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Do Plasticizers within the Indoor Environment Increase Airway Allergen Responsiveness?

There is an increasing appreciation that a wholistic consideration of the impact of air pollutants on health requires us to understand the continuum of exposures an individual may experience across the indoor and outdoor environment. This extends beyond the infiltration of ambient pollution into the home, school, or workplace to a consideration of exposures to the complex and highly heterogeneous chemical cocktail within indoor air. Although the literature on the adverse health impacts of ambient air pollution is extensive and mature, as highlighted by a joint European Respiratory Society/American Thoracic Society policy statement (1), work on indoor sources is less evolved (2). Although the population spends most of its time within the indoor environment, traveling from home to work and back again, a fraction that has increased as modern lifestyles have become more sedentary, the study of indoor air pollution has remained largely focused on a few common indoor pollutants: common allergens such as house dust mites and mold, carbon monoxide, second-hand tobacco smoke, radon, asbestos, and nitrogen dioxide. But the indoor environment is also a source of volatile and nonvolatile chemical species derived from modern synthetic building materials, furnishings, and household chemical products. The importance of these indoor sources has increased as our homes have become more airtight and energy efficient, such that now the indoor concentrations of volatile organic compounds are often significantly elevated compared with outdoor air (3). In addition, indoor air is also enriched with respirable microplastic fibers and particles that have the potential to deliver chemical additives to the lung (4).

In the paper by Maestre-Batlle and colleagues (pp. 672–680) in this issue of the *Journal* (5), the authors drill down onto the potential acute impacts of one common indoor air pollutant, dibutyl phthalate (DBP), on allergic airway responses. Phthalates (classified as plasticizers) are typically solvents found in plastic-based products that have aroused concern historically as endocrine-disrupting chemicals, but there is observational data also linking indoor concentrations, often in household dust, with increased risk of asthma, allergy, and wheeze (6).

The interaction between air pollutants and allergy has been shown by many studies (7, 8), with causative links proposed by epigenetic and other mechanisms (9), although these assertions have been questioned (10). Controlled human-exposure studies have also shown the potential of diesel exhaust and nitrogen dioxide to potentiate airway responses to allergen challenge (11–14). The findings have indicated that pollutants may affect the magnitude of the allergic response but also the threshold of allergen challenge demanded to induce a bronchoconstrictive response. In this issue, a team from the University of British Columbia, Vancouver, extend this consideration to DBP, investigating

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whether short-term exposures enhanced the bronchoconstrictive response, airway hyperresponsiveness (AHR), and the immune response to allergens in a placebo-controlled exposure study. This is the first human study to examine these responses under rigorous experimental conditions with the aim of providing causal support for the epidemiological observations linking phthalate exposure to adverse allergic responses. To achieve this objective, subjects with mild asthma and healthy volunteers, half with baseline airway hypersensitivity, and known to be sensitized to allergen (grass, birch, or house dust mites), were exposed to DBP for 3 hours, followed by an immediate inhalation challenge with the appropriate allergen. Lung function responses were assessed before, during, and up to 20 hours after exposure, with fractional exhaled nitric oxide assessed before and 3 and 20 hours after exposure and airway hyperreactivity assessed by methacholine challenge at 20 hours after challenge. Airway inflammation, including immune cell phenotypes, was assessed by BAL.

Although some of the responses observed were subtle, the authors found preliminary evidence that DBP exposure not only significantly enhanced the early allergic response, as compared with placebo exposure, but also increased AHR in subjects without preexisting hyperresponsiveness. One interpretation of this finding is that acute DBP exposure may move an individual with allergic sensitization and no AHR toward an endotype with hyperreactive airways when exposed to allergen. The selection of allergic-sensitized subjects both with and without AHR allowed the investigators to study the effects over a span in AHR, from normal to hyperresponsive, which is a strength, although this also had an impact on the power of the study. The authors also found an increase in M2 macrophages in BAL, whereas M1 were not affected, in line with the soluble mediator response including MIP-1α. The diverging responses in fractalkine and stem cell factor may have influenced leukocyte traffic, with the role of the mast cell in this scenario still elusive.

To conclude, the present study elegantly bridges indications from population-based studies, with placebo-controlled human exposures in allergen-sensitized individuals, to demonstrate evidence of enhanced allergic responses after inhalation of phthalate fumes. Interestingly, only allergic subjects with normal methacholine responsiveness at baseline experienced an increased hyperresponsiveness after BDP exposure. In the case of repeated exposures, this could potentially lead to worsening of allergic responses and manifest airway hyperresponsiveness, something that future studies should address. Overall, this study adds considerably to the field, highlighting the need for robust clinical experimental studies into the impact of indoor air pollutants on health. Human chamber studies, it should be acknowledged, are complex and difficult to conduct. They, for purely ethical and cost considerations, cannot cover numerous time points or every relevant clinical subtype or endpoint, so they should be viewed within the overall evidential context of population-level observations and *in vitro* and *in vivo* studies where there is greater experimental flexibility. They are, however, our clearest window into the acute causal pathways leading to adverse clinical endpoints. ■

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Ian S. Mudway, Ph.D.
MRC Centre for Environment and Health
Kings College London
London, United Kingdom

Thomas Sandstrom, M.D., Ph.D.
Department of Public Health and Clinical Medicine
Umeå University
Umeå, Sweden

ORCID IDs: 0000-0003-1239-5014 (I.S.M.); 0000-0002-0174-0882 (T.S.).

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