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ARTICLE

Embracing microbes in exposure science

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Abstract
Although defined more broadly, exposure science has mainly focused on exposures to environmental chemicals and related stressors, such as airborne particulate matter. There is an opportunity for exposure science to contribute more substantially to improving public health by devoting more attention to microorganisms as key stressors and agents in exposure. The discovery that pathogenic microbes cause disease in humans precipitated a revolution in public health science and disease prevention. With a continued global urgency to address spread of pathogenic microbes, contributions of microorganisms to both infectious and noninfectious processes merit more attention from the exposure science community. Today, discoveries of the importance of the human microbiome as a determinant of health and disease are precipitating a second revolution. Emerging knowledge creates a major opportunity to expand the scope of exposure science to incorporate the human microbiome as a target and modulator of exposure. A study committee of the National Academies of Sciences, Engineering, and Medicine has defined a research strategy to address health risks that pertain to the interaction of environmental chemicals with the human microbiome. Some aspects of this strategy pose important challenges and opportunities for the exposure science community.

Keywords Environmental chemical · health risk · human microbiome · infectious disease

Infectious agents, other microbiologic stressors, and exposure science

Among the greatest achievements of humankind is the understanding that infectious microbes cause disease. The consequent development and application of that understanding has contributed mightily to improvements in public health. Historical examples highlight the scale of importance. The black death (plague), caused by *Yersinia pestis* and peaking during the middle of the 14th century, was responsible for the deaths roughly 100 million people in Eurasia. Stenseth et al. [1] conclude that for today and future conditions, "plague should be taken much more seriously by the international community than appears to be the case." The 1918 flu pandemic, involving the H1N1 influenza virus, infected 500 million people worldwide and resulted in deaths of about 50 million [2]. In each of these cases, the mortality totals are similar in scale to those associated with the world wars of the 20th century. In reviewing the history of tuberculosis, "an ancient scourge," Daniel [3] suggests that "*Mycobacterium tuberculosis* may have killed more persons than any other microbial pathogen."

In the struggle to understand and effectively respond to diseases caused by microorganisms, many important scientific and technological contributions can be noted. An example is John Snow's demonstration of a role for drinking water contamination in the 1854 cholera outbreak in London [4]. Investigations of microbial agents as causes of infectious disease, such as tuberculosis, were central in the formulation of the Henle-Koch postulates, the "classical point of reference in relating causative agents to disease." [5] Robert Koch was awarded the Nobel Prize in Medicine or Physiology in 1905 "for his investigations and discoveries in relation to tuberculosis" (https://www.nobelprize.org/nobel_prizes/medicine/laureates/1905/). In efforts to battle cholera outbreaks, Max von Pettenkofer, the "founder of modern hygienic science," made important contributions to public health, including "promotion of sanitary reforms, adequate pressurized water supply, and a sufficient sewage network." [6]

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The scientific achievements of the 19th century in understanding the roles of microbes as the causes of infectious diseases were followed by major technological developments throughout the 20th century to prevent and treat infectious disease. A prime example is the use of chemical disinfection for municipal drinking water, building on seminal investigations of disinfection kinetics [7] and chemistry [8]. In 2007, readers of the *British Medical Journal* voted "sanitation (clean water and sewage disposal)" as the "most important medical milestone since 1840." [9] Other major achievements improving public health in response to the challenge posed by infectious microorganisms include the widespread use of antibiotics [10] and the development of vaccines based on immunology [11]. More mundane, yet still important, are handwashing and other hygienic practices in health-care settings [12, 13].

Despite major progress, understanding pathways of infectious disease transmission and how to control them remain important topics of scientific and public health concern. These issues are of keen interest with regards to specific diseases, such as influenza [14], tuberculosis [15], and SARS [16]. They are relevant to specific infrastructure components that may contribute to exposure pathways, as in the case of premise plumbing and its roles in Legionnaire's disease and pulmonary nontuberculous mycobacterial disease [17, 18]. Infectious disease transmission is also a major concern in high-risk environments such as passenger aircraft [19] and health-care facilities [20].

