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EDITORIAL

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An emerging paradox: Toward a better understanding of the potential benefits and adversity of microbe exposures in the indoor environment

The indoor air community is witnessing the emergence of a remarkable paradox: Credible lines of evidence are converging to suggest that indoor microbial exposures can be both protective and threatening to human occupants. Beyond the acute infectious diseases from near human contacts, there are increasing suggestions that the built environment can present chronic microbial exposure conditions which foster adaptive health benefits, in addition to those moist building conditions that are commonly recognized for negative health impacts. Adverse exposure is typically assumed in the case of moisture damage and "indoor mold" in buildings, whereas the protective quality of microbial exposure, in particular during early childhood, is mostly reported in the context of studies that are carried out in farming or rural environments. While the protective effect of growing up on a farm and the adverse impact of living or working in a moisture-damaged building are well established, the role and contribution of microbes to observed health outcomes are not fully understood.

Inhalation of indoor air contributes a dominant portion of our everyday inhalation exposures, certainly on a temporal scale. It is estimated that an individual spends more than 90% of their time in indoor environments and, on average, inhales about 10 m^3 of indoor air every day.[1,2] Inhalation of airborne microbes is a major exposure route between humans and microorganisms of all types: bacteria, fungi, including their spores and fragments, and viruses.[3] However, the direct ingestion of particulate matter—especially considering the hand-to-mouth behavior of infants—as well as direct dermal contact with microbes on surfaces, may also contribute considerably to the daily microbial exposure humans experience indoors. Infants are known to ingest significant portions of dust, with estimates reaching as much as 60 mg of dust on a self-administered, daily basis,[4] with this dust being typically heavily loaded with microbial material (in the range of 10^3-10^6 fungal and bacterial cells per mg of dust).

Complaints concerning poor Indoor Air Quality (IAQ) due to moisture damage are common.[5–7] Such complaints often perpetuate discussions about the public health importance of IAQ, which in turn catalyzes building investigations employing a wide variety of measurement, some of which lead to remedial actions. Numerous studies have established an association between observed mold or water damage and asthma,[8–11] and while quantitative evidence associating indoor microbial exposures and asthma has increased, there is still lack of broad consensus concerning causality.[12–14]

Juxtaposed to adverse health effects is a body of credible literature which presents evidence for protective health responses following sustained exposures—particularly early in life—to indoor microbes or microbial components. In addition to the relevance of the amount of exposure, several studies suggest that a wide *diversity* of exposure, including fungi, together with bacteria, can confer protection against certain diseases and symptoms.[15,16] This is in agreement with the tenets of the "hygiene hypothesis" which presents the potential benefits of exposure to a high diversity of microbes and /or their components, particularly early in life.[17]

The protective effect of microbial exposures is most clearly seen in infants, because the developing immune system benefits from being challenged with contact to microbes and their compounds.[18] Children growing up in microbe-rich farm environments are less likely to suffer from allergies than their urban counterparts.[15,19,20] In a recent pilot-scale study, Dannemiller et al.[21] found an association between lower fungal diversity in infancy and increased risk of asthma development at age 7. Other studies have also suggested that concomitant exposure to high levels of certain allergens and bacteria and fungi early in life could be beneficial against wheezing and allergic diseases[22–24] and offer protection against asthma by engaging and shaping the innate immune response of the individual.[25]

Despite the recognition of the importance of microbial exposure for human health, the precise role of microbes in the development and exacerbation of respiratory symptoms and allergies remains poorly understood. Over the last decade, environmental microbiome studies have leveraged advances in high-throughput DNA sequencing to take the study of indoor microbiota to an unprecedented level of detail. Thus far, however, only few epidemiological studies have been able to leverage health outcome data along with modern microbiota assessments from indoor environmental samples. As measurement approaches used in earlier epidemiological studies appear to lack the specificity to differentiate beneficial from adverse microbial exposure situations, identifying causal links between microbes and health outcomes has been impeded. There is a clear need for additional studies that aim at improving our understanding of the associations between the concentrations, detailed composition, and function of microorganisms we are exposed to in indoor environments and their potential to confer beneficial and harmful health effects.

In order to further explore indoor microbial exposures and their associated health effects, and to help establish research agenda

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priorities, a two-day workshop to discuss the key challenges in recognizing and resolving the emerging paradox of indoor microbe exposures, sponsored by the Alfred P. Sloan Foundation, was held in Kuopio, Finland. The workshop brought together 50 researchers/experts in the field of indoor microbiology, environmental engineering, asthma and allergy research, toxicology, and epidemiology, from North America and Europe. The workshop consisted of podium presentations from invited speakers and a breakout group discussion session, with the outcomes from these groups being reported to the general assembly in the course of a final discussion. We highlight here the key recommendations that stemmed from the group discussions and the final discussion, structured based on a set of questions (in italics) that were provided to guide the process.

