolein-evoked responses are completely absent in cultures from TRPA1-deficient mice demonstrates that TRP is an essential site for acrolein action.[49,55] ETS is already categorized as having sufficient evidence of an association with asthma exacerbation, suggesting that acrolein should at least be considered in this strength of evidence category.

Discussion

As summarized in this review, with respect to identifying potential risk factors in indoor air that might exacerbate asthma, the emphasis should be on exposures of most concern based on the level of empirical evidence for each factor. This is particularly relevant for childhood asthma, which has been growing in prevalence with indoor air, an important contributing factor. The only way to accomplish this in the most scientifically defensible and cost-effective manner is to focus research and communication efforts on those factors with the highest level of confidence that they are causally associated with asthma, either incident disease or exacerbations. This issue has been repeatedly addressed in comprehensive evaluations.[1,2] Both of these analyses rely on well-established strength of evidence evaluation factors to critically assess the available scientific data for various exposures of potential concern and the extent that each satisfies the strength of evidence categories: (1) causal, (2) sufficient, or (3) limited/suggestive. With respect to FA, as concluded by Kanchongkittiphon et al,[2] although epidemiologic studies have shown associations of indoor FA exposures with asthma development and prevalent asthma in children (as reviewed by McGwin et al[5]), evidence on exacerbation of asthma was not available. Clearly, the conclusions of the meta-analysis were not sufficiently persuasive to change the strength of evidence from "limited/suggestive" to a higher category. As discussed in this review, it is probably due to the fact that it is not credible to select 8 studies, some of which have methodological limitations, and use opaque manipulations of the data to erroneously conclude there are significant positive associations between FA exposure and childhood asthma. Few, if any, of the studies relied upon by the meta-analysis investigated potential associations of asthma with indoor air risk factors (ie, mite, cat, cockroach allergens, or mold) known to be causally associated with childhood asthma, much less than those factors significantly associated with asthma. Consequently, in their reported results none were capable of ruling out the role that these potential contributors played in exacerbating childhood asthma. In addition, since acrolein was not considered in any of the 8 studies, the most that can be concluded about any of them is that FA might have been a proxy for acrolein. Since childhood asthma is an issue of substantial public health concern, limited resources should not be spent on studies that are incapable of providing scientifically relevant information on this important issue.

This is particularly evident in more rigorously conducted studies that can reveal true causal associations between indoor air factors and exacerbations of childhood asthma. For example, an extensive investigation[56] of seasonal risk factors for asthma exacerbations was conducted in 456 inner city children aged 12 to 20 years in 10 large urban research centers in the United States. The most relevant statistically significant factors germane to this review were increases in positive allergen skin test results for rodents (OR: 2.05, 95% CI: 1.14-3.68), cockroach (OR: 1.93, 95% CI: 1.03-3.61), allergen-specific IgE levels to house-dust mite (OR: 1.46; 95% CI: 1.02-2.09) and cockroach (OR: 1.48, 95% CI: 1.06-2.06). Notably, all of the above exposure factors are known to be causally associated with asthma. These results highlight the need to investigate and focus on factors known to be causally associated with asthma exacerbations, rather than FA for which the evidence does not rise to this level of confidence. The discovery that acrolein virtually certain to have been present in the indoor air of all studies in which FA has been implicated as associated with asthma should raise a red flag with respect to their conclusions.

Based on this review, reported conclusions in the numerous studies that attribute respiratory and/or asthma effects to FA must be questioned. This is particularly evident at FA concentrations well below conservative guidelines (eg, WHO, Norway, Australia, Japan, etc [100 $\mu g/m^3$] and Canada [50 $\mu g/m^3$]) which underscore the likely contribution of acrolein. The implications of not considering acrolein in such studies are also suggested in a comprehensive review[57] of indoor residential chemical emissions as risk factors for respiratory and allergic effects in children. Twenty-one indoor air studies were the basis of this evaluation. As noted in this evaluation:

> 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 . . . . Furthermore, perhaps the most important source of bias in this body of research, even in the well-designed studies, is confounding.

Finally, in discussing elevated risks reported in some studies with questionable attribution to a particular factor, it was concluded that, "Yet with such highly elevated risks, it is not clear what confounding factor could produce these estimates other than a strongly causal indoor exposure emitted by renovation-related materials." Although it is unknown what "renovation-related materials" could plausibly be associated with "highly elevated risks," it seems clear that acrolein would fulfill this role.

