Army Public Health Center

Public Health Information Paper

The Microbiome and Health Risk Assessment: Workshop Summary

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APHC

Environmental Health Sciences and Engineering Directorate

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1. SUMMARY

1.1 Purpose

This Public Health Information Paper summarizes the proceedings of a workshop organized to bring together subject matter experts (SMEs) to share their knowledge of microbiome-chemical interactions, and discuss strategies for targeted research that will support the integration of microbiome data and insights into health risk assessment. The workshop was held on 20 April 2016 at Defense Health Headquarters, Falls Church, Virginia.

1.2 Abstract

A workshop to discuss microbiome-chemical interaction and strategies to support the integration of microbiome-associated data into health risk assessment was held on 20 April 2016 at Defense Health Headquarters. Four SMEs were invited to provide thought-provoking talks on the state-of-the-science of microbiome research. Workshop participants from the U.S. Army Public Health Center (APHC), U.S. Army Center for Environmental Health Research (USACEHR), U.S. Army Engineer Research and Development Center, Air Force Medical Support Agency, Air Force Research Laboratory, Naval Surface Warfare Center, Navy Marine Corps Public Health Center, Uniformed Services University of Health Sciences, National Academy of Sciences, National Institutes of Health, U.S. Environmental Protection Agency, U.S. Department of Agriculture, Johns Hopkins University, and Massachusetts Institute of Technology–Lincoln Laboratory participated in a prioritization exercise for research to support risk assessment. Due to the complexity of the microbiome and inability to relate microbiome-data to operationally relevant functional differences, it was the consensus of workshop participants that the information is not yet mature enough for integration into health risk assessment. The suggested course of action is to remain abreast of breaking results and research agendas of the various agencies performing research on the microbiome, and participate in the Department of Defense (DOD) Microbiome Collaboration Forum.

1.3 Recommendations

Because information on how the microbiome functions (as both an individual system and as a component of a complex web of systems) is not yet mature enough for integration into health risk assessment practices, at this time the suggested course of action is to remain abreast of breaking results and research agendas of the various agencies performing research on the microbiome. This can be accomplished through participation in the DOD Microbiome Collaboration Forum (led by USACEHR), following results from the National Institutes of Health (NIH) Human Microbiome Project, and including microbiome as a search term in routine literature searches related to professional development. The topic of incorporating changes to the microbiome into human health risk assessment should be revisited at a later date.

2. REFERENCES AND TERMS

Appendix A provides the references cited, and the Glossary provides a list of acronyms and terms.

3. BACKGROUND

The term “microbiome” is generally used to refer to the collective genomes (genetic material) of all of the microorganisms that inhabit the human body. The term was coined in 2001 by Joshua Lederberg, who defined it as “the ecological community of commensal, symbiotic, and pathogenic microorganisms that literally share our body space and have been all but ignored as determinants of health and disease” (Lederberg 2001; Peterson et al. 2009). Recognition of the microbiome’s importance to human health has gained widespread attention through data generated as part of the NIH of Health Human Microbiome Project (begun in 2007) as well as many other efforts across the globe.

The concept of interactions between microbial communities and chemicals did not begin with the NIH Human Microbiome Project; bioremediation has long been used for clean-up of environmental contaminants. Similarly, it is known that humans host a variety of microbial communities. However, it is only within the last few years that the scientific community has started to grasp the significant contribution that these microbial communities have on human health and disease, and their potential use to characterize exposure. Identifying these impacts and leveraging the information to improve methods for how exposure and response are determined will ultimately result in a more robust assessment of risk.

In the gastrointestinal system, the interface between chemicals and the microbiome is a two-way interaction (Figure 1). The chemical may alter the microbiome, named Toxicant Modulation of the Microbiome (TMM), resulting in a perturbation of the numbers and types of organisms present. Alternatively, the microbiome may alter the chemical, named Microbiome-Mediated Toxicity (MMT), resulting in a more or less toxic byproduct. Both types of interactions may play an important role in how we estimate chemical exposure and assess individual variability in response to a chemical exposure.

