**Office of Management and Budget (OMB) and Office of Science and Technology Policy (OSTP) Comments on the Interagency Science Consultation Draft IRIS Assessment of RDX (dated September 2014)**

Date: October 31, 2014

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October 28, 2014
Interagency Review (Step 3) of EPA IRIS Toxicological Review of RDX

Dear EPA IRIS:

Thank you for the opportunity to provide comments on the draft Toxicological Review of Hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX). We have comments on both the Preamble and the dose-response assessment.

*Preamble Comments*

There are statements in the Preamble that amount to policy positions or decisions rather than scientific ones. Several of these are noted here. The focus of the Preamble should be to describe the IRIS process as a scientific one.

- p. xv, lines 40-49: "**Step 5. Revision of draft Toxicological** 40 **Review and development of draft IRIS** 41 **summary**. The draft assessment is 42 revised to reflect the peer review 43 comments, public comments, and newly 44 published studies that are critical to the 45 conclusions of the assessment. The 46 disposition of peer review comments and 47 public comments becomes part of the 48 public record."
    - Comment: Should there be text to explain that if necessary, the document may undergo a focused 2nd round peer review by the peer review panel? Is there a policy yet?
- p. xv, line 53. Need period after the bold header sentence that begins with "Step 6."
- p. xvi, lines 59-60: "…some population-based surveys (for example, NHANES) provide the strongest epidemiological information…"
    - Comment: Population-based surveys, aka cross-sectional studies, should not be considered in the same category of clinical studies (which EPA has not mentioned), cohort studies, and case-control studies. Surveys have inherent methodological weaknesses that are well documented in epidemiological methodology texts, often to the extent that they are primarily considered hypothesis generating. The recommended remedy here is to split the first sentence, then add special reference to NHANES as a quality example of a survey design. "Cohort and case-control studies provide the strongest epidemiological evidence, especially if they collect information about individual exposures and effects. Population-based surveys, if conducted rigorously such as the NHANES survey, can also provide supportive information."

- p. xvi, lines 65-72: “Ecological studies (geographic 65 correlation studies) relate exposures 66 and effects by geographic area. They 67 can provide strong evidence if there 68 are large exposure contrasts between 69 geographic areas, relatively little 70 exposure variation within study areas, 71 and population migration is limited. “
    - Comment: Aren't these types of studies typically considered to be the weakest study designs for establishing chemical/hazard relationships (i.e. associations or causality)? These are hypothesis generating studies, and not of the rigor for demonstrating causality. Deleting the term “strong” would be a minimal necessary change to reflect this well-acknowledged limitation of ecological designs.
- p. xvi, lines 73-79: “Case reports of high or accidental 73 exposure lack definition of the 74 population at risk and the expected 75 number of cases. They can provide 76 information about a rare effect or 77 about the relevance of analogous 78 results in animals.”
    - Comment: There should be a caveat that case reports are (again) hypothesis generating types of studies (for potential hazard ID), and are inadequate for establishing causality.
- p. xvii, lines 34-39: “For developmental toxicity and 34 reproductive toxicity, irreversible effects may 35 result from a brief exposure during a critical 36 period of development. Accordingly, 37 specialized study designs are used for these 38 effects (U.S. EPA, 2006b, 1998, 1996, 1991).”
    - Comment: How will EPA treat the expansive literature exploring developmental tox endpoints that do not use the "specialized study designs" and instead are more "hypothesis generating" studies or academic laboratory studies? Many of these studies have been frequently cited in past tox reviews, but do not use the GLP study designs for regulatory purposes.
- p. xviii, lines 50-61: “In some situations, examination of historical 50 control data from the same laboratory within 51 a few years of the study may improve the 52 analysis. For an uncommon effect that is not 53 statistically significant compared with 54 concurrent controls, historical controls may 55 show that the effect is unlikely to be due to 56 chance. For a response that appears 57 significant against a concurrent control 58 response that is unusual, historical controls 59 may offer a different interpretation (U.S. EPA, 60 2005a, §2.2.2.1.3).”
    - Comment: Is there any guidance on using historical control data in the manner suggested in this paragraph? Historical control data are typically used to measure "genetic drift" of the species being used in the laboratory, to ensure that laboratory practices are faithfully maintained according to adopted GLP or other guidances. Only concurrent control data provide an appropriate comparison to the treatment groups. This proposed practice – implied here as an agreed EPA policy -- would benefit from a more robust scientific discussion. Alternatively, deleting this section would have no detrimental effect on the preamble, and leave the issue to a case-by-case evaluation, which is where evaluation of historical controls ought be vis a vis individual study results.
- p. xviii, lines 70-75: “Effects that occur at doses associated 70 with mild maternal toxicity are not assumed to 71 result only from maternal toxicity. Moreover, 72 maternal effects may be