Given the importance of pathogenic organisms as causes of disease and given the importance of infectious disease in the realm of environmental and public health, it is surprising that the exposure science community devotes relatively little attention to the subject.

The topic certainly lies within scope. Referring to definitions [21] in the official glossary of the International Society of Exposure Analysis (now the International Society of Exposure Science), exposure is the "contact between an agent and a target." An agent is "a chemical, biological, or physical entity that contacts a target." And the target is "any biological entity that receives an exposure or a dose (e.g., a human, human population, or a human organ)." This set of definitions clearly provides for exposure science to include characterizing the nature, scope, and conditions that influence human exposure to pathogenic microbes.

In 2012, the National Academies published *Exposure Science in the 21st Century: A Vision and a Strategy* [22]. That document defines exposure science as "The collection and analysis of quantitative and qualitative information needed to understand the nature of contact between receptors (such as people or ecosystems) and physical, chemical, or biologic stressors." That report frequently uses the phrase (or close variants), "physical, chemical, or biologic stressors." Yet, it is almost silent on any of the manifold specific exposure issues that would arise in considering pathogenic microorganisms.

Consider, too, the history of work published in this journal. As of June 2018, the Web of Science catalogued 1723 articles published in the *Journal of Exposure Science and Environmental Epidemiology* (*JESEE*) and its predecessor (with "*Science*" replaced by "*Analysis*"). Of these, only about 2% are selected in a search in which the topic is "microbe" or "microbial" or "bacteria" or "fungus" or "virus."

To its credit, a special anniversary release of *JESEE*, published in 2011, included, among the sixteen brief articles, two (13%) that were specifically microbial. They addressed, respectively, anthrax and the 2009 H1N1 pandemic flu virus. (Online source: https://www.nature.com/jes/articles?type = exposure-science-digests.)

Chemical methods for managing health risks from pathogens require contributions from exposure science to properly balance microbiological and chemical hazards. Among noteworthy examples in this regard are exposures to disinfection byproducts in drinking water [23]. Such concerns contributed to a transition in water quality engineering, substituting chloramines for chlorine as residual disinfectants. Triclosan was developed and introduced as a broad-spectrum antibacterial agent in health-care settings [24], but then more broadly applied in personal care and household products, raising a host of chemical toxicity concerns, which have contributed to an international call for limits on its production and use [25]. A third example is the finding that heavy use of bleach in household cleaning is associated with increased risk of nonallergic asthma [26]. In each of these cases, chemical exposures are clearly intertwined with microbial concerns.

In addition to infectious microbial agents, other biologic stressors contribute to adverse health risks. Issues related to exposure science are not yet well resolved in many such cases. For example, dampness in buildings is an important risk factor for adverse respiratory outcomes [27]. Until now, it has not been possible to determine the underlying cause for the associations, and it remains unclear whether the most important exposures are microbial or chemical in nature. A case could be advanced that understanding the cause isn't so important if an effective remedy is to remediate the underlying dampness. That pragmatic approach misses important opportunities for synergistic insights that can result from deeper understanding of the causal relationships.

Exposure science can make considerable contributions in improving knowledge about health risks associated with infectious agents and other biological stressors. For example, exposure analyses can be improved. Many studies acknowledge the importance of exposure yet rely upon qualitative descriptors or weak proxy indicators such as the abundance of a stressor in an environmental medium

without adequate attention to the extent of contact between the target and that medium. Exposure science can contribute improved mechanistic descriptions of the source-to-intake pathways in ways that would support mathematical modeling for risk assessment and risk management. Exposure science can effectively contribute improved knowledge about exposures that occur through multiple pathways, for instance in assessing nosocomial viral infection risk [28].

Exposure science also is well-positioned to incorporate explicit consideration of human factors for parameters such as inhalation and ingestion rates. Central tendency, population variability, and dependence on underlying factors (such as age, sex, and activity level) may be important considerations for quantifying exposures. Likewise, exposure science is well suited to provide explicit consideration of human activity patterns [29], illuminating where people are and when, essential information for properly relating a stressor's abundance in an environmental medium to the consequent contact that constitutes an exposure.