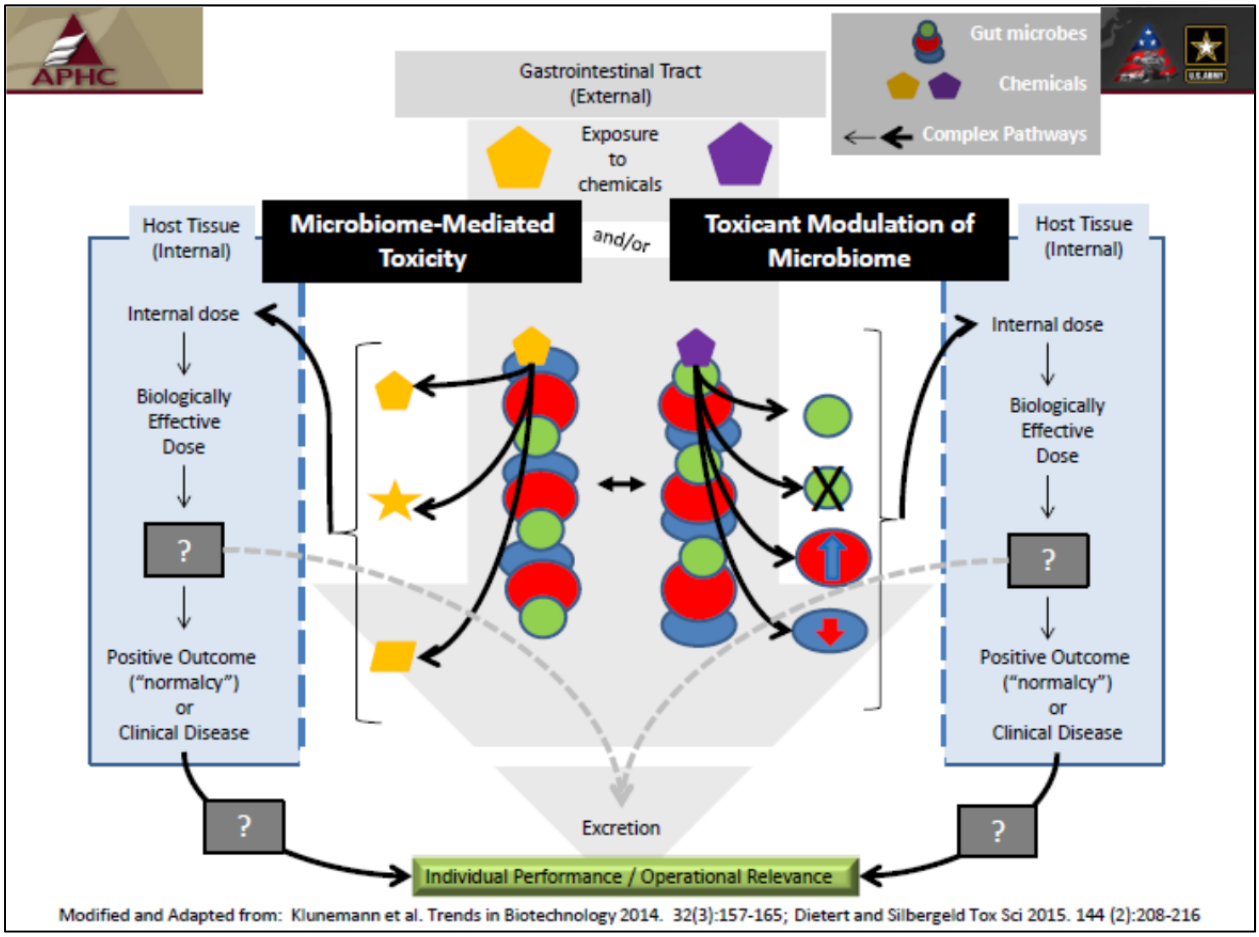

Figure 1. Schematic of Possible Host-microbiome Interactions and Relationship to Health Risk Assessment Components

Numerous laboratories are conducting studies to address TMM. The primary focus of these studies is how changes to the microbiome impact human health. It is possible that knowledge regarding the TMM relationship could assist with characterizing exposure. For example, pre- and post-microbiome profiles may be compared to determine if an exposure occurred. To our knowledge, this aspect of TMM (i.e., its utility as a biomarker of exposure) has not yet been addressed. Research on MMT appears to be less common, but results may provide information that informs risk assessment.

