

**Comments from Members of the Chartered SAB on the SAB Draft Report:
Review of EPA’s Draft Assessment entitled *Toxicological Review of
Hexahydro-1,3,5-12 trinitro-1,3,5-triazine (RDX) (September 2016)***

List of comments received
August 28, 2017

Comments from Lead Reviewers.....	1
Comments from Dr. Alison Cullen	1
Comments from Dr. Susan Felter.....	3
Comments from Dr. Sue Marty.....	8
Comments from Dr. Gina Solomon	10
Comments from Dr. Edwin vanWijngaarden.....	14
Comments from other SAB Members	18
Comments from Dr. Sylvie M. Brouder.....	18
Comments from Dr. Joel Burken	19
Comments from Dr. Joel Ducoste	19
Comments from Dr. Robert J. Johnston.....	20
Comments from Dr. Kristina D. Mena.....	20
Comments from Dr. Tara Sabo-Atwood.....	21
Comments from Dr. Daniel O. Stram	23
Comments from Dr. Charles Werth	23

Comments from Lead Reviewers

Comments from Dr. Alison Cullen

I have read the SAB Review Draft Report on RDX for overall quality, the quality of its response to the charge questions, its completeness and accuracy, and finally its support for the conclusions/recommendations presented, as queried by the four questions immediately. My responses appear interwoven below, with specific questions/comments next.

1. Were the charge questions adequately addressed?

The SAB panel responded in detail to the charge questions with careful and high quality responses in the Review of EPA's Draft Assessment of RDX. The Draft is well-written and the scope is appropriate and comprehensive.

2. Are there any technical errors or omissions in the report or issues that are not adequately dealt with in the draft report?

I am not aware of technical errors or omissions in the report. There are a few areas in which additional content and information would be helpful as noted below in the Questions/Comments section.

3. Is the draft report clear and logical?

Overall, the draft report is clear, logical, and concise despite including a tremendous amount of information and critical analysis. There are a few places where additional clarity is needed to address ambiguity, noted in the following.

4. Are the conclusions drawn, or recommendations provided, supported by the body of the draft report?

The conclusions drawn, and recommendations provided, are supported extremely well by the body of the draft report in general. I note a few places where this support could be strengthened with additional information.

Questions/Comments re: the SAB's Review Draft:

SAB's Review Draft expresses agreement with EPA that neurotoxicity including seizures or convulsions is a human hazard of RDX exposure but goes on to note that convulsions in rodents constitute a limited spectrum of the potential human hazard given the range of possible effects (pg 1 lines 35-42 and following pg 15 and beyond). The SAB Review then asks EPA to add further evaluation or explanation for these potential endpoints. It would be very helpful to detail further the desired content for these additions in order to highlight the key components.

Further on the topic of neurotoxicity, the SAB Review Panel consistently recommends that EPA

revisit the BMR. Specifically the Review suggests that at a minimum EPA should improve their justification for using 1% for the BMR for deriving the lower bound on the benchmark dose (BMDL) as the point of departure for convulsions, based on Crouse et al 2006 (pg 1 line 46 and top of pg 2 and supporting text in the main body). There is a concern stated that the BMR of 1% is a factor of 15 below the lowest observed response data, while 5% would be more consistent with the observed response at the LOAEL of 15%, and closer to the observable data. SAB's Review Draft requests additional justification for the use of 1%, and in particular 1% rather than 5%. If possible, it would be helpful for SAB to say more specifically what this additional justification should include. On page 38 lines 6-11 the text identifies a key issue with EPA's own Benchmark Dose Technical Guidance, regarding a lack of clarity about how to incorporate consideration of the frank nature of an effect into BMD modeling. It would seem that this issue should be flagged more generally across Toxicological Reviews, not just for RDX. Meanwhile, the EPA Guidance does make a key point, cautioning against overly diverging from the empirical data.

SAB's Review Draft also poses key questions about the uncertainty factors applied re: neurotoxicity. SAB requests stronger justification for a UF_S of 1 as well as suggesting an increase from 3 to 10 in the UF_D to account for a tabulated set of data limitations and gaps (pg 2 lines 22-24). It was not clear whether 10 would be sufficient – thus more should be said about this choice. Also, in this case it would be helpful if the SAB could provide further detail about the components of sufficient justification and/or could point to the locations elsewhere in the text where this information is presented.

SAB's Review Draft outlines concerns with the RfD for nervous system effects and a lack of scientific support with respect to not capturing all of the potential adverse nervous system outcomes or their severity, nor the uncertainties associated with the database (pg 2 lines 27-41). The text could be made a bit more clear in these sections. The Review first states that Crouse et al 2006 should be used as the primary basis for deriving an RfD for neurotoxicity. However, then the Review goes directly on to state that these data were rudimentary, and not sufficiently sensitive, and lays out other data concerns and gaps. Finally, in pg 2 line 40 the Draft states "Thus the SAB concludes that there remains significant uncertainty about the developmental neurotoxicity of RDX." This is picked up again on page 16 with a request that EPA account more fully for database uncertainty and on pages 31 and 41 with a call for more studies to address the complete spectrum of effects. Is the intent to support the use of Crouse et al as the basis for an RfD for neurotoxicity in general, while deliberately calling out the issue of data gaps associated with developmental neurotoxicity which should be filled by future studies? Or is something additional being communicated here?

SAB's Review Draft makes excellent points about data limitations that potentially compromise the application of the multistage model, e.g., high dose mortality, (pg 3 lines 22-28, and picked up again on pages 18, 67, 68, 69). Although SAB states that it has no specific recommendation on how EPA should address the limitations other than to include/exclude the highest dose in the sensitivity analysis, it goes on to suggest that other standard BMD model forms be fit to the available data, and that these fits be included when discussing model adequacy. Which models among the others facilitated by BMDS software is SAB specifically suggesting? Is there a specific set, or should EPA include all that constrain slopes to be positive, or is there something

other (e.g., pg 76 line 15-16) ? And this recommendation should also appear in the “Key Recommendations” section at the bottom of pg 76 and top of 77? Finally, should SAB consider whether to make a more general comment (beyond this single Toxicological Review for RDX) about EPA’s Cancer Guidelines policy of “discretion” regarding whether or not to use data from doses that exceed the maximum tolerated dose.

Two other suggestions relevant to modeling are to include additional detail about MS-COMBO and to add a summary of the strengths and weaknesses of the multistage modeling approach. Both of these additions would appear in the Supplemental Materials, and both would seem to be relevant suggestions for all EPA Toxicological Reviews. One clarification, is this a suggestion that EPA should include standard language about the multistage modeling approach and the MS-COMBO software package in toxicological reviews generally, or is it that EPA should specifically include a summary related to the particular case of RDX and relevant datasets, or both?

Specifically in Section 3.5 Executive Summary, under the Suggested Recommendations the first bullet suggests reducing emphasis “on the incidence and significance of suppurative prostatitis” while the second bullet suggests deriving an RfD based on suppurative prostatitis as a stand-alone endpoint while separate RfDs should be derived for other systems and organs. These two bullets read in a slightly disjointed sequence currently, the language could be a bit more clear since having a stand-alone RfD does not necessarily imply a reduced emphasis. The text of the third bullet also would benefit from a bit of reworking – is there an intention to imply order, i.e., for a causal sequence as to whether suppurative prostatitis may lead to bacterial infection, or whether bacterial infection may lead to suppurative prostatitis, or are these two effects without order? The answer to the previous question is also relevant in the section on Selection of Suppurative Prostatitis Endpoint (pg 45-48)- please clarify whether there should be a causal order suggested or not?

