

**Summary Minutes of the
U.S. Environmental Protection Agency
Chemical Assessment Advisory Committee Augmented for the Review of the Draft
IRIS Hexahydro-1,3,5-trinitro-1,3,5-triazine Assessment (CAAC- RDX Panel)
Public Meeting
December 12 – 14, 2016
Washington, DC**

Purpose: To peer review the EPA's draft *Toxicological Review of Hexahydro-1,3,5-trinitro-1,3,5-triazine (External Review Draft – September 2016)*

Meeting Participants:

CAAC- RDX Panel Members (See Roster):

Dr. Kenneth Ramos, CHAIR	
Dr. Hugh Barton	Dr. Melanie Marty
Dr. Maarten Bosland	Dr. Marvin Meistrich
Dr. Mary Boudreau	Dr. Marilyn Morris
Dr. James Bruckner	Dr. Victoria Persky
Dr. George Cobb	Dr. Isaac Pessah
Dr. David Eastmond	Dr. Kenneth Portier
Dr. Joanne English	Dr. Samba Reddy
Dr. Alan Hoberman	Dr. Stephen Roberts
Dr. Jacqueline Hughes-Oliver	Dr. Thomas Rosol
Dr. Susan Laffan	Dr. Alan Stern
Dr. Lawrence Lash	Dr. Robert Turesky
Dr. Stephen Lasley	

SAB Staff Office: Dr. Diana Wong, Designated Federal Officer
Mr. Christopher Zarba, Director, Science Advisory Board Staff Office
Ms. Khanna Johnston, Acting Deputy Director, Science Advisory Board Staff Office

Other Attendees: see Attachment A.

Meeting Materials and Meeting Webpage:

The materials listed below may be found on the meeting webpage at:

<https://yosemite.epa.gov/sab/sabproduct.nsf/MeetingCal/F5EC596D0298DE3685258020006E792D?OpenDocument>

- Agenda
- Federal Register Notice
- Charge Memos

- Review Documents
- Agency Briefing Material
 - EPA Presentation on Draft IRIS Assessment of RDX.
- Committee-Developed or Provided Background Material
 - Compilation of Slides developed as Draft Responses to Charge Questions based on discussion on December 12 -14, 2016
- Committee Members Comments
 - Compilation of Revised Comments from Members of the CAAC Augmented for the Review of EPA's Draft IRIS Hexahydro-1,3,5-trinitro-1,3,5-triazine assessment (September, 2016).
 - Preliminary Comments from Members of the Chemical Assessment Advisory Committee Augmented for the Review of the EPA's draft IRIS RDX Assessment.
 - Preliminary Responses to Charge Questions Additional comments from from Dr. Marvin Meistrich
 - Preliminary Responses to Charge Questions from Dr. Issac Pessah.
 - Preliminary Responses to Charge Questions from Dr. Stephen Lasley.
 - Preliminary Responses to Charge Questions from Dr. Marilyn Morris.
 - Preliminary Responses to Charge Questions from Dr. Thomas Rosol

Meeting Summary

The discussion followed the plan presented in the meeting agenda.

MONDAY, DECEMBER 12, 2016

Opening Remarks

Dr. Wong convened the meeting at 9:00 a.m. She explained that the SAB is an independent, expert federal advisory committee chartered under the authority of the Federal Advisory Committee Act (FACA). The SAB is empowered by law, the Environmental Research, Development, and Demonstration Authorization Act (ERDDAA), to provide advice to the EPA Administrator on scientific and technical underpinnings of the EPA's decisions. FACA and EPA policy require that SAB meetings be announced to the public in the Federal Register and that substantive deliberations, and interactions with EPA and the public, be conducted in open sessions where a DFO is present to ensure that the requirements of FACA are met. FACA also requires that advisory committees provide an opportunity for public comment. Dr. Wong explained that there were two opportunities for public comment noted on the meeting agenda. The agenda included a public comment session on Monday for members of the public who had registered in advance with the SAB Staff Office to make oral comments (No one has registered to speak). There would be another opportunity on Tuesday afternoon for the public to provide brief clarifying remarks.

Mr. Christopher Zarba, the Director of the SAB Staff Office, welcomed and thanked panel members for their willingness to serve on this panel. Dr. Wong turned the meeting over to Dr. Ramos, Chair of the CAAC-RDX Review Panel.

Dr. Ramos reviewed the agenda and asked panel members to briefly introduce themselves. He then invited the EPA representatives to begin their presentations. Dr. Vince Cogliano, director of the IRIS Program in EPA's National Center for Environmental Assessment (NCEA), thanked the Panel for their review of the assessment and provided a history of the development of the RDX assessment. He noted that the draft assessment had been revised after undergoing a public comments period, and the charge questions were augmented by public comments.

Dr. Lou D'Amico, the RDX assessment manager, then presented the key aspects of the RDX assessment and answered questions from the panel. The EPA presentation can be found on the meeting webpage.

Public Comments

After a short break, the panel reconvened to hear public comments. No public speakers registered to provide comments to the panel.

Discussion of Response to Charge Questions

Charge Question #1 – Literature Search

The panel agreed that the literature review process was well described and documented. The panel found that the literature search strategy was comprehensive, with the exception that some RDX metabolites, such as, MEDINA and related oxidative transformation products, have not been included in the draft assessment. In addition, the panel noted that a description of the role of GABA in brain development should be included in the draft assessment. The inclusion/exclusion criteria for studies were well described and, for the most part, appropriate. One exception was the exclusion of non-mammalian studies that may not be appropriate given the current use of zebrafish and other non-mammalian models for the determination of Adverse Outcome Pathways. The panel also provided additional references for consideration that address the toxicity of reductive transformation products, and the role of GABAergic systems during development and the potential for RDX developmental neurotoxicity.