reversible, while 73 effects on the offspring may be permanent 74 (U.S. EPA, 1998, §3.1.2.4.5.4; 1991, §3.1.1.4),."

  - Comment: misplaced comma at the end of the sentence. There should also be a caveat explaining that exposures that result in frank maternal toxicity may not be relevant in producing the developmental toxicity of interest, i.e., the flip side of this statement.

- p. xix, lines 43-49: "The finding of a large relative risk with narrow confidence intervals strongly suggests that an association is not due to chance, bias, or other factors."
  - Comment: Consider deleting "bias" from this sentence. Bias may indeed be the cause of a large relative risk, just the wrong linkage.
- p.xx, lines 47-71: Causation standard descriptors relating epidemiological information to causation.
  - Comment: Causation analysis inherently requires the package of considerations, from epidemiology, to bioassays, to mode of action, to … the Hill criteria. Yet, here, EPA is imputing causation analysis based on only the epidemiological parameter. Has EPA used these "epidemiological causation" descriptors before? One way to remedy would be to simply delete the words "consistent with causation" and leave the "association" terminology intact, because that is what is generally being addressed in such summaries of the epidemiological information.
- p. xxi, lines 33-36: "Negative results carry less weight, 33 partly because they cannot exclude the 34 possibility of effects in other tissues 35 (IARC, 2006)."
  - Comment: Why should negative results carry less weight? I think that the genetic toxicology assessment should evaluate the results as a whole, and not pre-judge the validity of negative genetic toxicity studies. Indeed, to be balanced, EPA might also note publication bias against negative studies.
  - p. xxi, line 60: "Toxicodynamic processes that lead to a health effect at this or another site (also known as mode of action).Comment: Does mode of action not include any consideration of toxicokinetics, which this section implies? What about metabolism leading to toxic moieties, is this not part of the mode of action? Or (de)activation through stomach acids?
- p.xxi, line 73: Suggest adding "Although important, information on mode of action is not required for a conclusion that the agent is causally related to an effect, in circumstances where there is compelling information supporting such a conclusion."
- p. xxii, lines 37-40: "It should be noted that in clinical reviews, the 37 credibility of a series of studies is reduced if 38 evidence is limited to studies funded by one 39 interested sector (Guyatt et al., 2008a)."
  - Comment: This is a questionable statement. Evaluations should be based on rigor of study design, reproducibility, etc. not funding source. One could cite HHS (NIH or NTP) or EPA as interested sector funding sources.
- p.xxv, lines 3-5: "For chronic effects, daily exposures are averaged over the lifespan."

- Comment: This is puzzling. Wouldn't it be more accurate to say that "For chronic effects, daily exposures are averaged over the duration of the study, and assumed to continue over a lifespan in the modeling."

- p. xxvi, lines 52-55: "Nonlinear 52 approaches generally should not be used 53 in cases where mode of action has not 54 ascertained."
  - Comment: Missing "been" between "has not" and "ascertained."

*Primary Comments*

- p. ES-1, line 8: "Although 6 mechanistic data are insufficient to establish a mode of action (MOA) for RDX-induced convulsions, 7 the available information suggests that nervous system effects are mediated by RDX binding to the 8 picrotoxin convulsant site of the GABAA channel, resulting in disinhibition that leads to the onset of 9 seizures."
  - Comment: this statement seems contradictory. The data (discussed later in the document) seems more than suggestive in regards to a MOA. Why is the conclusion "insufficient" to establish a MOA?