Small Issues

Address typo on page A-6 Line 2-3

“The draft assessment presents an overall oral reference dose of 3×10 mg/kg-day, based on...”
I believe this is missing an exponent of “-3” on the “10”?

Clarify language on page 29 lines 41-45

It is a bit confusing to follow parts 1, 2 and 3 within the sentence.

In the SAB suggestion to move section C.3.2 out of Appendix C and into the main body of the report, it was not clear if the associated tables were to be part of the move. This reviewer would encourage and support moving the section as a whole.

Comments from Dr. Susan Felter

Overall, the Draft SAB report is well-written, follows a logical flow, and responds clearly to most of the charge questions posed by the EPA (see below for one that I find lacking). It is a long report, and many of the points are made multiple times such that the report could be

significantly shortened while still providing the same information and recommendations. This is in part a reflection of the SAB responding to each individual charge question when I think some could be combined in a more effective way.

1. Were the charge questions to the committee adequately addressed?

The charge questions (CQs) were all addressed and most of them quite thoroughly. Following are 2 CQs that I think need additional consideration.

CQ 3a(ii): I found the response to part of *CQ 3a(ii)* to be lacking. This charge question actually had 3 separate questions; this is the middle one: “*Considering the difference in toxicokinetics between gavage and dietary administration (described in Appendix C, Section C.1, and in the context of specific hazards in the toxicological review), is it appropriate to consider the Crouse et al. (2006) study, which used gavage administration.*” The SAB’s response (p. 33) states: “The differences in toxicokinetics of RDX exposure by gavage versus dietary administration are clear, and must be accounted for when predicting risk,” but there is no further discussion of this and it is not clear if the SAB agrees that the differences have, in fact, been accounted for. Especially given that gavage administration is less relevant to human exposures to RDX and effects seen following gavage administration were not seen in most dietary studies (pointed out by the SAB), this CQ should be addressed more thoroughly.

CQ 3e(ii) (p. 67): This CQ is focused on the dose-response assessment for cancer and asks whether the assessment adequately explains the rationale for the quantitative assessment given that for an agent with “*suggestive evidence*” for cancer, “*the Agency generally would not attempt a dose-response assessment, as the nature of the data generally would not support one.*” The SAB highlights a significant number of issues with the cancer assessment, but does not question whether the Agency should be doing a quantitative assessment at all. I think this is a question that should be considered more explicitly. The SAB states its agreement (p. 63) that the “*relevant observations*” are liver tumors in female B6C3F1 mice and male F344 rats and lung tumors in female B6C3F1 mice. However, on the next page, the SAB describes each one of these and concludes that there were significant issues with each finding – either the MTD was exceeded (rat liver, mouse lung) or there were significant concerns with controls and overall confidence in the interpretation of the study (female mouse liver). This begs the question of whether all of those findings should be considered “*relevant observations*”. The SAB does a good job of summarizing a long list of significant issues with the cancer bioassays, but then goes on to support the use of the Lish et al. bioassay to support a quantitative cancer risk assessment for RDX. Given the significant issues, did the SAB consider a recommendation that the Agency not conduct a quantitative assessment, consistent with the Agency’s more common approach to substances with “*suggestive evidence*” for cancer? I find it troublesome that linear low-dose extrapolation is applied to a dataset (female mouse liver tumors) that has several notable issues (summarized by a Pathology Working Group) and a statistically significant response only at the second highest dose (the highest dose clearly exceeded the MTD and should be discounted). To put these doses in context, the *lowest* dose in the bioassay was 1.5 mg/kg/day, which is higher than the PODs for neurological endpoints. The *highest* dose (which exceeded the MTD) was 107 mg/kg/day (duration adjusted – initial dose of 175 mg/kg/day was lowered to 100 mg/kg/day after 11 weeks), and the dose below that was 35 mg/kg/day – this is still a very high dose (note that the highest dose in the gavage study by Crouse et al was 15 mg/kg/day; convulsions were reported at doses as low as 8 mg/kg/day).

2. Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

I do not see any technical errors.

One topic that would be helpful to expand on is the discussion around what is known about other seizurogenic compounds, specifically with regard to the potential for neurological effects at doses lower than those associated with seizures. On pp. 31 and 35, the SAB notes that data are available on other compounds (e.g., bicuculline). The SAB concludes: “*As such, the SAB agrees that the likely dose range between convulsion and other nervous system effects can be addressed using the UF adjustments.*” This is also highlighted in the Executive Summary on p. 2: “These concerns are especially compelling because of more recent peer-reviewed published data indicating that sub-convulsive doses of either bicuculline (which has a similar mechanism of action to RDX) or domoic acid (which has agonist activity on glutamate transmission) have been shown to cause developmental and behavioral impairments at doses below those that cause convulsions.” Given that this is a key uncertainty highlighted by the SAB, it would be helpful to include further details regarding *how much lower* other neurological effects are seen, esp. for bicuculline.

One topic that I don’t see addressed is the potential connection between the MOA for neurological effects (via GABA_A receptor) and an explanation for possible cancer response at high doses. For example, see:

Watanabe et al. 2006. Gamma-aminobutyric acid (GABA) and cell proliferation: focus on cancer cells. *Histol Histopathol*, 21: 1135-1141

Young & Bordey, 2009. *GABA's Control of Stem and Cancer Cell Proliferation in Adult Neural and Peripheral Niches*. *Physiology (Bethesda)*. Jun; 24: 171–185.

3. Is the draft report clear and logical?

Overall, yes. However, one part that is confusing is what the SAB is recommending with regard to the composite UF, which should only be discussed in the context of a specific POD. In the Exec Summary (p. 16) and in many places throughout the text, the SAB suggests that a 5% BMR for convulsions is more appropriate than a 1% BMR, “with an additional uncertainty factor to address the concern over using convulsions as the toxicological endpoint for the RfD.” It does not say anything further about what that ‘additional UF’ should be. [note – this is also the first “Key Reco” on p. 39 and it also does not indicate here what the “additional UF” should be]. The SAB then goes on to recommend increasing the database UF from 3X to 10X (specifically because of a lack of data on developmental toxicity), which would give a composite UF of 300 (vs 100). However, it’s not clear whether the SAB is recommending that composite UF be applied to a BMDL based on the 1% BMR or 5% BMR. It is also not clear in the main body of the report. Table 4 (p. 73) provides a summary of 4 possible approaches to calculate the RfD, with results ranging from 3E-4 to 3E-3 mg/kg/day. The last two rows show an UF of 300 applied to either the BMDL₀₁ or the BMDL₀₅ from the Crouse et al study, implying that the BMDL at the 1% response level is somewhat analogous to the BMDL at the 5% response level since the UF did not change. Regarding these different numbers, the SAB simply says that “These RfDs can be compared to the EPA’s proposed RfD...” but does not say how one should think about these. It seems to be just playing with numbers.

4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?