The relationship between the microbiome and chemicals could have a profound impact on the response of an individual (variability) to a chemical exposure, including exposure to chemical warfare agents or toxic industrial chemicals that can be used as weapons against DOD personnel. For example, a unit may be exposed to the exact same chemical and dose in the same environment, but the health effects may be very different due to variability among those exposed. In human health risk assessments for military populations, a "healthy Soldier" assumption may underestimate the variability that is inherent in the human population. Variability in the human microbiome may result from a number of factors, including environmental conditions (e.g., rural vs urban), diet, and health history. As the knowledge base regarding the role of the microbiome is better understood, the bounding of variability can also be better described; therefore, better health risk estimates can be derived and communicated.

While current research continues to examine the interaction between chemical exposures and the microbiome, efforts to integrate the information into risk assessment methodologies are just beginning. The consideration of both TMM and MMT is required to understand how the system can be used to characterize exposure and variability. Both appear to be critical elements that are not currently considered in the overall assessment of health risk.

A hard copy of Figure 1 was provided to participants as they entered the workshop. Participants were asked to provide comments regarding the figure and list any outstanding questions. Comments were collected at the conclusion of the workshop. A list of comments directly pertaining to the figure, as well as general comments/questions, can be found in Appendix D. The comments will be used to update the figure at a future date.

4. MICROBIOME AND HEALTH RISK ASSESSMENT MEETING

4.1 Workshop Purpose

The workshop goal was to bring together SMEs to share their knowledge of microbiome-chemical interactions, and discuss strategies for targeted research that will support the integration of microbiome data and insights into health risk assessment. A workshop was held on 20 April 2016, at Defense Health Headquarters, Falls Church, VA. (See Appendix B for Agenda.)

4.2 Workshop Attendance

Representatives from government, academia, and non-government organizations attended the workshop. (See Appendix C for a complete list of Workshop Attendees.)

4.3 Summary of Workshop Presentations

The human host-microbiome interaction is complex and isn't "new". The advent of molecular and high-throughput assays allows for the generation of a lot of data; however, understanding how to use that data is important in order to advance health risk assessment. Much of the microbiome research initiative is not asking new questions, per se, but instead is simply looking at age-old questions through a new lens. In this vein, four SMEs were invited to present on their research interests.

4.3.1 Dr. Ellen Silbergeld, Johns Hopkins Bloomberg School of Public Health.

"Gatekeeper and Watchman: The Microbiome Enters the Picture and What Does It Matter"—Dr. Silbergeld's presentation provided an overview of microbiomes (e.g., skin, gastrointestinal, and so forth) and why they may be relevant to toxicology and epidemiology. Specifically, Dr. Silbergeld described how the microbiome can be both a target and a transducer of toxicant actions. She discussed why considering the microbiome needs to be included in toxicology studies. The discussion that followed focused on specifics of the types of data that could be collected in a study as well as study design.

4.3.2 CPT Blair Dancy, U.S. Army Center for Environmental Health Research

"An Overview of DoD Microbiome Efforts: Context, Relevance, and Coordination"—CPT Dancy provided an overview of Federally supported efforts focused on understanding the human microbiome. These include a Fast-Track Action Committee on Mapping the Microbiome (Office of Science and Technology Policy) and the NIH Human Microbiome Project. Discussion included ways in which members of the military could provide a natural population for studying changes to the microbiome. Examples included

deployments to mega-cities and other deployment environments as well as longitudinal studies among military populations in different environments.

4.3.3 Dr. John Lewis, U.S. Army Center for Environmental Health Research

"The Role of the Microbiome in Toxic Exposure Assessment"—Dr. Lewis' presentation emphasized the role of the microbiome in military health surveillance and longitudinal assessments of health. Challenges to incorporating the microbiome data into health risk assessment include separating natural biological noise from information over time. For example, it is challenging to determine what changes to the microbiome are normal and which changes represent perturbations from chemical exposures. In addition, translating microbiome data collected in animal models to humans remains a difficult task.

