Consensus Study Report
December 2017
HIGHLIGHTS

Environmental Chemicals, the Human Microbiome, and Health Risk

A Research Strategy

The human microbiome is composed of a great number of diverse microorganisms that inhabit the human body. Until recently, the role of the microbiome in maintaining human health was not fully appreciated. Today, however,scientists are beginning to elucidate the important roles that it might play in a wide array of diseases, such as diabetes, asthma, and inflammatory bowel disease.

Recent studies have indicated that the human microbiome can metabolize environmental chemicals and might be affected by chemical exposure. Given those findings, some have argued that chemical-microbiome interactions should be considered in assessing health risk associated with environmental-chemical exposure.

This report proposes a research strategy to advance understanding of the interactions between environmental chemicals and the human microbiome and the implications of those interactions on human health risk. The report also highlights key aspects of the human microbiome and its relation to health, describes potential interactions between environmental chemicals and the human microbiome, reviews the risk-assessment framework and reasons for incorporating the proposed research, describes methods for studying the microbiome, and identifies barriers for research and opportunities for collaboration.

THE HUMAN MICROBIOME

Because of the diversity of microbial life that colonizes the human body, human beings are now regarded as ecosystems that are comprised of distinct ecologic niches or habitats, each housing a collection of coevolved microorganisms. Coevolution has led to interdependence: the human microbiome contributes an array of essential functions and influences a variety of biological processes. Perturbations in the makeup of these microbial communities are now being associated with disease.

One key aspect of the human microbiome is the variation in its composition and function among populations, over the human life span, and between different sites on the body. Multiple factors play roles in the observed variation among

body sites. For example, age and diet play primary roles in the variation observed in the gut microbiome, and water and nutrient availability drive the site-specific community states of the skin microbiome. Other factors—such as genetics, gender, socioeconomic status, disease state, geography, pregnancy, and environmental exposures—can also play a role in shaping the composition and function of the human microbiome.

Although animal models have provided valuable data on microbiome structure and function, it is important to note that the human microbiome differs from the microbiomes of other species in the relative abundance of dominant microorganisms, in which species are present, and in how the microbial community responds to a given perturbation. Whether there are functional differences between human and animal microbiomes remains to be seen. Given the differences, observations made in animal models, although informative and foundational, might not capture the full breadth of microbial interactions that occur in humans.

INTERACTIONS BETWEEN ENVIRONMENTAL CHEMICALS AND THE HUMAN MICROBIOME

Studies suggest that exposure to environmental chemicals can alter the composition and potentially affect the function of the human microbiome. Research has also indicated that the human microbiome can modulate environmental-chemical exposure, for example, by metabolizing the chemicals. Many molecular mechanisms probably underlie

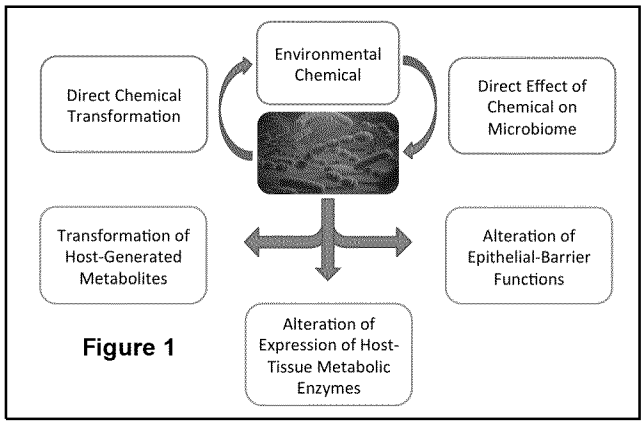

Figure 1

microbiome interactions, but research currently suggests the general mechanisms shown in Figure 1.

Although research has provided clues regarding microbial transformation of environmental chemicals and vice versa, there are still gaps in the understanding of how chemical exposure changes activity or function of a microbiome and the breadth of potential pathways for metabolism of environmental chemicals in a microbiome. It is important to note that each interaction can conceptually increase or decrease chemical exposure, and that the role of the interactions in modifying human susceptibility to toxicity at environmentally relevant exposures remains largely uncertain.