In general, yes. However, as described above, there are some recommendations that are not clear and there are 3 areas in which I don't feel the recommendations are fully supported by the report:

- The SAB makes a “strong” recommendation to increase the UF_D from 3-fold to 10-fold because of a lack of data on developmental neurotoxicity and lack of data on less severe neurological effects. It is not clear why the SAB feels that the EPA's choice of an UF_D of 3-fold is not adequate. As EPA has documented, the overall database for RDX is fairly robust compared to most chemicals (includes subchronic and chronic toxicity studies in the rat and mouse, a two-generation reproductive toxicity study in the rat, developmental toxicity studies in the rat and rabbit, and subchronic studies (with study design limitations) in the dog and monkey).

It is also noted that the SAB's reco on the UF_D is in contrast to its comments on the UF_S of 1 for subchronic to chronic – here the SAB indicates that it is “concerned” but does not make a recommendation to increase it and just says that the EPA should reconsider it and at a minimum, provide a stronger justification.

- Cancer Assessment: I do not feel a compelling argument has been made for the SAB's support of linear low-dose extrapolation for the cancer risk assessment based female mouse liver tumor data. I think the problems with this study that were documented by the Pathology Working Group (and noted by the SAB) are sufficiently concerning that serious questions are raised about basing a risk value on this dataset. It should be noted that this risk value is 2 orders of magnitude lower than the draft RfD, and will drive risk management decisions with potential significant cost. Hence, this is a highly impactful assessment. [as a side note – it is interesting that the SAB disagrees with the EPA's conclusion about male reproductive effects based on testicular degeneration in male mice. The SAB offers several reasons why those data are insufficient, even though the dose-response for that endpoint appears to be more compelling than the liver tumor data in the female mice).
- P69, Key Recos and Suggested Recos for the cancer risk assessment: The recos here are focused on additional BMD modeling, including fitting other standard models to the data. I find a tendency in cancer risk assessment to do more and more modeling while major issues related to the underlying data (biology) are left unaddressed. Given the significant issues with the bioassay data, I think the bigger issue is whether the data are suitable for dose-response analysis at all.

Page-Specific Comments

- Cover Letter, P3, ll 4-13: This paragraph starts with 1 sentence about male repro effect, then the rest of the paragraph is about developmental, and the last sentence is again about repro. This needs to be 2 separate paragraphs – one on male repro (with additional sentence about *why* the SAB disagrees with the draft assessment), and one on developmental.
- P19, ll 5-9: This is confusing. Text states that the SAB recommends that the EPA use the dose-response data of the Crouse et al (2006) study as the primary basis for the overall RfD in a way that implies this is not what the EPA draft does (this is also true later in the report). Suggest rewording this to say that the SAB agrees with the EPA's choice...
- P29, ll 13-16: “Key Reco” is just a bullet essentially agreeing with what EPA has done (use a full UF_H of 10). This is not a reco. For “Future Needs”, suggest adding context that these data are needed to move away from the current default UF (the risk assessment can be done

without these data).

- P32: Note that there are no “Key Recommendations” offered for Section 3.3.1.1. The “Future Needs” (II 3-8) suggests that EPA should “provide a means to commission” studies. Suggest that the 2 bullets in this section be combined and rephrased – these are the data needs to improve the risk assessment for RDX; it is not necessarily up to EPA to “provide a means to commission” the studies.
- P32, Section 3.3.1.2. Much of the text in this section is off-topic (does not directly address the CQ). It addresses data gaps, but that’s not the question being asked. As described earlier, it does *not* address the CQ about whether kinetic differences between gavage and dietary administration have been adequately considered and specifically whether it is appropriate to use the gavage study as the principle study for the quantitative risk assessment.
- P39, “Subchronic to Chronic UF”: The SAB expresses “concerns” about the use of an UF of 1 for duration extrapolation (note that this language is also used in the cover letter) but does not offer a specific recommendation. It acknowledges (starting bottom of p. 40) that the NOAEL from the 2 year dietary study is *higher* than the NOAEL from the 13-week gavage study but goes on to say that that might be due to gavage vs diet. That’s true, but the dietary administration is more relevant to human exposure, so the bottom line is that there is a 2-year study with a higher NOAEL that the one chosen as the basis for the risk assessment. The SAB states that “binding of RDX to the GABA_AR may provide for cumulative effects...” Is this speculation, or is there a basis to suggest this? The SAB refers (bottom of p. 39) to an *in vitro* assay in which the effects of RDX were not reversible following compound wash out – but it should also be mentioned that this was only measured for 40 minutes. The SAB has referred to other compounds with a similar MOA (e.g., bicuculline) – are there any data on that or similar compounds that can help increase confidence in whether an UF is needed for duration extrapolation?
- P44, “Key Recos” (II 6-11): The first key reco ‘strongly suggests’ that EPA apply an UFD of 10 to account for data gaps in developmental neurotoxicity, but the 2nd key reco then says that EPA should discuss whether this is sufficient. Seems quite odd.
- P44, “Key Recos” (II 42-43): Here and elsewhere in the text, the EPA states under a Recommendation that EPA should use the dose-response data of Crouse et al as the primary basis for the RfD. The EPA *does* use these data, so it’s not clear why this keeps coming up as a recommendation.
- P45, II 45-46: Text states that the SAB concurs with EPA’s position that the prostatitis was considered “secondary to the renal effects” but then goes on to conclude that it should not be used as a surrogate marker for renal effects, but rather should be considered as a stand-alone endpoint. This is a bit confusing.
- P52, II 2-6: The SAB is recommending an UF_D of 10 (vs 3) for lack of developmental neurotox data. It does not make sense to say that this UF_D would be relevant to a system-specific RfD for suppurative prostatitis. The SAB acknowledges this in the last sentence of this paragraph, but the wording needs to be fixed, specifically in line 4.
- P52, II 30-35: The first bullet is a bit confusing – how many ‘separate’ RfDs is the SAB recommending? It sounds like the SAB is recommending an RfD *specifically* for “renal papillary necrosis” but that this will not cover other renal effects (2nd bullet). This would seem to imply that if EPA were doing a cumulative risk assessment, that this RfD would only be applicable to assessments in which renal papillary necrosis is the endpoint (vs renal toxicity more generally). Is this correct?

- P.54, ll 39-40: The SAB implies here that the EPA is considering RDX to be a male reproductive toxicant. EPA's terminology is that there is "suggestive evidence for..." – the text here should be modified to reflect this.
- Pp 55-59: There is a lot of redundancy in this text that can be reduced. This section essentially states that the SAB does not agree that there is suggestive evidence for male reproductive effects and that an RfD should not be calculated for this endpoint. The basis for this is repeated several times and there are short sections on the PODs (3.3.3.3) and UFs (3.3.3.4) that can be condensed (they are irrelevant if an RfD is not calculated) and summarized just one time.
- P68, ll 28-29: The SAB recommends here that the EPA should do a sensitivity analysis of the mouse liver tumor data by both including and excluding the highest dose. The highest dose clearly exceeded the MTD – it should not be included in any quantitative evaluation.
- P70 ll 33-34: The SAB concludes here that "the scientific support for the proposed oral RfD is weak". This is a stand-alone sentence, and not well supported. It's also not clear if the SAB is disagreeing with the EPA's position that "overall confidence in the RfD is medium" (reflecting high confidence in the principal study and medium confidence in the database)?
- P72, ll 41-42: Text refers to the Cholakis study as being in a "potentially sensitive subpopulation" and offers that as an explanation why an RfD based on that study might be 10-fold lower. However, this is based on speculation (we don't know that pregnant animals are a sensitive subpopulation – this is acknowledged on p34, lines 1-4) and if it were true, then one would likely use a lower UF for intrahuman variability.