Exposure science can play an important role in outbreak investigations, in epidemiological studies of patterns of infectious disease, and in the evaluation of technical and administrative interventions for public health protection. Exposure science is particularly well positioned to contribute quantitative evidence needed to support rational tradeoffs when evaluating chemical interventions to protect public health against infectious agents [30].

These aspects pertain closely to current value-added opportunities for exposure science. A key point to consider is this: while exposure science is designed to address microbial agents as biologic stressors, contributions are occurring at a lower rate than would be justified by public health significance in infectious and noninfectious disease risk assessment and risk management.

Second revolution: healthy human microbiome

A second scientific revolution is underway in our understanding of the dependence of human health on microorganisms. The first revolution, considered in the previous section, was precipitated by the discovery that pathogenic microbes cause disease in humans. The second revolution is demonstrating that health depends in many important dimensions on proper composition and functioning of the human microbiome.

Awareness that humans have associated microbiota extends back at least several decades. However, understanding the nature of these microbes and their importance for their human hosts has shifted rapidly. Luckey wrote in the early 1970s about intestinal microecology, noting the evolutionary linkage between enteric bacteria and the mammalian alimentary tract. Drawing on experimental investigations of germ-free animals, Luckey stated that "microbes are dispensable. Life is possible without germs." [31] That opinion doesn't prevail today.

The idea that intestinal microbes might be health beneficial and that diet could influence their composition is identified with two terms: probiotic and prebiotic. Considering farm animals as well as humans, Fuller [32] provides a scientific review of probiotics and offers this definition: "A live microbial feed supplement which beneficially affects the host animal by improving its intestinal microbial balance." Fuller concludes that, "there is good evidence that the complex microbial flora present in the gastrointestinal tract of all warm-blooded animals is effective in providing resistance to disease."

Precipitated in part by the advent of molecular approaches for measuring microbes, including quantitative PCR and next-generation sequencing, we are now seeing an explosion of scientific attention focusing on the microorganisms associated with the human body. The earliest article in Web of Science with "human microbiome" in the title was published in 2007. Ley et al. [33] wrote then that, with advances in metagenomics, "we start to see ourselves as supra-organisms whose genome evolved with associated microbial genomes." In less than a half century, we are seeing a complete reversal from Luckey's "microbes are dispensable" [31] perspective to a view in which we study ourselves "as an integral and dependent part of our microbe-dominated world." [33]

Let's take a closer look at the human microbiome. First, how many human cells and how much bacterial matter are associated with humans? Sender et al. [34] have estimated that the number of bacterial cells (38 trillion) is comparable to the number of human cells (30 trillion). However, the number of nucleated human cells is estimated to be only 10% of the total, i.e. 3 trillion, indicating that— by count— the human is clearly outnumbered by associated bacteria. Furthermore, Ley et al. [33] observe that the human-associated microbial genes exceed our human genes by a factor of 100.

Here is a useful working definition: [35] "The human microbiome is an all-encompassing term that refers to all microorganisms on or in the human body, their genes, and surrounding environmental conditions." Several major reviews have been published on the role of the human microbiome in health and disease, highlighting the property of resilience [36], characterizing the "ranges and diversity of both taxonomic compositions and functional potentials" [37] along with influential factors, and emphasizing the roles of appropriate microbial exposure during early life in shaping an effectively active immune system [38].

The human microbiome exhibits enormous diversity along several axes. One portion of the diversity is biogeographical: the microbiota inhabiting different portions of the body vary markedly. With regard to exposure science, the

most important parts of the human microbiome are likely to be those that are in most intimate contact with environmental media: the gastrointestinal tract, the respiratory tract, and the skin.

