NANORELEASE FOOD ADDITIVE WORKSHOP/WEBINAR

September 24th & 25th, 2012
Minutes

With a total of 30 participants, all Task Groups and the Steering Committee were adequately represented. These minutes were shared with all participants to seek feedback prior to final approval.

DAY 1

Agenda

1) Task Group Summary Presentations

- TG1: Material Characteristics

    - TG1 member reviewed the progress, which has been split up into three subgroups. The summary powerpoint presentation is available on the internal website.
    - Members discussed the NanoRelease summary statement "Detect & characterize nanomaterial uptake and bioaccessibility from dietary sources." It was noted that an important aspect of this project is attempting to differentiate among nanomaterial types. It was agreed that the phrase "for the purpose of differentiating" will be added to the end of the statement.

    Points of Coordination
    (Please refer to the "Task Group Coordination and Dependencies" document and the "Mud Map" for more in depth explanations of coordination between TGs.)

    - It was pointed out that subgroup 2 (Properties Relevant to Uptake & Bioaccessibility) will have some overlap with Task Group 4.
    - TG1 member noted that subgroup 3 (Characterisation / Behaviour of Food and Food-Related (encapsulates) Nanomaterials in Food Matricies) is related to NanoLyse and may overlap with other TGs- in particular TG2 in regards to absorption.

    Challenges
    (Please also refer to the "Task Group Coordination and Dependencies" document.)

    - The question was raised of how comprehensive in covering materials TG1 should/can be. There has been a call for additional expertise in this area. It was noted that this is an iterative process and TG1 should attempt to bracket properties as much as possible while going along. The issue of being comprehensive can be revisited at the December workshop.

        - Members discussed using a case study approach to address the issue of materials to be included. This could be used across TGs and the project.
    - Issues of defining the term "nano" were discussed. It was noted that this project will not define what is nano, or specific ranges for nano. The intention is to explore these issues and create a catalogue of what is important in terms of methods development.
        - It was noted that there is a lack of information about what definition has been used in marketed products and that the TG is trying to get objective data of what is available.
        - Materials that aren't labeled as nano may also benefit from the methods development.
        - This issue has been addressed by using as many key terms as possible. When it comes to writing, a set of terms can be used to indicate relevance without defining the term nano.
    - TG1 raised the question of if a section of the catalog of who is developing reference material should be included.
        - It was noted that this is an important aspect and may come into TG4 discussion.
        - Members were advised to take advantage of existing reference material wherever possible. NIST, NanoLyse, and NIH RePorter references may be relevant.

- TG4: Measurement Methods
    - TG4 member reviewed the progress. The summary document is available on the internal website.
    - TG4 has added drinking water to the food being considered.
    - The definition of packaging has been expanded to food contact materials, which includes drinking water infrastructure and food preparation materials.

    <u>Points of Coordination</u>
    (Please refer to the "Task Group Coordination and Dependencies" document and the "Mud Map" for more in depth explanations of coordination between TGs.)

    - Regulatory requirements will now be covered by a new TG, but would be worth mentioning as a footnote in TG4. The new TG will be discussed on Day 2 of this webinar.
    - Chapter 2 Part I (Overview of detection methods requirements: Information and concepts) overlaps with TG1 characterization of particles.
    - Chapter 4 (Detection and characterization of nanomaterials in foods) overlaps with TG1 SG3 (nanomaterial properties). What characteristics are important to be measured? There is a need to discuss where TG1 will write up to and then where TG4 takes over.
      Action Item: A new paper by Julian McClements will be shared with TG4.
    - Chapter 5 (Detection and characterization of nanomaterials in the alimentary tract) overlaps with TG2 and TG3 in regards to uptake from the alimentary tract and impact of the lumen composition.

Challenges
(Please also refer to the "Task Group Coordination and Dependencies" document.)