Comments from Dr. Sue Marty

1) Were the charge questions to the committee adequately addressed?

- The committee adequately addressed the charge questions and provided detailed justification for the requested revisions. For example, with neurotoxicity, the suggestion to use a 5% benchmark response (BMR) with an additional uncertainty factor (UF) for database limitations seems reasonable instead of a 1% BMR given the limitations/uncertainties of modeling BMRs well below the observed data. Overall, the SAB gave sound rationale when the committee had an alternative viewpoint from the EPA. The recommendations are highlighted at the end of each section as "Key Recommendations", "Suggested Recommendations" and/or "Future Needs", making these suggestions easy to find and address. The SAB's proposed revisions will strengthen the report.

2) Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

- Overall, the draft report was very well done. Below are a few observations for consideration by the SAB.

- The SAB discussed the different exposure scenarios for RDX (oral gavage and dietary) and their support for using oral gavage studies, despite some issues with dose homogeneity and achieving nominal doses. While the SAB justified its choice, this section should include some discussion on relevant exposure scenarios in humans to clarify which of these scenarios most closely mimics human exposures (only mention of human exposures is one phrase on p. 43, l. 23-24). While this may not determine the studies selected for BMR analyses, it is a critical element of the discussion.

- Particle size is seldom determined in studies with orally administered doses; this limitation

exists for many studies. As the SAB has alluded, toxicokinetics is the most relevant way to compare dosimetry across studies.

- Page 41 l. 37-39: Can the SAB confirm that the two-generation study of Cholakis et al. (1980) only looked at histopathology of the F2 pups at weaning? Is this referring to histopathology of the brain of F2 pups at weaning? If so, consider adding this clarification. A two-generation study generally includes histopathology (minimally of reproductive organs) in the F1 offspring that were exposed throughout gestation, lactation and into adulthood.

- This reviewer agrees that neurotoxicity is the critical non-cancer endpoint. Furthermore, the SAB request to include information on the role of GABA(A) in neurodevelopment and the effects of interference with GABA(A) receptor during development will strengthen the report. The SAB recommended additional references to include in the EPA report; however, this reviewer is concerned about the inclusion of heavy metal references (e.g., lead) due to multiple modes of action for these compounds (also on page 42, l. 5-8).

- In addition, the SAB justifies its statement that the reference dose (RfD) for RDX neurotoxicity is not scientifically supported. Furthermore, the SAB requests additional data on developmental neurotoxicity is valid, particularly with respect to potential cognitive and neurobehavioral effects. This is critical data gap. As mentioned, seizures may not be the critical endpoint during developmental exposures to RDX. GABA is excitatory during early development. A switch in GABA(A) signaling from excitatory to inhibitory occurs during the second postnatal week in rats. The GABA(A) receptor antagonist bicuculline reduced the frequency or completely blocked seizure-like events (SLEs) and induced interictal clonic-like activity accompanied by a reduction in the frequency but an increase in the amplitude of the population spikes. As neurons mature, it is hypothesized that both excitatory and inhibitory GABA responses can be detected in less and more mature neurons, respectively. Species differences in developmental timing also should be considered as GABA is excitatory only until the third trimester *in utero* in primates (Khazipov et al., 2001). These data gaps support the proposed database UF.

-The SAB's request to include non-mammalian data in the assessment is supported as GABA(A) signaling is conserved across many species. In silico protein structural modeling of RDX interactions with the GABA(A) receptor may provide useful insights too.

3) Is the draft report clear and logical?

Yes, the draft report is both clear and logical. The summary highlights at the end of each section make the report recommendations easy to locate and understand.

4) Are the conclusions drawn or recommendations provided supported by the body of the draft report?

- The conclusions drawn by the reviewers seem reasonable and well supported.

Furthermore, the authors have provided good justification for their recommendations, including explanatory text and additional references. These recommendations merit consideration by the EPA during its revision of the *Toxicological Review of Hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX)* document

5) Does the Letter to the Administrator adequately reflect the findings of the SAB report?

The conclusions of the SAB review committee are clearly and consistently expressed in the Letter to the Administrator. The letter is well constructed and includes the primary findings and rationale for the SAB's key findings, including:

- Endorsement of the EPA's improvements to the physiologically-based pharmacokinetic (PBPK) model
- Request for information and generation of additional data on RDX's effects on

- neurotoxicity and neurodevelopment
- Request for additional rationale for the UFs (e.g., subchronic to chronic, database, etc.) and the use of BMR 1% (if not changed to BMR 5% with additional UF)
- Inadequacy of the EPA's reference dose for RDX neurotoxicity due to limitations in the available data
- Separating effects on kidney and urogenital system from suppurative prostatitis as these appear to be distinct findings (separate PODs and RfDs). These effects warrant greater description and analysis in the report.
- Disagreement with the EPA on the conclusion that RDX is a male reproductive toxicant (based on Lish et al., 1984 study) due to the lack of support for testicular effects across the RDX database
- The SAB encouraged the EPA to conclude that RDX did not induce structural malformations in the developmental toxicity studies
- SAB proposed that the EPA add summary statements for other non-cancer endpoints associated with RDX treatment – liver, ocular, musculoskeletal, cardiovascular, immune and GI effects
- The need for more discussion on gestational, perinatal and lactations RDX toxicokinetics
- SAB agreea that RDX has “suggestive evidence of carcinogenic potential” while recognizing that greater discussion to justify the cancer oral slope factor is needed.

Comments from Dr. Gina Solomon

1. *Were the original charge questions to SAB Standing or Ad Hoc Committees adequately addressed?*

Yes, the original charge questions were adequately addressed. In a few places the report has almost too much technical detail in its response to some of the charge questions. This is particularly the case in the extensive discussion of the suppurative prostatitis endpoint on page 46-49. This discussion could be shortened without sacrificing the responses to the charge questions.

On p. 28, line 25 there is a dangling sentence at the end of the response saying: “The uncertainties are numerous.” This appears to be referring to the mouse PBPK model. It might be ok to just delete this sentence (the rest of the paragraph above is adequate, as is the reference to the earlier discussion). If the committee wants to keep that sentence, they should include at least 1-2 additional sentences briefly enumerating some of the key uncertainties.

There are three issues in the response to charge, however, that seem like more significant issues:

- 1) The divided and confusing discussion of the Cholakis vs. Crouse studies;
- 2) A conflict between the committee's expressions of concerns that the RfD based on the neurotoxicity endpoint may not reflect lower level neurotoxicity in sensitive populations and the overall committee recommendation to derive an RfD that is essentially the same or a bit higher than the one derived by EPA; and

3) Language in the report that makes it appear that the committee is seriously questioning the science in the EPA draft, when the discussion suggests instead that there are mostly minor issues that could be resolved fairly easily.