4.3.4 Dr. Shawn Bearson, U.S. Department of Agriculture National Animal Disease Center.

"*Salmonella* Shedders and Spreaders: Reciprocal Influence of *Salmonella* and the Gastrointestinal Microbiota in Swine"—Dr. Bearson's research was provided as a case study of how microbiome data can be used to inform decisions. Dr. Bearson's research established a link between the *Salmonella* shedding by pigs and the composition of their gastrointestinal microbiota. This research is important because it provides actionable information. Understanding differing host characteristics can assist in developing diagnostic, predictive, and preventive tools with the potential to minimize transmission to reduce swine disease and decrease environmental contamination to limit food safety risk.

4.4 Prioritization Exercise

After the presentations, the workshop participants were invited to participate in a prioritization exercise. The goal of the exercise was to consider possible research topics and strategies and consider their impact potential on health risk assessment. A short presentation emphasized how data are an intersection between research and health risk assessment (i.e., research provides the data which health risk assessors use). Because, generally speaking, the generation of data is resource-intense (e.g., expensive and takes a long time), it is expected that forward-thinking discussions between researchers and risk assessors *before* data collection may improve data utility in health risk assessments.

The workshop participants were divided into small groups, and the following prompt was provided: "Brainstorm 'Where do we go from here to begin to integrate microbiome research into health risk assessment?' Think in terms of projects (current or future) or risk assessment steps that would move toward the integration and the ability to assess health risk to chemical exposures. Think big; assume we are in a perfect world (all the money, time and resources you can imagine)."

The outcome was identifying many topics that research could address (see list below). However, there was no actual prioritization of the topics; there was no "low-hanging fruit" identified. There was consensus that a common lexicon (vocabulary) would need to be established to join together research and risk assessment as well as Civilian and military counterparts. There was also agreement that one goal of microbiome research should be to have an emphasis on providing actionable information (such as the study described by Dr. Bearson).

Potential research topics suggested by the breakout groups included:

1. Determine changes in the microbiome and metabolites due to deployment. For example, characterize a group of Service Members prior to, during, and after a deployment, and report changes to the microbiome.

2. Establish functional changes mediated by the microbiome (or changes in the microbiome). For example, does intestinal permeability change, and is there an impact on absorption (of chemicals, nutrients, and so forth) with a changing microbiome?
3. Determine adverse effect pathways. For example, determine "bad actors" associated with particular locations or environments and their effects rooted in physiological and kinetic pathways.
4. Incorporate the microbiome into environmental surveillance by obtaining baseline microbiome profiles then manipulate an environment and determine any changes in the microbiome. For example, in a "sick building", establish the baseline microbiome, make the building "healthy," and reassess the microbiome.
5. Determine the point of difference. For example, determine how much stress is required to cause the microbiome to change?

4.5 Workshop Conclusions

There were three overall conclusions of the workshop:

1. Currently, observed changes to the microbiome determined in laboratory studies cannot be incorporated into health risk assessments. This is because there are too many unknowns regarding the microbiome and the many factors that impact it.
2. Consideration of the microbiome needs to be built into laboratory studies. This can be accomplished through piggybacking on well-annotated toxicology or epidemiology studies. Longitudinal studies would be especially helpful. As this is done, it is important that any microbiome research be related to functionality.
3. As more and more research is performed to better understand the microbiome and its impact on health, a dialogue is needed to determine how information regarding the microbiome and health is framed for leadership. When considered as an individual system (analogous to the immune system or nervous system) the microbiome is extremely complex, and senior leaders will need to be educated in an operationally relevant context.

5. CONCLUSIONS AND RECOMMENDATIONS

Because information on how the microbiome functions (as both an individual system and as a component of a complex web of systems) is not yet mature enough for integration into health risk assessment practices, at this time the suggested course of action is to remain abreast of breaking results and research agendas of the various agencies performing research on the microbiome. This can be accomplished through participation in the DOD Microbiome Collaboration Forum (led by USACEHR), following results from the NIH Human Microbiome Project, and including microbiome as a search term in routine literature searches related to professional development. The topic of incorporating changes to the microbiome into human health risk assessment should be revisited at a later date.

APPENDIX A

References

Dietert RR and EK Silbergeld. 2015. Biomarkers for the 21st Century: Listening to the Microbiome. Toxicol Sci 144 (2):208-216.