By mass and by cell number, the dominant subsystem of the human microbiome is found in the gut. This component is also the most thoroughly studied with regard to health [39, 40]. In their review, Lynch and Pedersen [39] note that "gut microbiota dysbiosis—imbalances in the composition and function of these intestinal microbes— is associated with diseases ranging from localized gastroenterologic disorders to neurologic, respiratory, metabolic, hepatic, and cardiovascular illnesses." Marchesi et al. [40] draw parallels between the gut microbiome and an immune system, "a collection of cells that work in unison with the host and that can promote health but sometimes initiate disease." Among the diseases and disorders considered in their review are "metabolic syndrome and obesity-related disease, liver disease, inflammatory bowel disease, and colorectal cancer." A fascinating feature of the gut microbiome is its influence in the two-way communication channel with the brain, referred to as the "gut-brain axis." [41] The gut microbiome is suspected to play "key role in the biological and physiological basis of neurodevelopmental, age-related and neurodegenerative disorders." [42] It has been posited that the dysbiosis of the gut microbiome may have central nervous system consequences contributing, e.g., to depression when the intestinal barrier function is disrupted [43]. "Recent research has also linked microbial dysbiosis to neurological disorders, such as Parkinson's and Alzheimer's diseases, multiple sclerosis, and autism." [44]

The mature gut microbiome is established during infancy and influenced by early-life exposures. "Cessation of breastfeeding was identified as a major factor determining gut microbiota maturation." [45] Focusing on differences between populations and over time, Rook et al. [46] write that the "immune system evolved to require input from at least three sources that we collectively term the 'old friends'". These include commensal microbes from mothers and other family members; organisms acquired from early-life environmental exposures; and the types of subclinical infections that could have persisted in "small isolated hunter-gatherer groups."

Gensollen et al. [47] speak to the importance of early life exposure conditions, writing that, "microbial colonization of mucosal tissues during infancy plays an instrumental role in the development and education of the host mammalian immune system. These early-life events can have long-standing consequences: facilitating tolerance to environmental exposures or contributing to the development of disease in later life, including inflammatory bowel disease, allergy, and asthma."

Stein et al. [48] have compared immunity and asthma risk in Amish and Hutterite farm children. These populations are from similar genetic stock and both rely on agrarian lifestyles. However, the Amish follow more traditional farming practices whereas the Hutterites farm in a more industrialized manner. The prevalence of asthma and allergic sensitization in Hutterite children was similar to that in the general US population, whereas it was 4–6 × lower in Amish children. House dust in Amish homes had elevated endotoxin levels. When instilled intranasally in mice, dust extracts from Amish homes were found to inhibit airway hyperreactivity.

Not long ago, the prevailing view was that the human respiratory tract was sterile. That view might seem surprising, given what we now understand about the ability of microbes to inhabit and populate challenging microenvironments throughout the biosphere. Notwithstanding considerable sampling challenges, we now know that the respiratory tract is well populated by microorganisms [49, 50]. However, the specific understanding of the role of the lung microbiome in health and disease is trailing investigations of the gut microbiome. Dickson et al. [51] highlighted "respiratory dysbiosis" as a factor in the "pathogenesis of exacerbations of chronic lung disease." In a recent review, Man et al. [52] write, "The microbiota of the respiratory tract probably acts as a gatekeeper that provides resistance to colonization by respiratory pathogens. The respiratory microbiota might also be involved in the maturation and maintenance of homeostasis of respiratory physiology and immunity." A specific area of concern is that certain respiratory tract microbes may contribute in a positive feedback cycle to inflammatory processes [53].

The skin microbiome is characterized, among other features, by substantial variation across body sites according to local physiology, clustered into dry, moist, and sebaceous (oily) [54]. The skin is an environmentally harsh and nutrient poor environment compared with the gut, and so the microbial biomass of the skin is considerably lower than that of the gut. The microbial communities on adult skin appear stable over years-long periods. Initial colonization differs between babies born through the vaginal canal as compared to those born by Caesarian section. Puberty is a time when the skin microbiota undergoes considerable change in composition. Some common disorders are associated with dysbiosis in the skin microbiome, including acne, eczema, and chronic wounds.