On p. 34, lines 1-37. The discussion of the Cholakis (1980) study and its deficiencies is central to the committee's responses to several charge questions. I read through this section several times and remain confused. This section explains that this study has a larger sample size than the Crouse study; it evaluates effects on a sensitive population (pregnant dams); and although the purity of the substance is slightly less, "it is not clear how much difference this would make in the study results" (lines 12-13). Later in the report (p. 40, lines 30-43), the committee discusses the importance of particle size for RDX absorption and mentions that the particle size of the substance used in the Crouse study was not reported, whereas it was characterized in the Cholakis study. So to my reading of these sections, it appears that the only reason that the Crouse study was preferred by the committee over the Cholakis study is that there may have been more difficulty keeping the test substance in suspension for uniform dosing in the latter study. However, on reading more closely (lines 21-22), it appears that the problem in the Cholakis study largely related to under-dosing with the exception of one outlier dose that "skewed the range of variability". Under-dosing the animals, of course, would tend to result in biasing the study results toward the null. However, in this study, effects were found at lower doses than in the Crouse study that the committee prefers.

There is significant additional discussion of the Crouse vs. Cholakis issue much later in the report on pp. 70-74. Some of the discussion is repetitive, but much of it is new. In this section, there is language saying that the low dose seizures in the Cholakis study "should not be entirely discounted" (p. 71, line 42). Ultimately, however, the committee appears to suggest precisely that the Cholakis study should not be used. These apparent conflicts are very confusing to the reader.

It would be much more helpful if the discussion of the pros and cons of these two studies on pp. 70-71 were consolidated with the earlier discussions on p. 34 and p. 40, so that a full treatment of this complex issue occurs in one place. It is clear that the committee struggled with this, and there may have been a range of views within the committee, resulting in the somewhat tortured and disorganized sets of pros and cons that are expressed in these various sections. Writing one unified discussion would help to address this problem. Perhaps even laying out the pros and cons in a table could be helpful. The discussion on pp. 70-74 is clearer than the one earlier in the report, so perhaps that could be edited and moved earlier, and then this later section could refer back to the discussion.

I also question whether the discussion really supports the committee's claim that "scientific support for the proposed oral RfD is weak." (p. 70, line 34). This strong language is not clearly justified by the discussion that follows. Also, in Table 4 (p. 73), one other key option is not presented (although it is mentioned in the text above), which is to use the NOAEL from Cholakis et al., with a composite UF of 100 (since this study was done in a sensitive subpopulation). This would generate an RfD in the range of 0.0009 mg/kg-day, which is very close to the one generated using Crouse et al, with the EPA-preferred BMDL₀₁ POD and the committee's recommended composite UF of 300 for that study. It might be good to include that option in the

table as well.

Overall, I am having a lot of trouble understanding how the committee can justify recommending what in the end would be a higher RfD, while at the same time expressing serious reservations about the failure of the analysis to sufficiently account for lower-level neurotoxic effects, and the refusal of the committee to dismiss the lower dose seizures reported in the Cholakis study. The committee's articulated concerns would all suggest that a lower RfD may be needed, but the issue related to the choice of BMDL₀₁ would more than counteract all of the committee's articulated concerns that the number may not be adequately health protective. From a 'big picture' perspective, the aggregate recommendations don't make a lot of sense. Furthermore, given that these recommendations would not change the RfD much (from 0.003 to 0.004 mg/kg-day), it's not clear how much all of this really matters. Is it worth holding up finalization of this EPA report and requiring the additional modeling in order to "tinker at the edges" and end up with essentially the same number? That's always a challenge to the SAB and its committees, since we do want to ensure that the EPA documents are scientifically justified, but we don't want to unnecessarily delay them over issues that end up being largely stylistic or academic. I question which category some of these recommendations fall into.

Related to the recommendations, I really like that the committee presents "key recommendations" and "suggested recommendations". This format is excellent and provides good guidance to the Agency. However, there are recommendations presented as "key recommendations" that don't seem to necessarily meet that threshold. This is particularly true of some of the recommendations related to the cancer assessment (more on that below). It would be advisable for the committee to look back at all the "key recommendations" and ensure that each one is truly critical to the scientific integrity of the overall effort.

With regard to the cancer assessment, the committee has an exhaustive discussion (too long?) in response to Charge Question 3e(i) on the cancer hazard, where the committee agrees with EPA's approach. However, for Charge Question 3e(iii), where the committee questions whether EPA's approach is scientifically supported, the discussion is lacking. As far as I can tell, the committee's concerns boil down to two issues: (1) for the selection of the multistage model, the EPA assessment refers to the BMD guidance document for justification (USEPA, 2012a), but the committee seems to feel that the assessment itself needs to separately justify the use of this model. It's unclear to me why EPA would need to write an extensive separate justification for using its own default approach, and why the committee feels that the failure to do so results in a decision that may not be scientifically justified. The paragraph discussing this issue (p, 68, lines 31-46) should either be revised to be clearer about why this concern is so major as to cause the committee to find the EPA approach potentially scientifically unjustified, or it should be softened to simply suggest additional justification. (2) The MS-COMBO methodology "is not clearly described". The paragraph describing this concern, which is also presented as major and as a "Key Recommendation", is on p. 69, lines 3-16, and it is not clear why the committee is so concerned. The discussion focuses on first questioning the assumption of independence of tumor incidence, and then contradicting itself by saying that the Lish et al. (1984) study data supports the assumption of independence of tumor incidence. In the end, it appears that the committee is merely suggesting some minor clarifying wording, so it's not clear to me why this rises to the level of "Key Recommendations". This paragraph either needs to be further clarified or it should

also be softened to “suggestions”.

Also in the response to question 3(e)(iii), the committee refers back to this response on p. 75 to “issues with the data” and “recommendations for improving the calculation of the POD” that will “change the estimated POD and thus the OSF” (lines 24-27). There are similar phrases in the letter to the Administrator (lines 23-28 on p. 3). So I went back to that charge question seeking the “issues” that would change the estimated POD and OSF, and don’t see anything clearly articulated there other than the need for some additional explanation on the choice of the multistage model and the MS-COMBO (discussed in my response above). There is also a discussion of modeling the data from the Lish (1984) study without the high dose group, but the committee appears to then reject that approach and suggest only that it be done as a sensitivity analysis. So I ended up uncertain about what the committee is referring to in the response to that charge question and unable to discern anything that would result in a change to the POD or OSF. Either the references back to this section should be clarified or deleted, or the section itself requires some significant additional clarification. It appears that the committee may be getting at their major concern later in the report on p. 76, lines 1-16. If this is the key issue, then it doesn’t make sense to refer back to the earlier charge question which doesn’t directly mention this issue.

2. *Are there are any technical errors or omissions in the report or issues that are not adequately dealt with in the Committee’s report?*

No, the report is quite thorough.

3. *Is the Committee’s report clear and logical?*

Yes, with the exception of the issue discussed above, the report is clear and logical.

4. *Are the conclusions drawn or recommendations provided supported by the body of the Committee’s report?*

The report, and especially the letter to the Administrator over-emphasizes areas of disagreement and in some places uses negative language when in fact the committee’s report is overall fairly positive. Some of the conclusory sentences could be misunderstood. For example, on p. 2, lines 40-41, the conclusion that there “remains significant uncertainty about the developmental neurotoxicity of RDX” could be read in various ways, as could the introductory sentence to this paragraph on lines 27-28 of the same page saying that the RfD for nervous system effects is “not scientifically supported”. Without reading these sentences in context it would be easy for the reader to conclude that the neurotoxicity RfD should not be finalized due to uncertainty and lack of scientific support. That’s not what the committee is trying to say here, so this paragraph should be revised to more clearly communicate the conclusions. Similarly, language on p. 2, line 19 (“The SAB recommends that EPA reconsider the UF...”) and lines 20-21 (“the SAB questions the application of a database uncertainty factor...”) are also prone to misunderstanding, especially if taken out of context. Here the SAB is recommending larger UFs, but that is not clear from this phrasing. On p. 3, lines 12-13 seem unnecessary, especially since lines 4-5 essentially say the same thing.