- Members discussed what measurement methods to include.
  - TG member noted the issue of identifying measurement methods that are critical vs those that are interesting.
  - The secretariat pointed out that it is easy to start cataloging a lot of methods that can be used and characteristics that could be measured. There should be a balance between covering methods and focusing on those that have more relevance for differentiating particle characteristics.
  - TG4 member noted that it is important to no be judicators, but an analysis of when methods can be applied would be useful making note of when multiple methods can be used to get the same information.
  - It was mentioned that multiple methods for looking at all characteristics of a nano material may be required.
  - This document can be a guide book for where new methods need to be developed. This may be more explicitly stated in the overview.

- TG member raised the question of whether discussion of measurement method output will include a description of interpretation of results.
  - It was noted that this maybe a lot of work to do for each individual method, so maybe wait until methods have been narrowed down or create an entire new group to look at output. This may not be important for the first pass.
  - Members discussed the need to include sample preparation at least partially. Including a general description may be the best approach instead of getting into the details with each specific test.

- TG2: Alimentary Canal Environment
  - TG2 member reviewed the progress. The summary document is available on the internal website.

  Points of Coordination
  (Please refer to the "Task Group Coordination and Dependencies" document and the "Mud Map" for more in depth explanations of coordination between TGs.)

  - Overlap with TG4 in regards to interactions with different food matrices.
  - Overlap with TG1 SG3 (Characterization / Behaviour of Food and Food-Related (encapsulates) Nanomaterials in Food Matrices).

  Challenges
  (Please also refer to the "Task Group Coordination and Dependencies" document.)

  - The challenge of translating anatomical facts to nano issues was pointed out.

- Challenges for chapters 2 and 3 in determining where macroscopic ends and microscopic begins were noted.
- Members discussed the inclusion of water in regards to its contact in the GI tract. TG4 has decided to include water as it may be relevant to discuss in terms of absorption in the lumen.
- Members discussed if particles that are inhaled and then swallowed would be considered.
  - No, group decided we are only considering particles that go into food (through various ways) and then end up in the GI.
  - A general statement should be made that inhaled nanomaterials may reach the GI tract, but that this is out of the scope for our purposes.
  - This may be best to be stated by TG1, and can also be stated in the discussion of state of the science report that it is an important issue that needs to be covered in the future.
- The challenge of scope in chapter 5 (Physiological Variability) was discussed.
  - The potential for time to be spent on disease states that may not inform methods development was pointed out. Members should remember that the purpose of project is not to focus on disease states that have been studied. These do not have to be excluded, but caution should be taken with what methods to include.
  - Physiological variability in regards to age differences should be included. (eg. infant and late stage changes)
  - TG member noted that TG3 has a subsection that is devoted to disease state. There are models out there that have been used in the context of nanomaterials, so they should be included. This may not be the highest priority, but will be an outcome.
  - Examining these methods could lead to methods improvements and identification of research gaps.
  - TG member noted that relevant models are developed from disease state models. (e.g. inflammation, immuno-toxicology, iron absorption)

- TG3: Alimentary Canal Models
  - TG3 member reviewed the progress of TG3. The summary document is available on internal website.

<u>Points of Coordination</u>

(Please refer to the "Task Group Coordination and Dependencies" document and the "Mud Map" for more in depth explanations of coordination between TGs.)

  - Chapter 2 (Description of Alimentary Canal Models) coordinate with TG1 in regards to what case studies will be used.

- Chapter 3 (Review of Model Systems for Lumen Conditions) coordinate with TG1 and TG2 in regards to describing material interactions.
- Chapter 4 (Potential mechanisms of nanoparticle translocation from the GI lumen to the circulation) is relevant to TG1 and other areas of the project.
  - TG member noted that chapter 4 may be useful as introduction to final report. Not necessarily in talking about models, but talking about particular mechanisms. The final output is not just analytics, but what models will be used to perform analytics.
  - The secretariat pointed out that this informs material characteristics as well as the model selection. Chapter 4 sets the stage for characteristics of particles. This may be included in TG1 case studies.
  - TG member noted that TG2 chapter 3 (Overview of gut wall/mucosa, microscopic level) is covering a similar topic.
- Chapter 6 (Provide and discuss suitable methods for detection of nanomaterials present and released in alimentary canal model conditions) overlaps with TG4, in particular Chapter 5 (Detection and characterization of nanomaterials in the alimentary tract).
  - It was pointed out that the relationship between trace, standard reference, and actual food component materials that are used in current models and methods is relevant to TG1 in regards to the characteristics of materials and TG4 in regards to methods. There may be a difference between the materials that have been studied and what materials are actually relevant in oral exposure.
  - Members discussed where the line would be drawn between TG3 and TG4 so as not to have identical chapters.