Built environment and the human microbiome

People spend 90% of their time indoors [29]. Do indoor environmental factors influence the human microbiome? A recent report of the National Academies of Sciences, Engineering and Medicine developed a "research agenda for indoor microbiology, human health, and buildings." [55] Among the

stated research goals was to "elucidate the immunologic, physiologic, or other biologic mechanisms through which microbial exposures in built environments may influence human health." The study committee reported that, "questions remain about the extent to which indoor microbiomes influence the composition and function of the human microbiome … and what that may mean for health outcomes."

There is ample evidence to support a concern that indoor environmental exposures to infectious agents can cause disease, even for healthy individuals. Indoor environmental reservoirs govern the risk of Legionnaires' disease [56] and probably contribute to the spread of norovirus [57]. Strong evidence has emerged that indoor airborne transmission is important for certain viral infectious diseases such as SARS [16] and influenza [58]. Evidence has also emerged that building microbiological factors can meaningfully interact with the human microbiome in the case of hospitalized premature infants [59] and for individuals with seriously compromised immune systems [60]. Strong evidence is emerging that the microbiome of building occupants influences the microbiology of indoor environments. For example, Luongo et al. [61] found that the sex of inhabitants could be discerned from bacterial sequencing of dust collected from dormitory rooms. Lax et al. [62] reported that household microbiota was "identifiable by family" and that "humans sharing a home were more microbially similar than those not sharing a home." Lehtimäki et al. [63] studied skin microbiota and found an age-dependent difference between rural and urban children. Given the pace of recent progress, we can anticipate the emergence of stronger evidence in the near future regarding the nature and extent to which microbiology of built environments interacts with the human microbiome [64–66].

Nexus: environmental chemicals, human microbiome, health risk

The concern that exposure to environmental chemicals can pose health risks combined with emerging knowledge that the human microbiome is an important agent in health and disease leads to a critical question: might interactions between the human microbiome and environmental chemicals influence human health risk? The US Environmental Protection Agency and the National Institute of Environmental Health Sciences commissioned the US National Academies of Sciences, Engineering, and Medicine (NASEM) to convene a study committee to address this topic. The primary charge: "to develop a research strategy to better understand the interactions between environmental chemicals and human microbiomes … and the implications of those interactions on human health risk." [35] The committee's report can be freely downloaded from the National Academies Press. What follows is a brief summary and update, viewed through an exposure science lens.

In reviewing the existing state of knowledge, the committee identified several mechanisms of potential interest. Exposure to an environmental chemical might directly influence the human microbiome in ways that impact health risk. Scientific evidence to support the plausibility of this concern has emerged from recent studies. For example, the vulnerability of gut microbiota to alterations induced by chemical exposure has been demonstrated in the case of noncaloric artificial sweeteners [67]. Impaired glucose tolerance, of concern in relation to type 2 diabetes, was shown to be a consequence of the changes. More specifically relevant for environmental chemicals, Hu et al. [68] found that low dose exposures to common environmental chemicals—diethyl phthalate, methyl paraben, and triclosan—altered the composition of the gut microbiome in adolescent rats. Jin et al. [69] have reviewed the influence on gut microbiota in relation to health of "environmental pollutants including antibiotics, heavy metals, persistent organic pollutants, pesticides, nanomaterials, and food additives."

The microbiome also could modulate exposure to environmental chemicals, e.g., by altering the chemical form in ways that would affect their absorption, distribution, metabolism, and elimination (ADME) [70–72]. Claus et al. [73] describe the capabilities of gut microbiota to metabolize environmental chemicals in terms of specific enzymatic families. They conclude that "there is a body of evidence suggesting that gut microbiota are a major, yet underestimated element that must be considered to fully evaluate the toxicity of environmental contaminants."

