

Panel Members' Comments on 3-22-2017 Draft SAB Report:

Comments from Dr. Maarten Bosland:

Page 2, line 27 of the letter: Insert the word “for”: renal inflammation and for suppurative prostatitis

Page ii, line 15; Add my middle initial to my name: **Dr. Maarten C. Bosland**

Page 11, line 12: Change (40 mg.kg-day) to (40 mg/kg-day)

lines 31-32: Add to the sentence this conclusion; and there several animal studies that did not find male reproductive system effects. There is no

Page 12, lines 30-32: Change this to: The SAB has concerns with the unexpectedly low 1.5% incidence of liver tumors in control female B6C3F1 mice and its impact on dose-response modeling. And delete: The 1.5% incidence of liver tumors in the control B6C3F1 mice is unexpectedly low.

Page 21, line 11: Add the word “made”: have in the past made and might in the future make

Page 25, lines 30-31: I have two questions here: This (**meaning the Crouse study? If yes add the word study**) and several other studies in the select group (**what is meant by the “select group”?**) reporting effects on neurological health utilized gavage administration as opposed to a dietary route of administration.

Page 28, line 5: Change: “The SAB believes that uncertainty” to: “The opinion of the SAB is that uncertainty”

Page 33, lines 27-28: Change to: The available human, animal, and mechanistic studies support the conclusion that toxicity to the kidney and other components of the urogenital system ~~toxicity are~~ is a potential human hazard of RDX exposure.

Page 36, line 29: Delete the first word, “However”, because there is no contrast made here.

Page 37, line 33: Change: Briefly include a discussion to: Include a brief discussion

Page 40, line 13: Change: renal inflammation for the kidney and urogenital system to: renal inflammation of the kidney and urogenital system

Page 41, line 6: Add this sentence: support this statement. In addition, there are several animal studies that did not find effects on the male reproductive system. There is no human evidence

Page 48, line 19: Delete the word do: humans, or ~~do~~ that existing data

Page 51, lines 17-18: Change: Similarly, the high dose in the Levine et al. dietary study in rats was 40 mg/kg, and mortality was high throughout the study period of 24 months. To: Similarly, at the high dose in the Levine et al. dietary study in rats (40 mg/kg-day) mortality was high.

line 36: Change: liver tumors in control males may have been on the high end To: liver tumors in control males was on the high end

line 44: Change: (175/100 mg/kg-day) were included in the trend test To: (175/100 mg/kg-day) was included in the trend test

Page 52, lines 34-35: Change: Non-neoplastic histopathological changes in the liver were absent in the majority of subchronic studies available in the literature, and pre-neoplastic lesions To: Non-neoplastic histopathological liver changes. Non-neoplastic histopathological changes in the liver were absent in the majority of subchronic studies available in the literature, and pre-neoplastic lesions.....

Page 53, line 14: Delete the word trace: to link ~~trace~~ gross lesions observed.....

Page 55, lines 14-16: Add and delete words: and at the low end of the range of ~~lower than~~ the incidences in control females reported for this mouse strain by the National Toxicology Program (NTP) (mean 8%, range 0-20%). This ~~unusually~~ low control incidence could significantly influence the estimate of the POD.

Page 56, line 43: Change to: the majority of ~~the~~ other dietary and gavage studies

Page 60, lines 10-13: Change: The SAB was able, using original study data, to determine that there is little biological or statistical support that the two tumors used in the MS-COMBO analysis have dependent tumor incidence, hence the assumption of independence is concluded, and the MS-COMBO approach is valid. To: The SAB was able, using original study data, to determine that there is no biological or statistical support for the notion that the two tumors used in the MS-COMBO analysis are interdependent. Hence, the assumption of independence of the two tumor sites and the MS-COMBO approach are considered valid.

line 40: Change “rate” to “control incidence”

Page 61, lines 16: Delete the word “per”

line 39: Insert the word toxicological: “.... are of more toxicological importance and”

Page 62, line 2: replace e.g., with i.e.

line 12: Change: effect could also be secondary to inflammation without a bacterial infection. To: inflammatory effect could also occur without a bacterial infection.

line 14: Replace the word “fine” with “justified”

