Dr. Preuss and Mr. Birchfield:

NASA thanks EPA for the opportunity to review and comment on the draft IRIS risk assessment for Formaldehyde.

NASA's review identified broad ongoing concerns identified in recent IRIS draft risk assessments and specific technical issues. NASA suggests addressing the identified outstanding technical issues through detailed questions provided in the Peer Review. NASA also notes that EPA's approach and analysis does not correspond to the analysis and scientific conclusions targeting airborne exposure to formaldehyde provided in the National Academy of Sciences report entitled, "Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants", Committee on Toxicology, National Research Council (NRC), 2007 or in current models used by EPA's Office of Air and Radiation, applying Clean Air Act requirements. We request EPA revisit these outstanding issues by ensuring independent Peer Review of these concerns, specific technical issues and inconsistencies with conclusions reached in the 2007 NRC report.

Broad concerns and specific technical issues include:
Setting of action levels at or below background levels found in the environment

- EPA sets the noncancer estimate and the age-adjusted cancer slope factor that result in an equivalent air concentration of 1-3ppb. As noted in the NRC 2007 report, human breath has often been measured to contain levels in excess or 1-3 ppb, raising the question of choice of an action level that is likely at or below the level found in the environment. EPA does not provide justification of setting of a level less or equal to normal thresholds of formaldehyde found in the human body.

Need for consistent regulation of chemicals in the environment/need for transparency in decision making:

- In the draft IRIS risk assessment, EPA does not apply the models suggested by the NRC 2007 report or internal EPA models utilized by the Agency's Office of Air and Radiation. Given the large body of research on formaldehyde, NASA questions why EPA's IRIS draft not clearly detail the applicability of these established models and scientific understanding in the development of the IRIS draft. EPA needs to clarify and support transparency in the development of IRIS draft risk assessments, especially when alternative approaches to established models are applied.
- EPA needs to also clarify the hypothesis considered and the technical support for evaluation of formaldehyde under the EPA Cancer Guidelines and supporting guidance. This discussion of the draft approach is of signficant concern to explain how uncertainty is identified and addressed by EPA in this draft risk assessment.

Application of peer-reviewed literature to estimate non-cancer impacts:

- In contrast to the EPA draft IRIS risk assessment reliance on three co-critical studies, the NRC (2007) stated a strong preference for application of numerous experimental studies of controlled human exposure to estimate short-term exposure levels. The NRC cited, " Thus, data from 22 clinical studies involving over 500 subjects form the most reliable basis for estimating health-protective short-term exposure levels for airborne formaldehyde". EPA needs to detail why the IRIS draft does not follow this recommendation and focuses on only 3 critical studies.
- Again, the NRC (2007) also identifies that irritation, based on the literature, is the first observed effect at 0.5-1ppm. In contrast, EPA does not address this NRC finding based on the literature and does not use this NRC finding in the establishment of the cRFC. EPA needs to explain why the NRC finding from the established literature was not applied in the setting of the proposed formaldehyde cRFC .
- Based on the precedent of the NAS report on Perchlorate (2005), robust human clinical data is superior to animal clinical data or ecological studies of human exposure. As with perchlorate, EPA is strongly encouraged to use human clinical data, including the NOELs, as the basis of setting its cRFC for formaldehyde. Without use of this preferred data, the proposed formaldehyde cRFC is not based on the most scientifically defensible data and this issue should be addressed more fully in the estimation of the cRFC and through evaluation by the Peer Review.

- Potential cofounders were not or simply could not be addressed in the three co-critical studies EPA used as the basis of the cRFC, raising significant concern over the application of these studies to set action levels. For example, Rumchev (2004) follows up the earlier paper determined to be co-critical by EPA with additional findings of statistically signficant associations for other VOCs and particulate matter with asthma with the same study population. EPA , in the draft risk assessment, does not explain or address the implications of potential bias on the identified co-critical Rumchev (2002) paper or its impact on setting the draft cRFC.
- EPA fails to provide the links of the associations identified chosen three co-critical papers to demonstrated reactions to formaldehyde exposure. This lack of clarification and causation is most concerning as EPA assumes that causation or triggers for asthma, due to formaldehyde exposure, to be at levels 1000 times lower that the first observed and reversible effect, irritation. The draft IRIS risk assessment does not provide key defensible links to biological responses documented for formaldehyde exposure.