- p.ES-2, line 10: Table ES-1 presents the conclusory snapshot of candidate and final RfDs, but omits critical information on the PODs and UFs. For full transparency, extra columns should be added to provide this transparency. We realize that this on the next page for the chosen study and endpoint, but now we have a reversal of information ordering from previous IRIS summaries where the critical information was packaged in the first table. An additional general request – given this new format -- is that now there is only summary information up front, and copious tabulated detail on each of the studies in the supplement. EOP has asked previously, to no avail, for critical data from just the selected study and endpoint of interest to be included up front, along with the BMD Software graph of the modeling (I could not find any such BMD software graphs in the documents reviewed – are they in an appendix?). Otherwise, the RfD, RfC, and CSF numbers retain their "magic" quality, isolated by an inability to expeditiously determine which of the many supplementary data tables is actually the origin of these reference doses. An alternative might be to add a link or table/page reference number with each study citation on this page, making the search a little easier.

- p. ES-2, line 20: "A 1% 20 response level was chosen because of the severity of the endpoint; this is supported by the 21 observation in Crouse et al. (2006) that for all the dose groups where unscheduled deaths were 22 recorded, mortality was strongly associated with convulsions." Also addressed on p. ES-5 line 9, and later in the dose-response assessment.
  - Comment: The rationale for a BMR of 1% needs to be better supported, especially since the preamble material (xxvi, lines 1-2) indicates that 5% would be the appropriate level for more severe effects. How is the "severity" of the endpoint determined? A sensitivity analysis using other BMRs (including the usual 10% BMR) is presented in the Supplemental Information appendix, however, it would be useful to include in the main document a table that compares the PODs of the selected BMR (1%) and the more usual 10% BMR. Is there a BMD Software graph of this BMR calculation, to aid in visually determining the extent of the extrapolation and the variability of the empirical data?

- p. ES-3, line 2: "…deficiencies in the toxicity database (3)."

- Comment: This database UF was not used in the previous RDX RfD derivation. There are developmental and reproductive tox studies. EPA justifies the value of 3 for this UF, citing the lack of developmental neurobehavioral studies. Is this standard practice for EPA to consider this an inadequate database, and require a specific developmental neurobehavioral study for a neurological endpoint, and developmental studies for other noncancer endpoints?

- p. 1-41, line 33: "In addition, the incidence of hepatocellular carcinomas showed a ~~cant~~ 33 positive trend with dose in male, but not female, F344 rats exposed to RDX in the diet for 2 years 34 (Levine et al., 1983) (Cochran-Armitage trend test performed for this review, p = 0.032)."
  - Comment: struck out a misplaced word.
- p. 1-42, lines 5-12: "In the female B6C3F1 mouse study by Lish et al. (1984), the finding of a statistically 5 significant increase in hepatocellular tumors may have been influenced by the incidence of 6 hepatocellular adenomas/carcinomas in the concurrent female control mice, which the study 7 authors noted was relatively low (1/65). However, as noted by the authors, the incidence of 8 hepatocellular adenomas or carcinomas at RDX doses ≥35 mg/kg-day (19% at both doses) was also 9 statistically significantly elevated when compared to the mean historical control incidence for 10 female B6C3F1 mice in National Toxicology Program (NTP) studies (147/1781 or 8%; range: 11 0−20%) (Haseman et al., 1985).[5]"
  - Comment: The purpose of this discussion is unclear. What is meant by "the finding of statistically significant increase in hepatocellular tumors may have been influenced..."?

*Comments on the Peer Review Charge Questions*

- There should be an explicit charge question on the use of a 1% BMR instead of the usual 10% BMR, and the recommended 5% BMR for more severe effects. The SAB CAAC should be provided with a table summarizing the sensitivity analysis of BMRs.
- There should be an explicit charge question on the database uncertainty factor.
- The Preamble should be critically reviewed by the SAB CAAC, particularly on those items that we commented on.