Question 1:

Is the method used to clean the cages and animal rooms in the animal studies reported in the manuscript by Dr. Hostetler available?

The laboratory where these studies were conducted closed several years ago when the owners retired. Records on laboratory management no longer exist. We do know that this laboratory followed strict animal husbandry requirements based on firsthand knowledge of individuals who formerly worked there. These standard practices are followed by other labs, many of which have confirmed to us that quat-based disinfectants are commonly used. These existing laboratories have never experienced developmental and reproductive issues with their animals, and we are not aware of any such issues other than those alleged by Virginia Tech researchers and Dr. Hunt. Standard practices for cage cleaning at contract laboratories performing large scale investigations require removing the animals from the cages, transferring them to a separate area, cleaning the cages either with hot water and steam or with disinfectant solutions, strictly following label directions for use. Cages dry completely before releasing them for re-use.

Question 2:

The White Paper you provided contains the following statement: *"Regulatory agencies, including the U.S. EPA, guided a study monitoring the concentration of Disinfectant Quats from occupational cleaning conditions. The study established that the exposure to a Disinfectant Quat for liquid pour, mopping and ready to use products is extremely low and falls significantly below the concentration that might result in respiratory irritation. Therefore, it is unlikely Disinfectant Quats cause irritant induced asthma (Allergy Asthma Clinical Immunology, 2019)."* It looked like the primary reference for this statement would be LaKind 2019, however we do not see that conclusion or information there. Could you direct us towards the correct primary reference?

The primary reference is <u>not</u> the LaKind 2019 article. It is an exposure study owned by the Antimicrobial Exposure Assessment Task Force II, a working group operating under the auspices of the American Chemistry Council's Biocides Panel. The data were developed under EPA guidance, submitted to and accepted by EPA. EPA uses the results of exposure studies in its ongoing human risk assessment reviews. The accepted exposure data is reflected in the ADBAC and DDAC Work Plans that have already been shared with you. All data on any pesticide product are available to stakeholders (but not commercial entities) under FIFRA Section 10.

Question 3:

At the SAB meeting, Dr. Hostetler said he would investigate and see if there is specific Endocrine Disruption data.

In ADBAC and DDAC work plans, the EPA provides a detailed discussion of how potential endocrine disruptor effects are assessed. EPA carefully evaluates potential endocrine effects in its reviews of guideline studies that focus on organ weight, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss and sex ratios in offspring. There is nothing in the data on these endpoints for ADBAC and DDAC to suggest any likelihood of endocrine disruptor effects. The Endocrine Disruptor Screening Program (EDSP) at EPA follows a 2-tiered approach employing a battery of 11 screening assays. ADBAC and DDAC were *not* included among hundreds of substances identified for screening priority, indicating an absence of concern by EPA for their potential for endocrine disrupting effects. In the EU, recent (2018) Endocrine Disruption reviews reached similar conclusions:

"Based on a thorough review of all identified data pertinent to the potential endocrine activity and ED–mediated adversity of ADBAC, it is concluded that the substance is not an endocrine disruptor according

to the criteria laid down in Regulation (EU) 2018/605. There is no evidence for ADBAC to cause adverse effects as a consequence of an endocrine mode of action."

"Based on a thorough review of all identified data pertinent to the potential endocrine activity and ED–mediated adversity of DDAC, it is concluded that the substance is not an endocrine disruptor according to the criteria laid down in Regulation (EU) 2018/605. There is no evidence for DDAC to cause adverse effects as a consequence of an endocrine mode of action."

Source: Respective sections of ADBAC and DDAC Documents III-A, Section A8.13.3, BPR Data Set IIA, Annex Point VI.8.13.3

Question 4:
Dr. Hostetler cited (Rutella NC ?) health care study, and a CDC MMWR report related to the asthma endpoint. Can you provide these or more specific references?
Drs. Rutala and Weber of UNC are world-class infection control experts. In personal communications and in peer-reviewed publications, they have stated that in 20+ years of working with personnel who are involved with infection control that respiratory issues with quat-based products are extremely rare. Two literature citations are provided:

- Occupational health risks associated with the use of germicides in health care. David J. Weber, MD, MPH, Stephanie A Consoli, RN, and William A. Rutala, PhD, MPH. *American journal of Infection Control* 44 (2016) e85-e89.
- Acute Antimicrobial Pesticide Related Illnesses Among Workers in Health-Care Facilities – California, Louisiana, Michigan, and Texas, 2002-2007. Morbidity and Mortality Weekly Report, May 14, 2010 (MMWR Weekly Vol 59 No. 18.)

  For the latter, this extensive multistate survey evaluated multiple disinfectant active ingredients. There were more than 2.8 million healthcare workers in these states during this time period and based on the cases of adverse occupational reports, less than 0.014% were attributed to quats and respiratory issues. The authors emphasized needs for better training and communications and safe-use practices in occupational settings.

Question 5:
Dr. Hostetler said he would ask for permission to share work others have done, which has been submitted to EPA, regarding Adverse Outcome Pathways (AOPs), and the detailed pathways developed for skin and mucous membranes, e.g., discussion in the literature of mitochondrial function, lipid interaction, etc.
The Adverse Outcome Pathway (AOP) for quaternary ammonium compounds was prepared by another group of end use product formulators and submitted to EPA. We anticipate this may be published but at the moment it is not available.

Question 6:
Dr. Hostetler will check to see if they have ambient water data, but would expect it to be low.
Please see:

- Assessment of ecological hazards and environmental fate of disinfectant quaternary ammonium compounds. DeLeo, PC et al. *Ecotoxicology and Environmental Safety* 206 (2020) 111116 (This reference has been shared previously).

  This paper provides an extensive review of published and unpublished research and discusses in a comprehensive fashion the environmental fate of QACs. We also note that the ADBAC and DDAC work plans include discussions of drinking water assessments which have been conducted. EPA concluded that antimicrobial uses were not expected to impact surface or ground water resources or quality.

  Question 7:
  Dr. Hostetler said who the authors of the second manuscript are, but we didn't capture them. Could you provide them?
  "Prenatal Developmental Toxicity of Alkyl Dimethyl Benzyl Ammonium Chloride (ADBAC) and Didecyl Dimethyl Ammonium Chloride (DDAC) in CD® Rats and New Zealand White Rabbits," has been accepted for publication in *Birth Defects Research*. The authors are Hostetler KA, Fisher LC, and Burruss BL. A second manuscript describing the two-generation reproduction studies conducted in rats with ADBAC and DDAC by the same authors is being prepared for submission to the same journal. As noted previously, data associated with each of these publications has been submitted to and accepted by both EPA and ECHA in their respective evaluations of the safety of quats.