Application of peer-reviewed literature in the estimation of cancer risks:

- EPA, as in the previous IRIS assessment, assumed a linear, low-dose extrapolation from the applicable point of departure. EPA does not in the draft IRIS risk assessment address or clarify its continue of a controversial and disputed approach. In the interest of transparency, EPA is strongly encouraged to address this assumption and solicit Peer Review of use of this approach specifically on formaldehyde.
- Use of the same linear, low-dose extrapolation approach used in the existing IRIS risk assessment for formaldehyde has been questioned as unsupportable by the NRC. The NRC report (2007) summarizes its conclusions on the current IRIS value as, " In reality, the risk is far lower. On the basis of the evidence that the contributory mechanisms of action at high doses in rodents (that is, cytolethality and regeneration) would not occur at lower doses, the EPA unit risk factor for formaldehyde overestimates the risk at doses not associated with cytotoxicity (NRC, 2007., pg. 130). The NRC goes on to state, "The available evidence, however, strongly suggests that the risk from formaldehyde at high doses in animal studies cannot be extrapolated to lower doses using the EPA's approach. (NRC, 2007, pg. 131). The draft IRIS risk assessment does not adequately respond to significant issue identified by the NRC in the development of the proposed action levels for formaldehyde. EPA needs to clarify its position and request that the Peer Review evaluate the proposed EPA approach in light of the NRC findings on formaldehyde.
- EPA finds that formation of DNA-protein-cross-links from formaldehyde exposure supports the draft's findings that formaldehyde induces mutagenic action below levels that are cytotoxic. In contrast to EPA's approach in the draft IRIS risk assessment, the NRC report (2007) and EPA's Office of Air and Radiation (under the Clean Air Act), utilizing peer reviewed literature apply an alternative approach in models for low-dose carcinogenicity for formaldehyde exposure. The NRC report (2007, pg. 121) states that, "Although DNA-protein-cross-link formation might not be directly relate to gene mutations at subcytotoxic doses, it has been used as a predictor of the probability of procarcinogenic mutation per cell division and has been incorporated in models for low-dose carcinogenicity in animals and humans." EPA needs to detail its reasoning to not apply established EPA models and NRC findings in the development of the IRIS cancer risk action levels. In addition, EPA should request the Peer Review evaluate EPA's approach in the draft IRIS risk assessment against these alternative approaches and EPA models.
- EPA uses human epidemiological data as its point of departure (POD) in the cancer assessment in the draft IRIS risk assessment. However, the NRC identified specific limitations with the primary study that found evidence of elevated levels of nasopharyngeal cancer or NPC (NRC, 2007, pg.122). Issues included that the majority of the documented NPC cases were at one plant with most of the cases found in workers with one year or less employment at the plant. The NCI study identified the signficant risk trend for NPC but was based on limited numbers of subjects. In addition, large cohort studies did not find any excess NPC cases. The draft IRIS risk assessment needs clarification of these limitations, consideration of the impact of additional uncertainty and alternative approaches to establish the POD. EPA needs to request the Peer Review evaluate the EPA proposed establishment of the POD, based on these studies and their documented limitations, and subsequent cancer assessment values.

NASA thanks EPA for the opportunity to review and comment on the draft IRIS risk assessment for formaldehyde. We request that EPA address the specific technical issues outlined above. To best ensure consideration of these outstanding issues, we request that the Peer Review evaluate EPA's proposed risk assessment, methodology, and supporting assumptions in light of the NRC report (2007) and EPA's Office of Air and Radiation models and cancer assessment approaches.

Thank you. If you have any questions or need additional information or clarification, please contact me.

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