Another area of concern is the paragraph in the letter to the Administrator on p. 3, lines 21-22, where the committee “questions whether these are scientifically supported”. Again, taken in isolation, this could be read as questioning the cancer assessment overall. In fact, the key issue described in the body of the report has to do with whether or not it makes sense for EPA to provide separate and additional justification for using the multistage modeling, and do an additional sensitivity analysis using other approaches. This section of the letter should be edited to clarify this important distinction.

Overall, the letter should be revised to ensure that it clearly communicates the committee’s support for most of the key aspects of the document, and makes recommendations to further strengthen several aspects.

The final paragraph on p. 3, lines 30-33 seems out of place, and should probably be discussed with the other non-cancer issues earlier in the letter.

As mentioned above, it would be beneficial to review the “key recommendations” in the report to ensure that each one is truly critical for ensuring the scientific integrity of the report. It appears to me that a number of these recommendations may fall into the category of “suggested” rather than “key”.

Comments from Dr. Edwin vanWijngaarden

1. Were the original charge questions to SAB Standing or Ad Hoc Committees adequately addressed?

Yes, but see recommendations in response to charge question 3.

2. Are there any technical errors or omissions in the report or issues that are not adequately dealt with in the Committee’s report?

- None that I was able to identify.

3. Is the Committee’s report clear and logical?

The draft assessment was prepared under the auspices of the U.S. Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS) Program, and consists of a review of available scientific literature on the toxicity of RDX. (The previous assessment for RDX was conducted in 1988.) The SAB was asked to comment on the scientific soundness of the hazard and dose-response assessment of RDX-induced cancer and non-cancer health effects. The SAB is to be commended for thoroughly reviewing and commenting on EPA’s draft assessment. Many suggestions for improvements on the draft assessment were made, including clarification of language, identification of inconsistencies, suggestions for different analytic approaches, and highlighting the need for additional evidence. Below are some considerations that may further improve the draft SAB report. These considerations include but are not limited to further clarification about how to address developmental neurotoxicity in EPA’s draft assessment, better distinguishing key vs. suggested recommendations, providing more details on the cross-sectional epidemiologic study of nervous system effects, providing more discussion of the relevance of

gavage studies to the human exposure, and clarifying earlier in the document (including the executive summary) the impact SAB recommendations would have on the RfD estimate.

Executive Summary

- P14, lines 20-27: The SAB makes several recommendations regarding nonmammalian species studies and toxicological data on metabolism. The SAB has identified additional literature that the agency should consider. For these SAB recommendations, it would be helpful to clarify how this would augment or especially modify the conclusions in EPA's draft assessment.
- P15, lines 13-16: The epidemiological data regarding nervous system effects appears rather limited. Both the draft assessment and SAB report put much weight on the epidemiological evidence presented in one cross-sectional study and case reports. However, the SAB report does not describe in detail the design and findings of this one cross-sectional study – at least not in as much detail as is provided for the experimental studies. It would be helpful to provide additional information on the Ma and Li (1993) study.
- P15, lines 21-27: On several occasions the SAB report mentioned that convulsions in rodents can only provide a limited spectrum of the human health hazard and that additional neurological outcomes can all be part of the neurotoxicological spectrum. However, the basis for this statement is not entirely clear as references are not provided. Furthermore, the SAB report states that additional future studies addressing more subtle neurocognitive effects of RDX would assist in the hazard identification, but such studies are not available and it is therefore not clear what the specific recommendation to EPA is.
- P15, lines 32-35 (also page 33, lines 32-41): In its discussion of the mode of administration of RDX (e.g. dietary vs gavage), it would be helpful if the SAB report could briefly remind the reader about the most likely route of exposure in the civilian population, i.e. oral exposure (inhalation and dermal are more likely occupational exposure routes), and its relevance to the draft assessment.
- P16, lines 13-23: the SAB report clearly describes the rationale for their recommendation that uncertainty about dose-response should be addressed through uncertainty factors and not through EPA's extrapolation of the dose-response data. While described in the body of the report (P36-), the executive summary could provide additional information about the impact of their recommendations on the RfD.
- P17-18: While it is appropriate that the developmental neurotoxicity study is discussed in the section on developmental and reproductive effects, but given that it is highly relevant to the nervous system effects section (and is discussed as such in the SAB report) it would be helpful to mention the possibility of developmental neurotoxicity a little bit more under nervous system effects.
- P18, lines 5-6: Given that the developmental neurotoxicity study was a pilot study, how confident is the SAB in the findings of this study to warrant highlighting developmental neurotoxicity as a possibility?
- P18, line 38: Perhaps clarify why the SAB questions whether the oral slope factors are scientifically supported.
- P19, lines 4-9: The SAB reports states that it finds the scientific support for the proposed overall RfD to be weak. While this seems like a reasonable statement, it does leave one to wonder what exactly this means. Is it sufficiently weak to not support an overall RfD? Is

it sufficiently strong to support an overall RfD? Or has the EPA not used the appropriate data to support the RfD? This should be clarified.

Section 3.1

- P21, line 28: Please clarify what the SAB means with “clearer and better coordinated.” Perhaps give an example?
- P21, lines 39-41: Is it necessary to include this sentence on future research recommendations?
- P22, lines 32-46: this paragraph sounds reasonable here but the points made here should be clarified in both the letter to the Administrator and in the Executive Summary.
- P23, lines 30-33: Here as well as elsewhere in the report, the distinction between “key recommendations” and “suggested recommendations” is not always clear. In this instance, the key recommendations are well described but the “suggested” recommendation states that the lack of data “should” be noted (which makes it not a suggestion).
- P23, lines 35-39: similarly, here as elsewhere it is not always clear whether a “future needs” paragraph should be included. How would the SAB like EPA to use the future needs information provided?

Section 3.2

- P25, line 41: Perhaps clarify why the changes the agency made are distinct improvements over the original approach?
- P26-27: the SAB made numerous suggestions for improvement of section C1. It would be helpful to clarify the priority of these suggestions (which ones are key?), as some of these seem like a lot of work (e.g. 4th bullet point, lines 25-36). Also, for the last two bullets (P27, lines 1-6) it is not clear what the suggestions are.
- P27, line 13: this sentence needs to be clarified.
- P29, line 16: see previous comment on whether a “future needs” paragraph should be included.

