Attachment A

Question 1: Carcinogenicity Health Effects Innovation Program

Group #1: Share your insights regarding whether there is clear alignment among the three. For example, do the Objectives align with the Problem Statement? Does the Value Proposition match what is being stated in the Problem Statement?

- Project on early onset colorectal cancer (CRC) is of high priority. It was not clear which partnerships were already existing in this work. A lot of groups that we did not have time to talk about. Ensure that NTP is fully connected with those doing research, such as in dietary restrictions.
- Great example of clear alignment of how NTP can build science that addresses science impacting human health. Not just bench research, but impacting human health.
- Questioning whether in vivo approach link to or inform the in vitro approach and whether those approaches are informative of the human condition
- Good approach, clear difference between minority groups.
    - Two weaknesses: Microbiome, rat models
    - Early onset CRC is distinguishing itself
    - Rat models: APC mutation, linking early onset CRC to
    - Parallelogram approach, building linkages. Molecular signatures from CRC patients is a critical part of how NTP is planning how to ensure their research is relevant to what is seen in human patients
    - Organizing an approach

- Problem statement was right on in terms of identifying the problem and the focus
  - Calling out disproportionately impacted groups
  - Disconnects: the objectives and approaches therein, how impactful those particular objectives relate to the overall problem
  - Unclear how approaches/objectives are incorporating the exposures, particular types of cancer in disproportionately affected groups
  - Question: How can this research be relevant to the real-world conditions of disproportionately affected groups?
    - Very likely that these groups have particular kinds of exposures
  - Doing research in partnership with organizations that have specific knowledge on those groups to ensure that the research reflects the factors that are important to the groups
    - EPA Environmental Justice Office

- Like to know more about purpose-built platform
  - Variables that go into platform
  - Get information to the public as quickly as possible and consider prioritizing in a timetable structure or find a way to integrate views of President Biden

Attachment B

Question 1: Carcinogenicity Health Effects Innovation Program

Group #2: Share your insights on the strategic fit of the overall program with DNTP's mission, goals, and capabilities.

- Thinks this fits, in preclinical space with collaborations to develop new capabilities. Bridging to human disease and collaboration with public stakeholder could strengthen this. (Anne)
- NTP is fundamental to identification of new carcinogens, how do we bridge the translation of this for stakeholders. Fits well into overall objectives. (David M)
- Overall, this fits nicely into overall NTP mission. Areas of expansion: how to interpret to human health and how training will fit into overall mission. Gene by environment interactions. (Pam)
- Missions and goals align with partnerships (internationally) and sequencing tech for mutational spectra. (David E)
- Mixtures are complex in how they drive cancer, is there active consideration of this for application to the cancer program? How do programs mixtures and cancer programs interact? (Pam)
- As the scientific community thinks of NTP through history, how are programs fitting into standard 2-year rodent bioassay? More on what NTPs role will be in these assays as a goal of NTP is to replace these? How does this integrate with NTPs plan to replace these assays? (David E)
    - Plan to address this going forward. Opportunity to build in mechanistic knowledge/understanding. (David E/Anne)

Attachment C

Question 1: Carcinogenicity Health Effects Innovation Program

Group #3: Share your insights on whether there is sufficient focus to deliver the intended value to stakeholders.

- Do not have enough information to answer these questions because we are unsure how you define “intended value”?
- Do stakeholders with less resources have the same opportunity to access the same data as those with more resources?
  - Who are the priority stakeholders for this team?
- Who is involved to help deliver the message to the stakeholders?
- Regarding the databases, have you engaged the stakeholders that will use this information to make sure the data is curated in the best way possible?
  - Potentially put out a call for proposals on how to use these tools (active engagement)
- The colorectal database is useful for stakeholders in the general public
- Etiology of cancer – there is a large group of stakeholders in the research community that will find this information useful
- How are you responding to the disparity between those develop cancer and how are you engaging these stakeholders?
- Communication aspect seems critical for all programs not just Carci

Attachment D

Question 1: Combined Exposures and Mixtures Program

Group #1: Share your insights regarding whether there is clear alignment among the three. For example, do the Objectives align with the Problem Statement? Does the Value Proposition match what is being stated in the Problem Statement?

- Overall, yes they align.
  - This is very complicated issue and NTP's approach is as good as any others.
  - There was a lot of emphasis on interactions at PD level but not so much on the PK level.
  - Some confusion around read-across approaches.
    - Would appreciate more clarity on how the read-across approaches can be applied to a class of compounds (or even in a mixture itself).
  - Getting clear communication on what methods should be applied is useful.
  - #3 is a fairly traditional approach (PACMAP).
  - #2 has very direct and practical applications.
    - Could approach on #2 be applied to #3?
  - #1 is still in conceptual development.
  - What is the process for developing the disease-based project?

- What is relationship between Carci and CEM?
  - A great opportunity for program staff to communicate.
- Surprised that contaminants in water was not addressed.
- You have mechanistic classes in real-life chemicals.
- Understand that it is a complex issue!
- Whole interaction of non-chemical stressors and their impact.

Attachment E

Question 1: Combined Exposures and Mixtures Program

Group #2: Share your insights on the strategic fit of the overall program with DNTP's mission, goals, and capabilities.

- Overall area of research is a good fit for public health need and impact. Disconnect around specific areas of investment and impact for public health needs. Where is public need for botanicals and wood burning stoves research? (Veena)

- Are NTPs efforts becoming diffuse? Taken on many activities and put into buckets because they seem to match. Sounds like many projects are ongoing, but difficult to determine NTP scope/capacity to take on this work. (Anne)

- Aligns with previous comments. Priorities typically come from epidemiological signals, often from distinct exposures. Glad to see PAHs cited, there are highly exposed working populations and is a rich area. Pay attention to epidemiological signals and how much burden a disease may be to society. (Mark)

- Something was missing from problem statement, clarifying the statement may help focus statement. Problem is mixtures are contributing to disease, assessments accounting for mixtures are not accounting for this. Get to public health problem and outcome with mixtures – call out specific populations (international? Within US?). What population is of interest here. (Veena)

    - Agree (Anne)

- Bring together the impact/outcome to the narrative of the program. In reading the document, it seemed to be risk assessment in the end; this is a tool to achieve better public health outcomes but is not the end goal. How do you get accurate assessment of risk? Need to have the ultimate outcome in mind. (Veena)

Attachment F

Question 1: Combined Exposures and Mixtures Program

Group #3: Share your insights on whether there is sufficient focus to deliver the intended value to stakeholders.

- Worried that approaches focused on adding individual components together may yield an unrealistic estimate of the true risk
- How are we defining mixtures? What humans are exposed to in the environment is very complex
- Looking at individual chemicals or multiple mixtures that can be additive
- Component based approach may not be ideal and needs refinement
- Long history of drug-drug interactions, encourage using a mechanistic approach to studying mixtures
  - Picking the mechanism may be tough, encourage looking how mixtures modify a known MOA
- How much can you generalize from these individual examples?
  - Maybe make a system of these interactions
- What is feasible when studying these mixtures, this is very ambitious
- How is disease-focused playing a part in this group? (Objective 1)
  - Are you starting with cancer/cardiovascular disease in humans or were those just examples?
- Will need to look at multiple possible outcomes in mixtures to make sure you don’t miss anything