<u>Challenges</u>
(Please also refer to the "Task Group Coordination and Dependencies" document.)

- It was noted that chapter 6 is a place where definitions are a hindrance rather than a help.
- It was asked if chapter 6 would have a subsection that deals with clinical and pre-clinical uptake mechanisms. TG member noted that this question should be directed to the authors of this chapter in regards to how many of the references refer to in vivo or ex vivo models.
- TG member asked if there is literature available on kinetics; mechanisms of speed, amount, and equilibrium conditions for uptake.
- It was also asked if it would be constructive to look at nanoparticle size dependent property changes over ranges.
  - TG member noted that size is an important influence determining the uptake mechanism, but is not the only one. Surface charge and surface properties may also be relevant. Models that are as broadly applicable as possible will be focused on, but other models will not be ruled out.

2) Final Notes for Day One

- The secretariat noted that a list of overlaps and challenges will be gathered to share with the TGs before tomorrow's discussion.

DAY 2

Agenda

1) Coordination between TGs

- TG member presented the coordination figure that was put together based on Day 1 Webinar discussion of TG overlap and the follow-up document.
    - It was noted that this figure may not be comprehensive.
    - Of particular interest is that TG1 is predominantly providing input into TG4. TG2 and TG3 are connected with TG2 providing input into TG3. TG3 is feeding into TG4 and this coordination needs to be worked out for efficiency.
    - There are other interactions as well between subgroups in TG1 and TG2.
    - The TG4 white paper should be priority for the SOST writing.
    - The key criteria for what areas methods need to be developed may be pulled from the work that is done by TG1.

- Members discussed how to optimize TG function noting the overlaps.
    - It was noted that during Day 1 of the Webinar there was discussion of case studies, which should be harmonized between groups.
    - The secretariat suggested chapter titles in white papers that show the overlaps we have noted.
    - TG member suggested making a table of contents for a final paper as a way of consolidating a final product.
    - It was pointed out that the current plan is to have five, maybe more, independent publications. The state of the science (SOS) document will take into account the findings from all of these individual documents.
    - TG member pointed out that this may be more of an issue of sequencing rather than overlap. Can TG4 make much progress before knowing the output of TG1? This would suggest TG dependency in addition to overlap.
    - The need to prevent contradictory work was noted.
    - It was pointed out that there is also a feedback loop between TGs, information from TG4 may influence TG1 in addition to the other way around.

- TG member noted that members should communicate in areas where there is direct interaction.
- Members discussed adding information to other papers and case studies, without necessarily redesigning the process for this project.
  - TG member suggested that TGs can expand on the manuscript written by Julian McClements.
  - The secretariat mentioned a paper from Food Safely Australia New Zealand is that laid out with similar information. This document could be used as a model for the project.
- It was noted that co-chairs will be able to address overlaps using the outcomes from this two day Webinar.
- *Action Item*: Members decided to have a meeting of SC and TG co-chairs to discuss the idea of a single document.
  - TG member suggested writing a single monograph to pull connecting pieces from the TGs. TG member agreed, stating that it is difficult to see connection when TGs are just referencing each other.

- Members went through TG coordination and dependencies identified yesterday and this document was updated accordingly.

  - Members decided that these "overlaps" are really more of areas of coordination and the language was changed.
  - TG member noted that TG2 will focus more biologically and physiological, TG1 Subgroup 3 is more chemical, and TG3 is more models, so there should be enough separation with regard to particle behavior.
  - Members discussed the development of case studies in TG1, which will consider full sequencing of a particular material. This may be useful for weaving together other TGs.
  - The high degree of overlap between TG3 chapter 6 and TG4 chapter 5 was discussed.
    - TG member noted that the author of this TG3 chapter was unable to participate in this call and this coordination should be discussed with them.
    - TG4 member noted that this chapter will reference back to TG3. TG4 will explain the methods that are developed in more detail, so that there is more cross reference rather than coordination

2) TG Challenges

- Members went through TG challenges identified yesterday and this document was updated accordingly.