Section 3.3

- P29, lines 33-35: The SAB appropriately states that case reports provide limited evidence to deduce the hazards of RDX, but in the executive summary these case reports appear to be given more weight than what the language here suggests. In addition, the case-reports are likely acute exposure studies at high levels of exposure. To what extent are these relevant to the more likely exposure scenario in the civilian population?
- P29, lines 36-42: The SAB should provide more details on the only cross-sectional study. What was its sample size? What neurocognitive test battery was administered? What was the study’s time period? What covariates should have been taken into account? More detail on the study would provide a better context for the limitations mentioned which seem to be numerous and may partly be the basis for the SAB statement that the scientific support for the overall RfD is weak (P19).
- P31, lines 8-17: As mentioned previously (in my comments on the executive summary), the SAB makes this point on several occasions but no references are provided to support the statement which may make it difficult for EPA to address the issue.
- P31, lines 21-25: Given the lack of studies conducted to date addressing prenatal

exposure and developmental neurotoxicity, it is unclear how the SAB would like the EPA to address this issue in its draft assessment.

- P32, lines 2-8 (also pages 32-33): no key recommendations? How realistic are the suggestions to address future needs?
- P35, lines 6-7: the SAB should clarify the suggestion “more consideration should be given...” Same comment on the “future needs” paragraph as before.
- P36-37, and P39: very nice discussion of the BMR considerations and clear key recommendations.
- P43, lines 24-26: the SAB should clarify the take home message here. Is a UF of 3 appropriate, or is a UF of 10 ok?
- P44, lines 10-11: this key recommendation may be difficult to address by EPA given the lack of data available.
- P50, lines 1-5: these key recommendations seem reasonable.
- P51, lines 8-17: this recommendation was clearly described and supported by the SAB.
- P53, lines 15-19: it would be helpful if the SAB could provide more guidance here on how the EPA could include this information in the overall risk assessment.
- P58, lines 1-3: should this statement be part of the key recommendations?
- P60, lines 4-23: could the SAB provide references?
- P62, lines 30-34: the body of the text makes it appear that the “suggested recommendation” should really be a key recommendation.
- P64: should the points be renumbered to 1a, 1b, and 1c (instead of 2, 3, and 4)? The organization of pages 63-65 is a little confusing.
- P66, lines 44-46: should the suggested recommendation be included in the key recommendations?

Section 3.4

- P70-72: it may be helpful to refer to the specific section of the report for details.
- P73: Table 4 is very helpful and should be highlighted better earlier on in the SAB report, especially in the executive summary.

Section 3.5

- P77-78: should some of these recommendations be “key” rather than “suggested”?
- P78, lines 22-30: this seems like an important point that the SAB should comment on more in their discussion of exposure route and the gavage study findings.

4. Are the conclusions drawn or recommendations provided supported by the body of the Committee’s report?

- Yes, the committee’s findings are thoroughly documented although on some occasions additional references should be provided (see response to charge question 3).

Comments from other SAB Members

Comments from Dr. Sylvie M. Brouder

Q1) Charge questions adequately addressed?

Yes, although this is definitely the assessment of someone without specific domain expertise. The charge questions to the SAB CAAC for the evaluation of the report (Appendix A) are extensive but generally quite specific. In addressing the questions, it seems the review panel has prepared extensive analyses and the arguments for Key and Suggested Recommendations are thorough and well-reasoned. The text itself is a bit repetitive as key points of analyses were presented multiple times (e.g. the observation that liver cancer in female control mice was suspiciously low) in highlighting the dangers of over-interpreting a study for one purpose of another. While it may be possible to reorganize text a bit to reduce repetition and highlight the collective limitations associated with a particular study artifact, the point-by-point approach to addressing the charge questions may make this simply too hard to do given completeness of the answers to each question is probably the more important goal.

Q2) Technical errors or omissions / issues not adequately addressed?

Regarding the letter to Administrator Pruitt and the Executive Summary, I think it would be helpful to include a few more specifics on the charge questions themselves. Right now the Letter only gives a one sentence summary of the charge questions given to the SAB CAAC (“The SAB was asked to comment on the scientific soundness of the hazard and dose response of RDX-induced cancer and noncancer health effects.”). Given that the remainder of the letter is quite specific, providing a few specifics on the charge questions would give context to the content of the letter that follows. Likewise, adding a couple of sentences regarding specifics of the charge questions to the first paragraph of the Executive Summary would preface the subsequent content and its order or presentation and emphasis.

Given my non-expertise in toxicological studies, I had to refer back to the list of Abbreviations and Acronyms (pp 12 – 13) many times. It seems that there are some abbreviations and acronyms that appear in the text but not in the list. For example, FOB is introduced and used on page 31 but does not appear on the list. Likewise, CNS is used on page 71 and MTD on page 76. I could not find their definitions in the text and they are not listed on pp 12-13. It’s possible the list is not intended to be comprehensive but there is no indication that the terms in the list are “selected”.

Q3) Draft report clear and logical?

Yes, the report is logically constructed and the narrative is easy to follow given the presentation of the questions in Appendix A (see comment on Q1, above, regarding repetitiveness). I read the materials in the order organized and, as a non-expert, the first read of the Letter to Administrator Pruitt and the Executive Summary were somewhat confusing and hard to follow and digest. After reading the main document, I reread the Letter and Exec. Summary and found them more comprehensible. This led me to wonder if we are somewhat missing the mark in level of communication. Both summaries tend to emphasize the findings literally but can we add language that gives important context to the non-expert. For example, can we add introductory

and closing sentences to paragraphs, ones that are jargon-free and capture the main findings and conclusions in simple but directional statements. For example, on page 2, line 10, can a sentence be added that captures the main finding regarding how EPA has dealt with the uncertainties introduced when one attempts to combine data from experiments performed on a disparate array of non-human subjects, using varied methodology, etc.

Q4) Conclusions drawn / recommendations provided supported by body of draft report?

I noted some inconsistencies in the reporting of Key Recommendations, Suggested Recommendations and Future Needs. I found the overall inclusion of such comments at the close of addressing a specific charge question or portion of a charge question to be very useful and suggest that each section have parallel structure. Right now some sections don't end with all 3 categories. Why not state explicitly that there are no further Key Recommendations at this juncture rather than omit the category. In some cases the category is omitted but in others the Key Recommendation actually not a recommendation but an endorsing statement that the SAB CAAC supports the EPA's strategy, conclusions, etc. I suggest the Key Recommendations be only the statements regarding critical changes or adjustments to the reports and, if there are none, state that there aren't any perhaps followed by a specific statement of endorsement if there is something that is worthy of explicit highlighting.

Comments from Dr. Joel Burken

1. Were the original charge questions to SAB Standing or Ad Hoc Committees adequately addressed?

Yes the original charge to Comment on the scientific soundness of the hazards or RDX exposure and dose-response assessment of RDX-induced cancer as well as noncancer health effects

2. Are there are any technical errors or omissions in the report or issues that are not adequately dealt with in the Committee's report?

None were noted.

3. Is the Committee's report clear and logical?

Yes, as a non-toxicologist, the findings were clear and I can follow the rational and information Presented

4. Are the conclusions drawn or recommendations provided supported by the body of the Committee's report?

Yes, the information provided supports the committee's report.

Comments from Dr. Joel Ducoste

- 1) **Were the charge questions to the committee adequately addressed?**

Yes

- 2) **Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?**

No

- 3) **Is the draft report clear and logical?**

Yes. However, I found the letter to the Administrator to be filled with significant technical jargon that only domain experts will likely understand its content. I would like to think that the letter should be more general to help non-domain experts to understand what are the significant challenges and/or issues related to the review. I'm ok with the Executive summary having more specific technical jargon.

4) Are the conclusions drawn or recommendations provided supported by the body of the draft report?