RISK ASSESSMENT: INCORPORATING CHEMICAL-MICROBIOME INTERACTIONS

The 1970s saw a growing awareness and concern that exposure to some environmental chemicals could cause adverse health effects. Government programs were created to protect against harmful exposures, and agencies developed methods for estimating risks posed by chemical exposure. Although there have been significant advances over the last decades, the core elements of risk assessment—hazard identification, dose-response assessment, exposure assessment, and risk characterization—have remained the same (see Figure 2).

Traditionally, animal toxicology studies have provided the data for hazard identification and dose-response assessment, although epidemiology (human) studies have provided the primary evidence on a few chemicals, such as arsenic and formaldehyde. However, no research approach has explicitly considered or incorporated the human microbiome. Therefore, risk assessments might mischaracterize the nature of a hazard associated with an exposure or overestimate or underestimate the risk associated with the exposure, particularly when results from studies in animals or a specific population are used to characterize risk to another species with a different microbiome.

Research in this field is important because it might explain differences between animal toxicology studies and human responses, provide greater confidence in extrapolating findings of animal studies to humans, and identify unrecognized health consequences of environmental exposures. Furthermore, differences in responses to chemical exposure reported in human studies conducted on different populations might be explained by the variation in microbiome composition and function. It is reasonable to hypothesize that adequate consideration of the microbiome in risk assessment could improve the understanding of health risks posed by exposures to environmental chemicals.

RESEARCH STRATEGY

Developing a research strategy is complex because our understanding of how perturbations of the human microbiome might cause or contribute to the development of disease is in its infancy. Therefore, a straightforward approach similar to a flowchart

or decision tree in which the results of one or more experiments would lead naturally to the next set of experiments is unfeasible at present given the state of science. Thus, the committee's research strategy focuses broadly on the following three general topics:

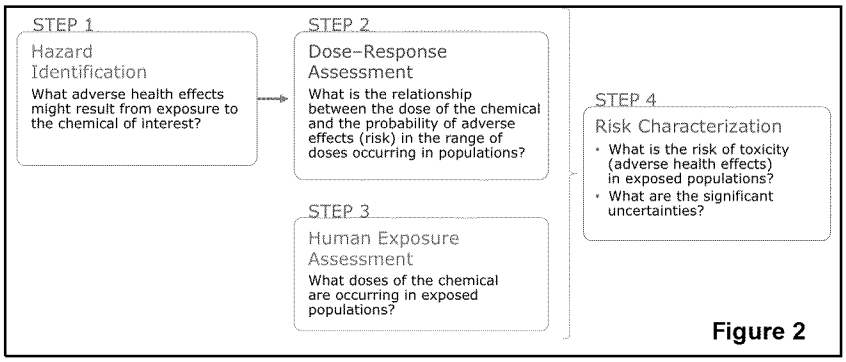

Figure 2

The Effects of Environmental Chemicals on the Human Microbiome. The goal of this research is to determine whether environmental-chemical exposures or doses that are in range of known or anticipated human exposures can induce microbiome alterations that modulate adverse health effects. To achieve that goal, the research program should focus on defining toxicity end points for the microbiome, identifying environmental chemicals that can perturb the microbiome, and using animal and epidemiology studies to demonstrate that microbiome perturbations by environmental chemicals cause or modulate a change in health.

The Role of the Human Microbiome in Modulating Environmental-Chemical Exposure. The goal of this research is to determine the role of the human microbiome in modulating absorption, distribution, metabolism, and elimination (ADME) of environmental chemicals. Accordingly, the research program should focus on generating ADME data from animal and in vitro experiments. Ultimately, the research should identify specific microorganisms and their enzymes that mediate chemical transformation processes by using new chemical probes and screening technologies. That information is critical in addressing individual susceptibility and interspecies extrapolation at a mechanistic level and in understanding the degree of functional redundancy that exists within a microbiome.