1 | WHAT ARE THE KEY CHALLENGES IN RESOLVING THE PARADOX ROLE OF INDOOR MICROBES?

Understanding the basic biology and clarifying composite exposure conditions of indoor microbes is vital. In addition to their identity, distribution, and abundance, we need to know what effects microbes can induce individually and in combinations as a community. If these aspects are well understood, the indoor environment could potentially be altered to favor human health benefits, if at least, be less harmful.

Interactions of exposing agents are important as not only additive but also synergistic effects are to be expected; co-exposure of both microbes and microbial components as well as co-exposure to other environmental pollutants should be considered not only in mechanistic, but also large epidemiological health studies.

Consideration should be given to focus on and separate the relevant exposure routes (i.e., inhalation, ingestion, dermal exposure) and "windows of opportunity" in order to decide what, when, and how long to sample and measure. Exposure measurements in future assessments should be tailored toward those needs, with a goal of improving time resolutions for indoor sampling.

Understanding the relationship between the built environment and the human occupant microbiome is important as it is plausible that the indoor microbiome can interact with the human microbiome altering its composition and function.

2 | WHAT ARE THE MOST IMPORTANT QUESTIONS WHICH THE RECENT ADVANCES IN MICROBIOLOGICAL METHODS COULD HELP IN ADDRESSING?

It was recognized within this group of researchers that, up to this day, it is not entirely clear what and how to sample and measure in indoor microbial exposure studies that are designed to explore associated health effects. Recent advances in microbiological methods show promise in determining whether the microbes recovered during indoor sampling campaigns may in fact be causative agents as such, or only surrogates of an underlying harmful or beneficial exposure. Given the lack of knowledge on the specificities of the relevant exposures, assessments at this stage need to be kept broad and comprehensive.

Understanding and differentiating the fate and transport of microbes in built environments is important. New microbiological methods may be used for source tracking of environmental isolates to clinical isolates. Consideration should be given to human microbiota (e.g., those found in the gut, throat, nose, or skin). This will help in understanding the effects of these microbes via the various exposure routes (inhalational, dermal, or ingestion).

A broad consensus was reached regarding absolute quantification likely being necessary and crucial in supporting health-related studies on microbes in the built environment, in addition to diversity measures. For example, the use of quantitative PCR for targeting microbial groups of interest identified by next-generation sequencing, for absolute quantification and confirmation purposes, is powerful but requires support from the research community as to primer and assay design and QA/QC procedures.

3 | WHAT STUDIES ARE NEEDED?

Cross-sectional studies: Studies with a robust epidemiological framework including well-defined populations, good (temporally and spatially resolved) exposure assessment, and a statistical power that allows sound data interpretation are needed. Large sample size could be accomplished by combining cohorts across multiple studies and countries.

Intervention studies: Targeted interventions make it possible to compare exposures and health status in two distinct exposure groups and to follow the changes in exposure and outcome. Such studies could be very revealing and should be conducted, in particular in the context of adverse microbial exposure, for example, following moisture damage interventions, despite the recognition that such studies can be expensive or otherwise difficult to follow-up because of time frames and site access.

Validation studies: Validations of the exposure assessment methods to improve epidemiological studies are also needed. These include studies to improve sampling and analysis and also for determination of improved sampling schemes regarding spatial and temporal stability of the matrices of exposure, especially dust samples. This will help to characterize specific exposure situations in crucial time windows.

Toxicological exposure studies to address the synergistic potential of microbes, their fractions and components and chemicals in the indoor environment, should be run in parallel with epidemiological studies.

As a summary of the discussion, the group recommended that in the future epidemiological studies, the health outcomes of interest have to be defined beforehand, the relevant exposure routes and windows should be reflected in the sampling strategy, and the best available exposure assessment applied. The group concluded that to understand the health effects of microorganisms in indoor environments better, it is imperative that both beneficial and adverse effects are considered in future research agenda. The ultimate goal of indoor microbiome research has to be healthy occupants, and therefore, the starting point of future research should be health oriented.