Although the majority of research attention concerning the environmental chemical–human microbiome–health risk nexus has focused on the gut microbiome, evidence is also emerging about other microbiome subsystems. For example, Adar et al. [74] reviewed the evidence concerning microbiome interactions with inhaled pollutants. They reported: "The respiratory microbiome has been shown to influence chronic lung disease exacerbations, and increasing evidence indicates a role in disease development. Research also suggests that the respiratory microbiome could plausibly metabolize inhaled pollutants or modulate host inflammatory responses to exposure."

The research strategy put forward by the NASEM committee emphasizes three subcomponents of the human microbiome associated, respectively, with the gut, the respiratory tract, and the skin. Two categories of processes were the primary focus: effects that environmental chemicals might have on the composition and especially function of the human microbiome; and the roles that the microbiome might play in modulating human exposures to environmental chemicals. Also, being responsive to the

statement of task, the research strategy was explicitly attentive to the variation and variability in the microbiome, where variation captures differences in central tendency associated with factors such as body site, age, and sex, and variability describes the potentially continuous differences across populations in composition and functional attributes once other parameters are fixed.

Highlights of the research strategy priorities advanced in the committee's report include the following: [35]

> Investigating "…the effects of environmental chemicals on the human microbiome and consequent changes to human health. The question is whether environmental-chemical exposures or doses that are in the range of known or anticipated human exposures can induce microbiome perturbations that modulate adverse health effects."
> Understanding "… the effects of the human microbiome on exposure to environmental chemicals. Specifically, what is the role of a microbiome in modulating absorption, distribution, metabolism (activation or inactivation), and elimination (ADME) of environmental chemicals?"
> Considering implications of variation and variability in microbiomes for assessing risks from chemical exposures. "The human microbiome structure and function vary with, for example, body site, life stage, genetics, geography, and health status. The human microbiome also differs from microbiomes of animal species."

Exposure science would play a key role in research that aims to illuminate the relationships among environmental chemicals, the human microbiome, and health risk. To that end, here are some key exposure-science findings quoted from the committee's report: [35]

> "Adequate consideration of the roles of the human microbiome will improve understanding of the health risks posed by exposures to environmental chemicals."
> "Characterization of animal and human exposure and health risk has advanced through the use of biomonitoring, biomarkers, and physiologically based pharmacokinetic models. Those methods have not been consistently applied to or do not encompass aspects known to be important for the microbiome, such as life stage, sex, and disease state."
> "There is a need to expand the scope of exposure science to incorporate the emerging understanding of the roles of the human microbiome and its components as agents that influence exposures to and risks posed by environmental chemicals."

The NASEM report presented illustrations of several environmental chemicals for which incorporating full consideration of the human microbiome might alter the way that exposure is assessed or interpreted. Three examples are briefly recapitulated here.

Formaldehyde is a toxic air contaminant and common indoor air pollutant [75]. IARC has judged that there is "sufficient evidence in humans for the carcinogenicity of formaldehyde. Formaldehyde causes cancer of the nasopharynx and leukaemia." [76] Formaldehyde is also used as a preservative for biological specimens. These features lead one to question whether some of the physiologic response to inhalation exposure for formaldehyde might be modulated by microbiota in the upper respiratory tract. "What is particularly germane is whether exposures to formaldehyde at concentrations encountered (or potentially encountered) in the environment interact with the microbiota in the upper airways in a manner that materially influences associated health risks, considering both irritancy responses associated with acute exposures and cancer risk associated with cumulative exposures." [35]

Phthalates are a class of compounds widely used in consumer products. Among the health concerns associated with phthalate exposures are insulin resistance [77], metabolic syndrome [78] and reproductive and developmental toxicity [79]. Exposures can occur via multiple pathways, including ingestion, inhalation, and dermal absorption [80, 81]. A recent study demonstrated that transdermal uptake from air could make a meaningful contribution to exposure to diethyl phthalate and di(*n*-butyl) phthalate [82]. There are clues that microbes might influence exposure to phthalates. For example, it has been demonstrated that the skin is more permeable to the metabolite mono (2-ethylhexyl) phthalate (MEHP) than to the parent compound di (2-ethylhexyl) phthalate (DEHP) [83]. Nakamiya et al. [84] have shown that microbes extracted from house materials can convert DEHP to MEHP. It is an open question whether skin microbiota carry out a similar conversion process.