Comments from Dr. George Cobb:

Statements on p.12 LL16-19 contains text: *The SAB identified a number of limitations for these studies and determined that the evidence for a positive tumor response to RDX in two species, two sexes, or two sites, required by EPA's Guidelines for Carcinogen Risk Assessment (USEPA, 2005) for a "likely to be carcinogenic to humans" descriptor, is weak or absent.*

This statement is overly critical of data that support the descriptor of likely to be carcinogenic. Any data limitations that exist are a function of studies being poorly controlled and a lack of follow up testing to improve data quality. The last phrase of this sentence should more appropriately read, "would require more testing to confirm."

This comment also pertains to wording on p.53 L43.

Comments from Dr. Melanie Marty:

Page 2 (letter to the Administrator), line 20 (and elsewhere, see comments below): The document states "The SAB recommends the assessment use the NOAEL from the Cholakis study as the primary basis for the derivation of a RfD for neurotoxicity in addition to the dose-response data of the Crouse study." It is not clear from this wording what we mean by "in addition to the dose-response data form the Crouse study". Also, we should clarify what NOAEL we are talking about, since Cholakis reports a number of experiments. Perhaps we could reword this sentence (underlined) as follows: The SAB recommends the assessment use the NOAEL of 0.2 mg/kg-d from the Cholakis teratology study as the primary basis for the derivation of a RfD for neurotoxicity, while including the analysis of the dose-response data of the Crouse study as supporting information". I think this fits with what was discussed by the Panel.

Page 9, line 16. The sentence starting with "However, the evidence presented in the draft assessment does not adequately depict RDX's hazards to the nervous system, that convulsions in rodents ... " needs a grammatical fix. Suggest we add "The SAB concludes that" so that the sentence reads: However, the SAB concludes that the evidence presented in the draft assessment does not adequately depict RDX's hazards to the nervous system, ...".

Page 10, line 32. Suggest to modify the sentence with the changes underlined as follows: "The SAB recommends the assessment use the NOAEL of 0.2 mg/kg-d from the Cholakis teratology study as the primary basis for the derivation of a RfD for neurotoxicity, while including the analysis of the dose-response data of the Crouse study as supporting information".

Page 11, line 31. It would be appropriate to add a bit more of the rationale for indicating the SAB does not agree that RDX is a male reproductive toxicant. Suggest adding the underlined text: "The available animal evidence based on testicular degeneration in male mice exposed to RDX in their diet for 24 months (Lish et al. 1984), is weak, unsupported by other endpoints in that study showing no effect, complicated by the age of the mice and general toxicity of the RDX dose, and contradicted by most other studies. In short, the database as a whole does not support this conclusion.

Page 12 line 2. It would be clearer to amend the sentence (underlined) as follows: “The SAB recommends EPA use the NOAEL of 0.2 mg/kg-day from the Cholakis teratology study as the POD to calculate the RfD.”

Page 13 line 24. The sentence would be clearer if amended as follows: “There are no toxicokinetic data from inhalation studies of RDX in laboratory animals or humans, no inhalation carcinogenicity bioassays of RDX, nor data on cancer incidence in humans.”

Page 16, line 11. The sentence starting on line 11 should start a new paragraph.

Page 17, line 8. The sentence needs a minor modification to be grammatically correct as follows: “Although these are minor metabolites in aerobic systems, some reductive transformation products of RDX are present in ground waters near munitions and training facilities, and some are produced in the GI tract of mammals, and are present in the blood and target tissues of dosed mammals.”

Page 17, line 26 The recommendation needs the word “briefly” before “discussed. We aren’t asking for a whole new assessment of the breakdown products of RDX.

Page 22, line 23. There is a typo (*Quesiton* instead of question), and Line 35 Toxicokinetics needs to be capitalized.

Page 23, line 30. Need to either use the words greater than or the symbol, but not both.

Page 31, line 32 The sentence needs amending to be grammatically correct as follows: “In ~~the a~~ reproductive toxicity study of Cholakis et al. (1980), dosing pregnant dams with RDX, Cholakis et al. (1980) recorded incidence data for convulsions that resulted in a 5-fold lower POD than the subchronic study of Crouse et al. (2006), and the candidate RfD.”