Lederberg J and AT McCray. 2001. 'Ome Sweet 'Omics - A Genealogical Treasury of Words. *Scientist* 15(7):8.

Klunemann M, Schmid M, and KR Patil. 2014. Computational Tools for Modeling Xenometabolism of the Human Gut Microbiota. *Trends in Biotechnology* 32(3):157-165.

Peterson, J., and the NIP Human Microbiome Project Working Group. 2009. The NIH Human Microbiome Project. *Genome Res*, 2009. 19(12):2317-23.

APPENDIX B

Workshop Agenda

Army Public Health Center
Microbiome and Health Risk Assessment Meeting
Wednesday, April 20, 2016
Defense Health Headquarters, Falls Church, VA, Room 3SW407

Agenda (DRAFT)

0800	Registration	
0830	Welcome, Introductions	
0900	*Asking the Right Questions: What can we Measure and how can it Help?*	**Ellen Silbergeld, Johns Hopkins Bloomberg School of Public Health (JHSPH)**
0930	*An Overview of DoD Microbiome Efforts: Context, Relevance, and Coordination*	**CPT Blair Dancy, (USACEHR)**
1000	*Discussion:* 1. What evidence is there about how microbiome research can help to identify significant variations between individuals or populations? 2. Can the contribution of the microbiome to individual variability be quantified? 3. Given control of confounding factors (diets, sleep schedules, location) can military populations contribute data to further the impact of the microbiome?	**Panelists:** **Dr. Ellen Silbergeld, (JHSPH)** **Dr. Robyn Barbaro, (USACE)** **CPT Blair Dancy, (USACEHR)**
1130	Working Lunch	
1230	*Perturbation of the Fecal Microbiome from Metal Exposed Rats*	**Dr. John Lewis, (USACEHR)**
1300	*Case Study on Information from Microbiome Research Changing Actions: Salmonella spreaders and Slaughter*	**Dr. Shawn Bearson, (ARS-USDA)**
1330	*Incorporation of the Microbiome Concept and the Potential Impact on Military Decisions. What the Future may Hold.*	**Dr. Steven Cersovsky, (APHC)**
1400	Break	
1415	*Discussion:* 1. Should the microbiome be considered a "target organ"? 2. Are measured/measurable changes to the microbiome sufficient to change risk assessment approaches (*i.e.* which side of the decimal point are we talking about)?	**Dr. John Lewis, (USACEHR)** **Dr. Shawn Bearson, (ARS-USDA)** **Dr. Steven Cersovsky, (APHC)**
1545	Prioritization Exercise	**Dr. Brandolyn Thran, (APHC)**
1615	Wrap-up	
1630	Adjourn	

APPENDIX C

Workshop Participants

Participant	Organization
Linda Duffy, PHD, MPH	National Institutes of Health
Jeffrey Freeman	Johns Hopkins University
Robyn Barbato	US Army Engineer Research and Development Center
Phil Karl	US Army Research Institute of Environmental Medicine
Nancy Kelley-Loughnane	Air Force Research Laboratory
David Butler	National Academy of Sciences
Camilla Mauzy	Air Force Research Laboratory L
David Jackson	US Army Center for Environmental Health Research
Roy Vigneulle	US Army Medical Research and Materiel Command
Laura Kolb	US Environmental Protection Agency
Lindy Caffo	US Army Center for Environmental Health Research
Aarti Gautam	US Army Center for Environmental Health Research
Jackson Lee	Massachusetts Institute of Technology Lincoln Lab
Jed Eberly	US Army Engineer Research and Development Center
Brian Kupchak	Uniformed Services University of the Health Sciences
Brad Gutting	Naval Surface Warfare Center Dahlgren
Michael Dempsey	Air Force Medical Support Agency
Camila Almeida	Uniformed Services University of the Health Sciences
Resha Putzrath	Navy Marine Corps Public Health Center
Tom Timmes	US Army Center for Environmental Health Research
Elane Cohen Hubal	US Environmental Protection Agency
Isabel Walls	US Department of Agriculture
Valerie Trabogh	US Army Center for Environmental Health Research
John Lewis	US Army Center for Environmental Health Research
Chris Bradburne	Johns Hopkins University Applied Physics Laboratory
Laurie Roszell	Army Public Health Center
Brandolyn Thran	Army Public Health Center
Blair Dancy	US Army Center for Environmental Health Research

APPENDIX D

Exit Ticket Comments

A hard copy of Figure 1 was provided to participants as they entered the workshop. Participants were instructed that this paper would be their "exit ticket", and they were to write directly on the paper to provide comments regarding the figure and list any outstanding questions. A list of comments directly pertaining to the figure, as well as general comments/questions, is below. The comments will be used to update the figure at a future date.

