Office of Management and Budget (OMB) Comments on the Interagency Science Consultation Draft IRIS Toxicological Review of 1,4-Dioxane (dated May 2011)

Date: June 16, 2011

General Science Comments:

• While we recognize that EPA staff are trying to provide clarity, we suggest either revising or dropping the fact sheet. The RfC derivation as described in the tox review does not fully track with the fact sheet. For example, in reading the Fact Sheet, we were confused as to why EPA was treating Kasai 2009 as a subchronic study. It may be easiest to just drop the Fact Sheet.

• It seems that EPA is proposing an RfC which is in the range of background level. According to HSDB, the average value of 1,4 dioxane in US air was 1.029 ppb. Rough calculations tell us that this is equivalent to about 4x 10-3 mg/m3, which is less than an order of magnitude away from the proposed RfC. Considering the closeness of the values, and what may be known about ranges of background exposures, it would be helpful to ensure that the RfC is plausible and that the incidences of nasal lesions expected can be predicted by current exposures. In particular, we recognize that rats are obligate nose breathers while humans are not. It is not clear how EPA has taken this into account when considering the relevance of the RfC to humans. We note that EPA applies an UF of 3x for interspecies comparison but this implies that humans would be more sensitive, not less sensitive to a similar dose.

• Similar to the comment above, what would be the expected cancer risks at current background US levels (1ppb or about 4ug/m3) and is this consistent with cancer incidence data? Similarly, do we expect the same risks from 1,4 dioxane as we do from other compounds with a similarly low IUR? Discussion of this in the cancer section would be helpful.

• While 1,4 dioxane is not a chemical of great broad concern, if EPA is going to propose an RfC and IUR that is within the range of background exposures, EPA may want consider a more robust SAB or NAS review (compared to a contractor run panel review) to assure that the scientific underpinnings of the values are scientifically sound.

• In discussing the mode of action (MOA) for nasal tumors, as per page 95, it appears that data exist to support a non-linear mode of action as the Kasai studies show accumulation related to saturation at high doses. We recognize that data gaps exist, could this MOA still be considered plausible and having significant biological support as per EPA cancer guidelines? Page 104 states that data on key events is missing, however it is not clear that this implies that there is not biological support for a non-linear MOA. EPA's discussion could be strengthened and clarified here.

• It is not clear why EPA uses and presents data only for the male rats from Kasai 2009. Page 117 discusses that no mesotheliomas were seen in female rats exposed via drinking water, however it is unclear why female data, relating to the RfC and nasal effects should not be considered and presented. If Kasai 2009 evaluated female rats (page 117 implies that it did), we suggest including this discussion and considering the effects seen in females.

• More clarity is needed regarding EPA's determination of the level of adversity of the nasal lesions (atrophy of the olfactory epithelium) throughout the RfC discussions. As per page 120, throughout the document and in the charge, EPA should clarify that this is a precursor effect, likely to occur early in the continuum of pathological events associated with the respiratory tract.

• EPA states that the BMD modeling resulted in a poor fit for the RfC. However when we look at Appendix F, many of the p values for fit, were >0.1 and thus wouldn't they be considered to have a good fit (for example, see page F-14 where this is the criteria as defined by EPA)? EPA clearly states that if the p value is <0.1, then there is a lack of fit. However in most tables in Appendix F, the p value is greater. Additionally, it is unclear what model uncertainty EPA refers to (page 118) when discounting use of some of the BMD values.

• As the RfC is based upon effects in the nasal epithelium, it is not clear why EPA is saying there is a lack of clarity regarding whether or not these are portal of entry effects. It would be helpful to run the analysis treating 1,4 dioxane as a Category 1 gas to see what impact this has on the RfC. Presenting this information to the public and peer reviewers will help them to understand the impact of EPA's decision. A charge question on this determination would also be helpful.

• EPA uses an uncertainty factor of 10x to account for use of a LOAEL. Since the effects seen are minimal and early in the continuum, it is not clear why a full 10x factor is needed. Further justification of this choice would be helpful for peer reviewers and public commenters.

• To support the choice of 3x for the database uncertainty factor, it would be helpful to provide more discussion of the doses used in the oral prenatal development study to see if effects would be predicted at the point of departure used for the RfC. Even a back of the envelope calculation, taking kinetics into account, would be helpful.

• It is not clear why EPA has medium confidence in the RfC. There are three orders of magnitude of uncertainty, including uncertainties in four different areas. We suggest that the confidence in this derivation should be considered low.

• Page 130 shows that there were no statistically significant increases in hepatocellular carcinomas. Thus it is unclear why EPA has combined hepatocellular adenomas and carcinomas to look at combined impact. It is obvious that this will be driven by the statistically significant adenomas, seen only at high doses. Further rational for combining these tumors is needed. If EPA had evaluated hepatocellular adenomas only, what would the IUR have been? This information should be presented in Table 5-13 and should be discussed. Similarly, it is not clear why EPA is calculating IUR estimates for cancer endpoints that were not statistically significant. We suggest adding a charge question on this.

Editorial Comments (with Scientific Impacts):

• Page 56, and elsewhere, when referring to Kasai, et al, it is important to always be clear about whether the reference is to the 2008 or 2009 study.

• Page 57, lines 17-28, it may be helpful to present this information in a table.

• Page 139, line 26-28, this discussion should mention that rats are obligate nose breathers while humans are not. The impacts of this on the RfC should be discussed.

• Page 142, table 5-14, please revise this to reflect the uncertainties in the RfC.

Comments on the Draft Charge:
[Note: some suggestions for charge questions are provided in comments in the above sections. Many of those comments have not been reiterated here, but should be considered as equally important.]

• It would be helpful if paragraph 2 of the charge discussed current background exposure levels in the context of the proposed RfC and IUR. This will also help to frame the issue of whether we are seeing results in the general population consistent with the final values EPA proposes.

• Please add a question asking reviewers about how they would interpret the proposed RfC and IUR in the context of known background levels.

• General Questions 2: It is unclear how reviewers will be able to tell if additional studies "would have a significant impact on the conclusions." Suggest reframing this to simply ask about relevant studies and then EPA can conduct further evaluation to determine if the studies will have a significant impact.

• In B2, EPA calls 'atrophy of the olfactory epithelium' a critical effect. Please clarify for reviewers that this is precursor effect and not adverse. Suggest also taking comment on EPAs determination of it as being a precursor effect.

• In section B, please have separate questions taking comment on EPAs use of the dosimetric adjustment factor, the HEC calculation, as well as the determination to treat 1,4 dioxane as a category 3 gas (not solely with portal of entry effects) for the purpose of deriving the RfC. Similarly, if they are relevant, these questions should also be added to section C.

• In section C, please add the following specific questions:
    • Ask reviewers to comment on EPAs approach of combining hepatocellular adenomas and carcinomas.
    • Ask reviewers to comment on EPAs decision to calculate a combined IUR using tumor endpoints that were not statistically significant.
    • Please ask reviewers to comment on whether or not each of the endpoints used in the IUR is relevant to humans and should be part of the combined IUR calculation.