  - The importance of continuing to avoid defining nano was noted. For the sake of completeness, a paragraph about why there is no definition of nano should be

included. There could also be reference to existing definitions. The catalog will follow the approach of not defining nano.
    - TG member pointed out that reviewers may ask what criteria was used for nano if the project does not define the term. There will be boundaries for searching and the authors will be open about what search terms were used.
    - Reviewers will ask, but a very clear reason for not having a definition will be explained.
    - TG member noted that the documents being developed could be used for reference in regulations. Regulatory documents do not define nano, so it is in our best interest to not define the term.
- It was pointed out that in regards to all of these challenges and issues of scope TG white paper authors will use their scientific knowledge and expertise to make determinations.
- Members discussed TG3 chapter 5 on physiological variability.
    - TG member mentioned that a subsection on normal and a subsection on abnormal (disease) physiology maybe be included.
    - Disease models, such as irritable bowel syndrome, should be considered in regards to their value for methods development.
    - It was noted that this may be a good place for case studies, though it may be premature to decide on specific case studies at this time.
    - It was pointed out that this is a large amount of work for a single author, so it might be worth going out to find additional experts.
      Action Item: Dora Pereir and John Powell will be contacted to see if they have interest in assisting with this chapter. The secretariat could also be of assistance.
- Members agreed that inhaled nanoparticles are beyond the scope of this document, but it could be discussed as part of the SOST.
- For TG3 challenges, it was noted that John Powell maybe helpful in regards to information on kinetics data.
- It was pointed out the struggle with different size and uptake limitations and this point may be raised to the SC. This is relevant to TG3 for choosing canal models with appropriate size ranges. Authors agreed to discuss this with TG1.
- Members discussed what materials to include as food. Water and nutracuticals will be included and feed (animal food) will not. TG1 gives a clear explanation by stating that the project is considering human dietary sources. Bioaccumulation is implicitly included but TGs have not taken it as a scope item yet.
- For discussing methods output, it was noted that the European Commission JRC Reference Report titled “Requirements on measurements for the implementation of European Commission definition of the term ‘nanomaterial’” provides a good organization of existing methods. This may be a good starting point or source of inspiration. This document is available in the Information Catalogue of the website under Related Projects and Efforts.
- An interlaboratory test group will go into evaluating the details of specific methods that are identified as important or most relevant for methods development.

- *Action Item*: The secretariat noted that on the next SC call the project timeframe will be revisited to strategize what findings could be complete in time for the December 11th & 12th workshop.
  - It was noted that the project may have an idea of what areas to focus on for initiating methods development by the interlaboratory testing group in time for the December workshop. This phase should be started in the first or second quarter of next year.
  - TGs can continue to work on developing their documents. TGs should have a draft of their document, which can still be edited, around a March timeframe.
  - There are no hard milestones in terms of statutory goals or policy objectives.

3) New TG 5 Regulatory Group

- Some TGs have noted the need for a group that can identify risk management decision points in regulatory risk management and product development risk management.

- This is a way of limiting scope and deciding where methods can be informative.

- The identification of check points within the decision framework will be useful for deciding where to focus attention in methods development.

- We are currently looking for 4-5 people for this group. Those with expertise in regulatory or product development may have a particular interest in this group.
  Action Item: Those who would like to participate may email the secretariat.

4) December workshop

- The NanoRelease Food Additives workshop will be held December 11th and 12th at The Pew Charitable Trusts in Washington, DC (9th and E Street).
  Action Item: An official Outlook invitation will be sent to all members soon, in the meantime members are asked to please save the date.

- *Action Item:* Members were asked to please contact the secretariat in regards to availability and funding requirements, so that logistics can be worked out as best as possible.