Triclosan presents a challenging case for exposure science. Its widespread incorporation into household and personal care products such as soaps and toothpastes have contributed to a high level of exposure intimacy [85]. Concerns have been raised about triclosan as a possible endocrine disrupting compound [86] and as a contributor to antibacterial resistance in environmental media, such as indoor dust [87]. As a broad spectrum antibacterial agent, there is also a basis for health-risk concerns in which microbiota in the human microbiome are an exposure target. Scientific understanding of health risks associated with triclosan as an environmental chemical is still developing. In a recent review, Goodman et al. [88] concluded that "the current body of epidemiologic literature does not allow a meaningful weight of evidence assessment due to the methodological limitations of individual studies and lack of inter-study consistency." Evidence for concern is

accumulating, however. Ribado et al. [89] conducted a randomized intervention study of triclosan and triclocarban (TC) in personal care products in households with new babies. They found that "antibiotic resistant species from the phylum Proteobacteria … were enriched in stool samples from mothers in TC households after the introduction of triclosan-containing toothpaste." They reported that—independent of treatment —"infants with higher triclosan levels also showed an enrichment of Proteobacteria species." Bever et al. [90] studied triclosan in breast milk in relation to personal care product use by mothers. They reported that "bacterial diversity in the fecal microbiome of the infants exposed to breast milk with detectable triclosan levels differed compared to their peers exposed to milk containing non-detectable amounts." Using a mouse model, Yang et al. [91] found that brief exposure, "at relatively low doses, causes low-grade colonic inflammation, increases colitis, and exacerbates colitis-associated colon cancer in mice." They attribute adverse effects of triclosan, in part, to "modulation of the gut microbiota." "Given widespread human exposure, research to investigate the effects of triclosan on the human microbiome and to answer such questions as whether early-life exposure to triclosan is predisposing infants to adverse health outcomes seems warranted." [35]

Way forward for exposure science

Exposure science is an important domain and a young discipline. Evidence of importance include the existence of this journal, an associated international society (the International Society of Exposure Science, ISES), and consensus reports of the National Academies focused on the discipline [22]. Evidence of youth include the relatively recent dates of founding of this journal (1991) and of ISES (1989). With young disciplines, efforts toward systematization are necessary, as illustrated by the effort to define an exposure science ontology [92]. Paradigm shifting discoveries and discernment should also be anticipated, as in the case of the exposome [93, 94].

At the time exposure science began, knowledge about microbes as agents of infectious disease was already well established, whereas knowledge about health risks associated with environmental chemicals was sparse. Consequently, one might view the almost exclusive focus of exposure science on environmental chemicals as a rational approach. However, in the succeeding decades, accounting for progress made and recognizing the relative importance of the topics for public health, it seems worthwhile to adjust the balance, explicitly expanding the areas of concern in exposure science to include exposure aspects pertaining to infectious and noninfectious microbes as agents and as biologic stressors.

Over a time-scale comparable to the age of exposure science, knowledge about the microbes associated with humankind has undergone a revolutionary transformation, the ultimate outcomes of which are not yet clear. In the early 1970s, Luckey's view may have prevailed: although microbes were common and prevalent on and in humans, they were nonessential. By the late 1980s, an understanding of our dependence on microbiota as factors influencing our health had begun to take root. In the past few decades, we have seen a strong shift: human-associated microbes are no longer thought of being apart from us, but rather are increasingly recognized as an integral part of us, the human microbiome. The ramifications of this radical shift in perspective have not yet been absorbed in the exposure sciences.

ISES operates as a "global community of exposure science professionals." To achieve its vision "to better our world, its ecosystems, and inhabitants," much more attention is needed to the microbial aspects of exposure science. In this perspective, I have aimed to provide a constructive critique, grounded in the belief that exposure science has much to offer and much to gain by increased attention to microbial aspects of its endeavors.

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Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

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