Comments from participants specifically about the Figure:

1. What about chemical mixtures? Should those be shown?
2. Label blue boxes as "Risk Assessment"
3. What about precision medicine? Does that correlate with the outcome/disease?
4. In green box, consider "Health and Readiness"
5. Use an upward arrow to show reversibility of biological effect?
6. Add an arrow between organisms to show the interaction between organisms.
7. Likely that the microbiome is "personal" and not as predictable as perceived.
8. Use wearable/ingestible sensors to monitor in real-time or near real-time those operationally-relevant metabolomics/biomarkers of harmful shifts to microbiome. If measure beneficial ones, would have a harmful/beneficial ratio).
9. Overall, microbiome to be incorporated as a "data point" of the individual "Personalized Health Risk Profile"
10. What about non-chemical agents? Large molecules? Proteins?
11. Alongside of figure, show community and/or functional shifts in metabolome from baseline.
12. From chemical metabolites, show that metabolites may be consumed by the organisms.
13. Better match light blue boxes to grey arrows.
14. Microbiome is really just another organ or tissue.
15. Instead of "Positive Outcome or Clinical Disease" use "Adaptation" and "Adverse Response (disease or impaired performance)"
16. Outputs to place on top of the green box include, "new normal", "persistence", or "return to baseline".
17. Include "presentation dose" in the light blue box.
18. Include a feedback loop from outcomes back to microbiome.
19. Include arrows after changes to show signals to _____ (can't read) system and/or target organs.
20. Diagram is very busy.
21. Do not understand the left side of diagram.
22. What does "biologically effective dose" mean?
23. Label left-hand side as "Biotransformation"?
24. On left side, include a stressor that changes host signaling to microbiota.
25. Include arrow off grey dashed arrows that allows for "signaling to other organ systems".
26. Include options of "change in functional proteins" prior to excretion (i.e., increase or decrease in kinase, etc = metaproteomics)
27. For "Drugs on Bugs" consider "Modulation of Microbiome Activity" or "of Bacterial Members" or "of Enzyme Inhibition"

28. Missing other routes of exposure (inhalation, dermal, pollutants that are inhaled can be swallowed).
29. Not just bacteria, include virus, fungi, prions?

Generic comments, statements or questions found on Figure:

1. What are the implications for people who frequently “mouth breathe”?
2. Gut microbiome contaminate indoor environments that humans occupy
3. Indoor environments are a reservoir for silver nanoparticles and other pollutants
4. Respiratory exposure is usually harder to control than ingestion
5. Military challenges in particular. A) non-typical sources of pollutants B) microbiome interaction/ indoor chemicals
6. Megacity exposures—(e.g., South Korea. How much of Soldiers time is spent indoors? How significant are exposures? Also consider respiratory exposures.
7. Cleaning and maintenance practices?
8. Ventilation, filtration, and heating, ventilation, and air-conditioning practices?
9. Consider performance and productivity as part of health?
10. The NAS Built Environment Study will be looking at these (#7 and 8) in respect to health

GLOSSARY

Acronyms/Abbreviations

APHC
Army Public Health Center

DOD
Department of Defense

MMT
Microbiome-Mediated Toxicity

NIH
National Institutes of Health

SME
subject matter expert

TMM
Toxicant Modulation of the Microbiome

USACEHR
U.S. Army Center for Environmental Health Research

Terms

Microbiome
The collective genomes (genetic material) of all of the microorganisms that inhabit the human body [Lederberg, 2001].

Microbiome-Mediated Toxicity
Microbial alteration of a chemical [this document].

Toxicant Modulation of the Microbiome
Chemical alteration of the microbiome [this document].