Yes

Comments from Dr. Robert J. Johnston

1) Were the charge questions to the committee adequately addressed?

This report is outside of my area of expertise. However, based on my reading and understanding of the material, the report has adequately addressed the charge questions.

2) Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

No, to my knowledge there are no technical errors or omissions that are not adequately addressed by the draft report

3) Is the draft report clear and logical?

Yes

4) Are the conclusions drawn or recommendations provided supported by the body of the draft report?

Yes

Comments from Dr. Kristina D. Mena

1) Were the charge questions to the committee adequately addressed?

Yes

2) Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

No, and the draft report has many citations from the literature to support comments and suggestions. In addition, the discussion surrounding the use of a 5% BMR is appropriately explained. Further, the justification for proposing a different composite uncertainty factor for

consideration is also appropriate.

Should it be recommended that EPA includes an overall, unifying section that (1) summarizes the lack of RDX studies regarding low-level exposures and dose-response effects and (2) provides specific examples of data needs along with explanations of their (potential) significance?

3) Is the draft report clear and logical?

Yes

4) Are the conclusions drawn or recommendations provided supported by the body of the draft report?

Yes

Comments from Dr. Tara Sabo-Atwood

1. Were the charge questions to the committee adequately addressed?

Yes, overall the draft SAB report responds clearly to the majority of the charge questions. A few points of clarity are highlighted below.

2. Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

I did not see any major technical errors or omissions in the report but some additional information could improve the clarity of a few points in the report (see below)..

3. Is the draft report clear and logical?

For the most part the report is well written and follows a logical flow. There are however a few areas where additional information or restructuring could provide clarity in the report:

The differentiation between 'Key Recommendations' and 'Suggested Recommendations' is not clear. While this applies in general to the report in its entirety, the recommendations for section 3.3.1.3. charge question 3a(iii) become a bit muddled, for example. The report describes a Key Recommendation to use a BMR of 5% yet this is followed by 2 additional Key Recommendations related to not adopting the first recommendation (essentially maintaining a BMR of 1%). This is in contrast to other sections where a primary Key Recommendation is followed by Suggested Recommendations. Further, each section does not have Future Needs. I think it is ok to have subsections of recommendations however the process for differentiating between Key and Suggested categories should be well defined.

There is lack of clarity regarding how ‘ecological’ or ‘nonmammalian’ studies are utilized. While the extrapolation of data from zebrafish studies are typically mechanistic in nature due to the proposed conservation of signaling networks, particularly with regard to neural systems, which is somewhat alluded to on Page 21, line 37, it is not clear how other studies may be utilized. For example, the addition of a fathead minnow study is listed as a new reference to consider (Gust et al). Expansion to more clearly relay how the addition of such nonmammalian studies contribute (or not) to the toxicological evaluation of RDX as described in the report would be useful and relevant to include in the key recommendations proposed, beyond addressing which species/studies to include.

Minor points of clarity:

- Clarification between ‘advice’ and ‘recommendations’ in the coverletter: P1, line 27.
- Page 17, line 41: the text ‘contradicted by other studies’ does not have much meaning without further explanation as to what this means in the context of testicular degeneration. Is it merely that the other studies did not note this as an observed effect? Did they specifically examine this endpoint?
- Add reference(s) to support statement on page 18 line 16: effect of RDX exposure elsewhere.
- Page 29 lines 16: ‘receptor binding and responses’ – define what ‘responses’ is referring to.
- The Key Recommendations related to inhalation reference concentrations, essentially not attempting to derive an inhalation reference concentration due to lack of data, make sense. However, there is no discussion as to whether there is a need for such data to be produced based on the relevance to exposure route of the human population. There is no ‘future recommendation’ for these sections which implies that there is no need for such studies. It is not clear if this is the intent in the report.
- Page 44 line 16: The recommendation (future needs) for ‘adequate studies’ is vague. What is meant by adequate?
- In the discussion of reproductive and developmental outcomes (Page 54 lines 18-36) there is mention of the importance of window(s) of susceptibility during development yet such windows are not defined in reference to the Hess-Ruth study discussed nor is there translation of defined windows to the recommendations and future needs.
- Assessments of immune function are discussed in the context of oral exposure studies (page 61 lines 16-27). Is this because they are the only studies available that assessed any sort of immune endpoint or is the discussion limited to an oral route of exposure (i.e. are there inhalation or aerosol studies that were not included?). Immune responses can vary greatly between oral and inhalation routes so this would be important to clarify.

4. Are the conclusions drawn or recommendations provided supported by the body of the draft report?

The conclusions and recommendations provided are well supported by the draft report in general.

I note a few places where this support could be strengthened with additional clarification (see above).

Minor editorial comments:

Page 39, line 22: 'to derive a benchmark dose'

Comments from Dr. Daniel O. Stram

1. Were the original charge questions to SAB Standing or Ad Hoc Committees adequately addressed?

Yes, they appear to have been comprehensively addressed.

2. Are there any technical errors or omissions in the report or issues that are not adequately dealt with in the Committee's report?

None that I could identify

3. Is the Committee's report clear and logical?

Overall yes

4. Are the conclusions drawn or recommendations provided supported by the body of the Committee's report?

Overall the SAB review is in agreement with the EPA report on the most important point (choice of neurotoxicity as the key hazard). Suggested changes in the uncertainty factors (specifically UF_D) and the BMR for this hazard nearly cancel out (Table 4) in terms of the recommended RfD value. Specific suggestions for other changes are made and these appear to be well-discussed in general. Some of these recommendations will take EPA some work to accommodate (e.g. separate analysis of renal effects distinct from the analysis of prostatitis provided in the EPA report)

I judge the rationale for the recommendations (even when they tend to cancel out) to be clearly articulated.

Comments from Dr. Charles Werth

- 1) Were the charge questions to the committee adequately addressed?

Yes, they were adequately addressed.

- 2) Are there any technical errors or omissions or issues that are not adequately dealt with in the draft report?

I could not identify any technical errors or omissions or issues.

3) Is the draft report clear and logical?

Yes, overall it is a very well organized and clear document. I have two minor suggestions to improve clarity that that authors can consider:

i) Page 14, Lines 3-11: This is a formatting preference, but it might help the readers if there is a brief summary of the major charge questions addressed in the report, and these could correspond to the sections that follow in the executive summary. For example, the text in this paragraph could be revised as follows:

"The Science Advisory Board (SAB) was asked by the EPA's Integrated Risk Information System 3 (IRIS) program to review the agency's Draft IRIS Toxicological Review of Hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX) (September 2016) (hereafter referred to as the draft assessment), and this involved responding to the charge questions that generally address the adequacy of i) literature search, ii) toxicokinetic modeling, iii) hazard identification and dose-response assessment for the nervous system, kidney and other urogenital systems, developmental and reproductive system, other noncancer hazards, and cancer, and iv) the oral and inhalation dose-response analyses for noncancer and cancer.

ii) Page 16, line 10: I'm assuming a BMR of 1% is a factor of 15 below the LOR data because the 1% response has to be extrapolated from higher incidents of response. Might want to add a short phrase that clarifies this, as it's not immediately clear.

4) Are the conclusions drawn or recommendations provided supported by the body of the draft report?

Yes, the conclusion drawn and recommendations provided are supported by the body of the draft report.