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REFERENCES

1. Dacarro C, Picco A, Grisoli P, Rodolfi M. Determination of aerial microbiological contamination in scholastic sports environments. *J Appl Microbiol*. 2003;95:904–912.
2. Tringe SG, Zhang T, Liu X, et al. The airborne metagenome in an indoor urban environment. *PLoS One*. 2008;3:e1862.
3. Prussin AJ, Garcia EB, Marr LC. Total concentrations of virus and bacteria in indoor and outdoor air. *Environl Sci Technol Lett*. 2015;2:84–88.
4. USEPA. *Child-Specific Exposure Factors Handbook (Final Report)*. Washington, DC; US Environmental Protection Agency; 2008; EPA/600/R-06/096F.
5. Daisey JM, Angell WJ, Apte MG. Indoor air quality, ventilation and health symptoms in schools: An analysis of existing information. *Indoor Air*. 2003;13:53–64.
6. Meklin T, Husman T, Vepsäläinen A, et al. Indoor air microbes and respiratory symptoms of children in moisture damaged and reference schools. *Indoor Air*. 2002;12:175–183.
7. Heseltine E, Rosen J. *WHO Guidelines for Indoor Air Quality: Dampness and Mould*. Copenhagen, Denmark:WHO Regional Office Europe; 2009.
8. Mendell MJ, Mirer AG, Cheung K, Douwes J. Respiratory and allergic health effects of dampness, mold, and dampness-related agents: A review of the epidemiologic evidence. *Environ Health Perspect*. 2011;119:748.
9. Quansah R, Jaakkola MS, Hugg TT, Heikkinen SAM, Jaakkola JJ. Residential dampness and molds and the risk of developing asthma: A systematic review and meta-analysis. *PLoS One*. 2012;7:e47526.
10. Pekkanen J, Hyvarinen A, Haverinen-Shaughnessy U, Korppi M, Putus T, Nevalainen A. Moisture damage and childhood asthma: A population-based incident case-control study. *Eur Respir J*. 2007;29:509–515.
11. Sahakian N, Park J, Cox-Ganser J. Dampness and mold in the indoor environment: Implications for asthma. *Immunol Allergy Clin North Am*. 2008;28:485–505.
12. Reponen T, Willeke K, Grinshpun S, Nevalainen A. Biological particle sampling. In: Kulkarni P, Baron PA, Willeke K, eds. *Aerosol Measurement: Principles, Techniques, and Applications, Third Edition*. Hoboken, NJ: John Wiley & Sons, Inc.; 2011:549–570.
13. Reponen T, Lockey J, Bernstein DI, et al. Infant origins of childhood asthma associated with specific molds. *J Allergy Clin Immunol*. 2012;130:639–644 e5.
14. Kanchongkittiphon W, Mendell MJ, Gaffin JM, Wang G, Phipatanakul W. Indoor environmental exposures and exacerbation of asthma: An update to the 2000 review by the institute of medicine. *Environ Health Perspect*. 2015;123:6–20.
15. Ege MJ, Mayer M, Normand A, et al. Exposure to environmental microorganisms and childhood asthma. *N Engl J Med*. 2011;364: 701–709.
16. Genuneit J. Exposure to farming environments in childhood and asthma and wheeze in rural populations: A systematic review with meta-analysis. *Pediatr Allergy Immunol*. 2012;23:509–518.
17. Martinez FD. Role of viral infections in the inception of asthma and allergies during childhood: Could they be protective? *Thorax*. 1994;49:1189–1191.
18. Heederik D, von Mutius E. Does diversity of environmental microbial exposure matter for the occurrence of allergy and asthma? *J Allergy Clin Immunol*. 2012;130:44–50.
19. Ege MJ, Frei R, Bieli C, et al. Not all farming environments protect against the development of asthma and wheeze in children. *J Allergy Clin Immunol*. 2007;119:1140–1147.
20. von Mutius E, Radon K. Living on a farm: Impact on asthma induction and clinical course. *Immunol Allergy Clin North Am*. 2008;28: 631–647.
21. Dannemiller K, Mendell M, Macher J, et al. Next-generation DNA sequencing reveals that low fungal diversity in house dust is associated with childhood asthma development. *Indoor Air*. 2014;24:236–247.
22. Behbod B, Sordillo JE, Hoffman EB, et al. Wheeze in infancy: Protection associated with yeasts in house dust contrasts with increased risk associated with yeasts in indoor air and other fungal taxa. *Allergy*. 2013;68:1410–1418.
23. Lynch SV, Wood RA, Boushey H, et al. Effects of early-life exposure to allergens and bacteria on recurrent wheeze and atopy in urban children. *J Allergy Clin Immunol*. 2014;134:593–601 e12.
24. Iossifova YY, Reponen T, Ryan PH, et al. Mold exposure during infancy as a predictor of potential asthma development. *Ann Allergy Asthma Immunol*. 2009;102:131–137.
25. Stein MM, Hrusch CL, Gozdz J, et al. Innate immunity and asthma risk in Amish and Hutterite farm children. *N Engl J Med*. 2016;375:411–421.