The Importance of Microbiome Variation. Two aspects of microbiome variation need to be investigated. The first is variation in the human microbiome; the question is whether knowledge of population variation in the human microbiome improves understanding of individual health risks and susceptibility to effects of environmental chemicals. Here, comparative studies should assess functional similarities and differences of the factors known or hypothesized to affect microbiome diversity and emphasize populations that represent key windows of potential vulnerability.

The second aspect that needs to be explored is variation between species. One question is whether the differences are so great that effects are being missed or mischaracterized by using animal models to predict human health risk associated with environmental-chemical exposure. Another question is whether the factors that are used to extrapolate effects in animals to humans account adequately for the microbiome variation. Here, comparative studies could ultimately reveal the functional capacity encoded by the human microbiome so that animal species and study designs that are most appropriate for extrapolating to humans can be identified.

BARRIERS TO RESEARCH

Tools will need to be developed, and barriers will need to be overcome to accomplish the research described in this report. A few overarching barriers are highlighted below.

- *Resources.* Many experiments are likely to require substantial investments of time and resources and would require multidisciplinary expertise not found within a single laboratory.
- *In vitro model systems.* Despite advances, in vitro model systems that faithfully model the host environment have not yet been developed. Additionally, current systems are unable to incorporate microbial communities that fully represent naturally occurring microbiomes
- *Standardization.* Lack of standardization in experimental approaches can result in an inability to reproduce findings related to chemical-microbiome interactions.
- *Microbial reference communities.* Past initiatives have provided data on the composition of microbial communities from healthy adults, but additional microbial reference communities and standardized microbial populations that accurately represent the variation in the human microbiome are needed.
- *Reference information.* Genomic, transcriptomic, and metabolic databases and libraries will need to expand their coverage and annotation of relevant strains, genes, enzymes, metabolite identities and function, and associated characteristics of microbiome sources to enable understanding of microbiome dynamics.

COLLABORATION

Progress in fields related to risk assessment and in microbiome research has occurred largely independently, and the segregation of such research programs poses a barrier to advancing knowledge on interactions between environmental chemicals and the human microbiome and the implications of the interactions for human health risk.

To support such efforts effectively, interdisciplinary collaborations should be sought out, encouraged, and supported to make the best use of available knowledge and resources in each agency or organization. Such interdisciplinary initiatives could also serve as an ideal training environment for the next generation of researchers whose expertise spans several fields.

CONCLUSION

Implementation of the proposed research strategy should advance understanding of whether and to what extent the human microbiome affects the nature and magnitude of adverse health effects caused by exposures to environmental chemicals. In the near term (2–4 years), results of the proposed research should allow judgments to be made about whether explicit consideration of microbiome interactions in the study of environmental-chemical toxicity yields information that is not available from traditional studies that do not explicitly consider microbiomes. Within a similar time frame, it should also be possible to determine whether new information is gained by studying the effects of chemicals on the human microbiome, the role of the human microbiome in modulating chemical exposures, or both. The research should lead to the type of information needed to assess the importance of the human microbiome as a contributor to human health risks associated with exposures to environmental chemicals and thus permit informed decisions about the need for and nature of continuing research in this field.

COMMITTEE ON ADVANCING UNDERSTANDING OF THE IMPLICATIONS OF ENVIRONMENTAL-CHEMICAL INTERACTIONS WITH THE HUMAN MICROBIOME

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For More Information . . . This Consensus Study Report Highlights was prepared by the Board on Environmental Studies and Toxicology and the Board on Life Sciences based on the Consensus Study Report *Environmental Chemicals, the Human Microbiome, and Health Risk: A Research Strategy* (2017). The study was sponsored by the U.S. Environmental Protection Agency and the National Institute of Environmental Health Sciences. Any opinions, findings, conclusions, or recommendations expressed in this publication do not necessarily reflect the views of any organization or agency that provided support for the project. Copies of the Consensus Study Report are available from the National Academies Press, (800) 624-6242; http://www.nap.edu or via the Board on Environmental Studies web page at http://www.nationalacademies.org.

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