Session I Roundtable Summary

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Can a healthy gut microbiome be defined through quantifiable characteristics? and how does that change? Through life changes? i.e. Maternal, sensitive populations and variability

- It was acknowledged that there was a lack of a concrete definition of the microbiome and a specification, or an ‘average’ characterisation, of a healthy gut microbiome is not yet able to be established. Global harmonisation of a potential definition would prove challenging, as varying factors will need to be considered including different life stages, disease states, ethnicity, diet etc. Due to the complexity of the topic, there was acknowledgement that this may not be as simple as a definition but rather a specification or guidelines containing parameters, ranges, diversity and species information. It was noted that what may be considered a ‘healthy’ gut microbiome for one individual may not be the same for another.
- Although it was noted that every microbiome is unique to each individual; by using a comparison with a large database of microbiomes it would allow researchers to see if there were any common factors for a ‘good’ microbiome.
- Identify a baseline: what does the microbiome look like before any interventions to the core diet.
- Defining the principles that we apply in a risk assessment setting could take into account age, sex, genetics, disease effects/changes.
- We should move away from trying to establish a definitive healthy/normal microbiome due to inter-individual variability, and factors affecting this (diet, lifestyle, health status). We should try to define ‘reference populations’ with less dependence on an individual’s health status, rather incorporating the contextual factors mentioned above, such as diet.
- It needs to be determined whether a change in the microbiome is a marker of a separate causative event or if the change in the microbiome is the cause itself. It is possible to provide evidence in both directions, which increases complexity. In this way, the microbiome will adapt in terms of population composition as a result of a sustained dietary change, whereas if the change is temporary, only the metabolic activity of the current population will change. Therefore, linking a microbiome change to a marker is complex. Additionally, when considering “unhealthy” markers, are they reactive to an effect or pre-emptive of one? It was suggested that research conducted on a single family could help identifying these markers.
- Bacteria are not the only constituent of the human microbiome, e.g. there are also fungi and yeast, and thus they should also be considered in research.
- With the increase in genomic sequencing of bacteria in the microbiome, it was suggested that it is important to establish the phenotypic properties as well as the genotypic profile of the microbiome, particularly as these are not always correlated and could be impacted by external factors other than just

the genetic makeup.
- It was commented that different species can provide different functions, but it is not always clear which species are responsible. Once these functions are further understood there may be a better understanding of the microbiome as a whole. Some species can be ‘good’ or ‘bad’ dependent upon circumstances and surroundings.
- State what model organisms are available to researchers that accurately reflect the behaviour of bacteria found in the gut microbiome.

Main Themes

- “Healthy” microbiome not yet defined i.e. a baseline.
- Specification, or an ‘average’ characterisation.
- Guidelines containing parameters, ranges, diversity and species information.
- Should try to define ‘reference populations’.

How much variability in an individual’s gut microbiome is normal, and how resilient is the microbiome to change?

- It was noted that as there is so much variability it would not be possible to tell by looking at the microbiome itself what is good and what is bad, instead the focus should be on looking at the adverse health outcomes.
- Underlying socio-economic factors are some of the biggest determinants of individual health outcomes.
- Microbiome changes dramatically over a lifetime.
- UK Biobank may provide the variability of an individual’s gut microbiome.
- Attendees stated that an adaptation of the microbiome is not necessarily beneficial, it depends on the host-microbiome interactions. For example, a certain microbiome population in a specific individual will have no immune system consequences, whereas the same population in a different individual will result in adverse effects.
- It was discussed that there is a need for better quality microbiome data, suggesting that, as there is not yet a defined link between the microbiome and adverse outcomes, that adverse outcome pathways (AOPs) are required to strengthen the evidence base.
- Rather than studying the microbiome in isolation, microbiome analysis could be incorporated into other studies as supporting information. Emulsifiers

have been identified as a possible cause of adverse effects, and it was proposed that these could serve as a case-study for risk assessment.
- It was noted that it is the long-term impact on the microbiome that is important. While antibiotics have a large impact, they are mostly used short-term. However, other medicines that are used long-term also have effects on the microbiome, e.g. statins and proton pump inhibitors. It was stated that hundreds of pharmaceuticals administered for other purposes have antimicrobial effects.

