- 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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