If FA is believed to be an important risk factor with respect to its potential contribution to asthma exacerbations in children, as emphasized in this review, this conclusion cannot be supported until contributions from acrolein are considered. Other than a single study,[4] none of the other studies currently relied upon with respect to the FA/asthma issue in childhood considered coexposures to acrolein. Consequently, conclusions with respect to FA alone can only be considered as suspect. This is particularly the case since acrolein is a demonstrably more potent respiratory tract irritant than FA, with the clear ability to exacerbate asthma symptoms. The only way that this dilemma can be resolved would be to conduct additional studies, in which air concentrations of both FA and acrolein are quantified in order to assess possible correlations between these irritants.

Since there are no meaningful physiological differences between children and adults with respect to irritant responses to FA in the upper respiratory tract, asthmatic children would appear to share with adult's similar insensitivity to FA exposure and asthma. Although asthma exacerbations from substances in indoor air are clearly a public health issue that needs to be addressed, the focus should be on those constituents for which the data are either causally or significantly associated with this disease. With the potency of acrolein far greater than FA as a respiratory irritant and now identified as either (1) a probable confounder of previous studies in which FA was a principal focus or (2) at least significantly (or causally) associated with asthma on its own, should serve to minimize the present emphasis on FA. For example, if a study on potential risk factors for childhood asthma is conducted in inner city dwellings it would be remiss to ignore the substantial known contribution from cockroach antigen as a contributor to asthma symptoms. Similarly, as summarized in this review, the same should now be obligatory for acrolein in all studies moving forward. Since EPA has concluded that acrolein is responsible for about 75% of noncancer respiratory health effects attributable to air toxics in the United States, and with indoor air levels up to 10 times or greater than outdoors, there should be a reasonable effort to address this issue. Until and unless this is done, it is inappropriate to focus solely on FA as playing a meaningful role in asthma symptoms without accounting for the almost certain contribution from acrolein.

Author's Note

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Declaration of Conflicting Interests

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Notes

1. Sufficient evidence of a causal relationship, sufficient evidence of an association, limited or suggestive evidence of an association, inadequate or insufficient evidence to determine whether an association exists.[1]
2. Because asthma is a disease of the lower respiratory tract and lungs, for causation it is obligatory that a sufficient dose of FA reach these anatomic sites. As noted in the regulations of the Occupational Safety and Health Administration (29 C.F.R. Sec. 1910.1048. Formaldehyde (FA) Appendix C): "Concentrations of above 5 ppm readily cause lower airway irritation characterized by cough, chest tightness, and wheezing." Since indoor air levels of FA would never reach this concentration, throughout this review, FA is only considered in the context of its potential role in exacerbating existing asthma as a consequence of its well-established irritant properties in the upper respiratory tract.
3. As noted in a critique,[10] one of the studies[11] was afforded substantial weight in the meta-analysis, even though no odds ratios were reported for asthma. In an effort to transform all data into comparable units (ie, FA increases/10 $\mu g/m^3$), the odds ratio (OR) for atopy was apparently "recalculated" into the asthma OR = 1.27 (95% confidence interval [CI]: 1.04-1.55), even though the original OR for atopy was already expressed per 10 $\mu g/m^3$. It is unknown how this manipulation affected the outcome of this meta-analysis.
4. Attributed to this study[12] was an OR = 1.07 (95% CI: 0.81-1.43) for asthma that was listed in table 1 of the meta-analysis. As noted in this analysis, Because most studies reported their results as odds ratios (ORs) per 10 $\mu g/m^3$ unit increase formaldehyde, this unit was chosen as the common metric. Thus, results for those studies using different units were "transformed." However, since this study[12] did not present any ORs, there is no way to discern how the insignificant OR was "transformed" from the data presented.
5. Although correlations between FA and acrolein were not provided, it is noteworthy that mean indoor air concentrations of acrolein were approximately 25 × less than FA, thereby demonstrating its greater potency as a respiratory irritant.
6. Extensive efforts were made to identify and/or locate documents from the European Union in which acrolein was independently assessed in the context of potential adverse respiratory effects from indoor air, particularly with respect to asthma. Only 1 document mentioned acrolein in the asthma context.[4]

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