- It was questioned whether having a less diverse microbiome has a negative impact on health outcomes. It was also questioned whether individuals could decide for themselves how healthy they felt.
- Defined principles may have to be applied to given populations and will vary according to age and sex.
- The resilience and/or stability of an individual's microbiome may also be an indicator of health state. It was further suggested that laboratories performing studies in humans could compile a database to help define 'normal' in a way similar to the collection of historical control data in animal studies.
- Within this, susceptible populations also need to be considered for example, early life. It was further discussed that the microbiome is more malleable at an early phase in life becoming more stable over time. As a result of this, newborns would be a difficult population to monitor.
- It was commented that when considering risk assessment, any change in the microbiome could be suspect and therefore a potential risk, however the challenge is defining what constitutes a meaningful change.
- From a risk assessment standpoint each group/ life stage should be evaluated differently. From current knowledge a cross-control design would not be possible, however it may be possible for change to be predicted in some groups.

Main themes

- Microbiome changes dramatically over a lifetime.
- Microbiome analysis could be incorporated into other studies as supporting information.
- Focus should be on looking at the adverse health outcomes.
- Any change in the microbiome could be suspect and therefore a potential risk, however the challenge is defining what constitutes a meaningful change.
- In the future, may be possible for change to be predicted in some groups.

What is normal, and the complexity of factors contributing to susceptibility i.e. to what extent will the COT need to take account of impact on the microbiome in its toxicity assessments?

- Defining a ‘range’ of microbiomes may be one way forward, but it is unclear whether this should be based on structure, function, or both.
- For a risk assessment: what increases or decreases the risk, and what impact does that risk have.
- One challenge is how to account for the different factors internally and externally.
- Chemical conversions occur in the gut, which have to be taken into account in a toxicological assessment.
- Assume 5-10% of individuals have a deleterious biochemical conversion. Do we acknowledge the 10% and as a precaution cannot approve the chemical or mention the possibility of a side effect as would be the case for the pharmaceutical industry?
- Clinical data is as important as dietary information especially treatment data e.g. antibiotics used, medicines used.
- It was agreed that one of the aims of current scientific research is to establish markers that represent a healthy microbiome. However, linking a microbiome change to a marker is complex, including accounting for any epigenetic changes. Additionally, when considering “unhealthy” markers, are they reactive to an effect or pre-emptive of one? It was suggested that research conducted on a single family could help in identifying these markers.
- It was suggested that research on what types of microbiomes increase the risk of adverse effects was necessary. Additional research may include looking at different populations with different gut microbiomes and observing what populations have more resilience to xenobiotics.
- Consider a toxicological endpoint and a microbiological endpoint and which biomarkers should be used when investigating the microbiota including the possibility of how disruption (e.g. antibiotics) could potentially affect the value of the selected microbiological and toxicological endpoint.
- Susceptible populations must also be considered along with groups such as IBD, IBS patients. Other populations such as infants and children have

immature microbiomes. Special considerations and studies need to take place to protect the establishment of these microbiomes.

- Could diversity be considered a barrier in determining these endpoints. There is already so much diversity in ethnicity, age, sex, diet, lifestyle factors anyway, is it even possible to account for all of it. Is there a way that all of these can be a contributing factor and go from there.
- Incorporating and factoring in the risks but also the advantages of understanding how we can change the composition of the microbiome when it comes to regulatory products and scientific advice.
- As it currently stands, it was agreed that the data and knowledge are not yet sufficient to allow for conclusions, however where there is knowledge of function this could be used as a starting point and proceed from there.

Main themes

- Defining a ‘range’ of microbiomes e.g. structure, function.
- Chemical conversions occur in the gut, which have to be taken into account in a toxicological assessment.
- What types of microbiomes increase the risk of adverse effects.