Page 33, line 11. Suggest a rewording of the sentence for clarity and consistent with suggestions above. “Therefore, the draft assessment should utilize the NOAEL and data from the Cholakis et al. (1980) teratology study as the primary basis for the RfD, while including the analysis of the dose-response data of the Crouse (2006) study as supporting information”

Page 33, line 11. Should replace the word “warranted” with “scientifically-supported”, which is more in line with the charge question.

Page 43 , line 31. Suggest we modify this sentence: “Regarding the application of such results to the human population, effects of a toxicant on sperm production in aged men is not considered an important reproductive risk, as such men rarely desire to have children.”. Whether or not an older man wants children, if a toxicant acts on sperm production in an older man, then there is toxicity and this should be recognized. Suggested amendment: “Regarding the application of such results to the human population, effects of a toxicant on sperm production in aged men, although indicative of toxicity, may not be considered an important reproductive risk, as such men rarely desire to have children.”

Page 43, line 41. Need the word “by” in front of Lish et al so that the sentence reads correctly.

Page 44, line 19 “at” should be “a”. And line 25, need a period at the end of the sentence.

Page 51, lines 11-38. This section discusses the high mortality in the high dose groups in the Lish et al cancer bioassay. It is not clear to me how this links with the decision regarding the hazard descriptor. The comment seems to say the high doses should not be considered given excessive mortality in both the mouse and rat studies. If there is high mortality that reduces the number of animals living long enough to develop tumors, then that reduces the chance of observing an effect. Yet, for the female B6C3F1 mice, a statistically significant increased incidence of liver tumors is observed in the high dose group relative to control, and there is a positive trend test when including the high dose group. In the rat study, including the high dose results in a positive trend test for carcinoma in males. Despite a smaller sample size in the high dose group in both rats and mice, elevated incidence of liver tumor is still observed. From a statistical point of view, this adds to the evidence for carcinogenicity because of the lower power to detect an effect. I agree that the rat liver tumor evidence is weak, and note that the draft assessment indicates the trend is positive only for carcinoma and not adenoma plus carcinoma. But, I would prefer to delete the phrase “and does not support a carcinogenic effect of RDX” at the end of the sentence on line 38 “Although the incidence of benign liver tumors in control males may have been on the high end of the range for historical controls (Haseman et al. 1985), the evidence for an association of RDX exposure with increased liver tumors in this rat study is weak and does not support a carcinogenic effect of RDX. In my view, the data in the rats contributes to the findings of carcinogenicity (although I agree with the hazard descriptor of suggestive rather than likely).

Page 52, lines 16-21. The report discusses the concern around a low incidence of liver tumors in the female control mice in Lish et al. We cite the mean incidence in the NTP historical control dataset as 8%. We should probably add the range which runs from 0 to 20%. It is the case that the concurrent control incidence was lower than the mean historical incidence, but in my view, that does not negate the observations of elevated tumor incidence. The draft assessment (p. 1-62, lines 4-9) states that there was still a statistically elevated liver tumor incidence in the high dose female mice compared to the historical control incidence. I note that it is always preferable to utilize concurrent controls when evaluating hazard for a number of reasons (including differences across labs, housing, feed, pathologists, etc). As noted in our report discussing the dose-response assessment, a low concurrent control incidence relative to historical controls introduces some uncertainty in the result.

Page 52, line 24. We should change “a pathologist” to “pathologists”. According to the draft assessment, there was a group of pathologists in the PWG re-examining the female liver tumor slides from Lish et al.

Page 53, lines 18-38. This section discusses evidence regarding a mechanism of action of RDX as a carcinogen. We should add that there are some data indicating the minor metabolites MNX and TNX are mutagenic. Also, I note that knowing the mode of action is not a pre-requisite to identifying a chemical as a carcinogen. Perhaps we could add a sentence similar to the

following: While understanding the mode of action can sometimes support a concern for carcinogenicity, it is not requisite to the determination of hazard.

Page 53, line 23 typo. 4-nitro-2,4-diazbutanal should be 4-nitro-2,4-diazabutanal.