Charge Question #2 – Toxicokinetic Modeling

#2a – Model Evaluation

The panel agreed the PBPK model used in the draft RDX assessment was a reasonable model for use in the assessment. The model and inputs were well documented and supported by the available scientific information, which was adequate but limited. The panel also commented that EPA had made distinctive improvements on the published models and the uncertainties in the model were well described.

#2b – Selection of Dose Metric

The panel agreed the use of plasma RDX area under the curve (AUC) was the preferred and appropriate dose metric for neurotoxicity. For other rat toxicity endpoints, the rationale for the selection of the AUC as the dose metric needed to be explained.

#2c – Intra-human Variation

The panel agreed that given the limitations of the available data, it would not be reasonable to assess human variability using a PBPK model. Therefore, use of the default human inter-individual variability uncertainty factor (UF_H) of 10 was supported.

After lunch, the panel reconvened to discuss Charge Question #3b before continuing to address Charge Question #3a.

Charge Question #3 – Hazard Identification and dose-response Assessment

#3b – Kidney and Other Urogenital System Effects

#3b(i) – Kidney and other Urogenital System Hazard

The panel agreed that kidney and other urogenital system toxicity was a potential human hazard of RDX exposure. This conclusion was primarily supported by animal data. Available human studies were sparse. There were no pertinent mechanistic data. The panel believed all hazards to the kidney and urogenital system were adequately assessed and described, except for the description of inflammatory changes in the rat prostate. The panel noted that the description of prostatic inflammatory changes in the draft assessment should include not only suppurative inflammation, but also chronic inflammation.

The panel found that the selection of suppurative prostatitis as the endpoint to represent this hazard was clearly described, but not scientifically supported. There was no known biological basis for using suppurative prostatitis as a surrogate marker for renal and other urogenital system effects. The panel also concluded that there was uncertainty about the association of suppurative prostatitis with the renal toxicity effects which were found only at the highest dose.

#3b(ii) – Kidney and other Urogenital System-specific Toxicity Value

The panel agreed that the selection of Levine et al. (1983) study which found kidney and other urogenital system effects were clearly described, but not fully supported scientifically. Kidney effects were found in other animal studies. Renal medullary mineralization was found in male and female Cynomolgus monkeys, and cortical tubular nephrosis was found in male mice at very high RDX dose. The panel noted that the marked sex differences in renal toxicity due to RDX exposure found in rats by Levine et al. (1983) was not discussed in the draft assessment.

#3b(iii) – Points of Departure for Kidney and other Urogenital System Endpoints

When using suppurative prostatitis as an endpoint, the panel found the calculation of a POD and HED for Levine et al. (1983) to be scientifically supported and clearly described.

However, the panel strongly recommended that the EPA treat suppurative prostatitis as a stand-alone endpoint, separate from kidney and other urogenital system endpoints.

#3b(iv) – Uncertainty Factors for Kidney and other Urogenital System Endpoints

The panel found the application of uncertainty factors to be appropriate, except for the database uncertainty factor (UF_D). EPA applied an UF_D of 3 to account for inadequacies in the database. The panel recommended an UF_D of 10 be applied to derive the overall RfD. For an endpoint-specific RfD, a different UF_D may be warranted.

#3b(v) – Kidney and other Urogenital System-specific Reference Dose

The panel found the organ/system-specific RfD derived for kidney and other urogenital system effects not scientifically supported and not clearly characterized. This was because the selection of suppurative inflammation of the prostate observed in Levine et al. (1983) study as “surrogate marker” of the observed renal and urogenital system effects was not justified. The panel recommended separate RfDs be considered for renal papillary necrosis and associated inflammation, and for suppurative prostatitis.

#3a – Nervous System Effects

#3a(i) – Nervous System Hazard

The panel agreed that available human, animal, and mechanistic studies support the conclusion that nervous system toxicity is a human hazard of RDX exposure. However, the panel found all hazards to the nervous system have not been adequately assessed, and believed the draft assessment did not fully depict RDX’s hazards to the nervous system. Convulsive or non-convulsive seizures, epileptiform discharges, reduction in seizure threshold, subchronic sensitization, and neuronal damage were all part of the spectrum of RDX’s nervous system hazards. Endpoints such as convulsions, tremors and aggression are appropriate as part of the spectrum of effects.

#3a(ii) – Nervous System-specific Toxicity Values

The panel concluded that the selection of studies reporting nervous system effects was scientifically supported and clearly described. The panel agreed the gavage study of Crouse et al. (2006) was adequate for dose-response assessment as it has the most dose points and was longer in duration. However, there were uncertainties associated with the study since the animals were not monitored 24 hours per day, 7 days a week. The panel also agreed with the selection of convulsions as a severe endpoint, and its potential relationship to mortality were appropriately described. The panel noted that death may occur without seizure or convulsions.

#3a(iii) – Points of Departure for Nervous System Endpoints

The panel found the selection of convulsions as the endpoint to represent nervous system hazard for RDX was clearly described. Evidence from other seizurogenic compounds with similar modes of action suggested additional subtle cognitive and behavioral neurological effects likely existed for RDX. The panel agreed the probable dose range between convulsion and other nervous system effects could be addressed using the uncertainty factor adjustments. The panel found that given the presumption that the Crouse et al. (2006) was the appropriate choice for the derivation of an RfD, and given EPA’s choice of

a BMR of 1% for deriving a BMDL from Crouse et al. (2006) by benchmark dose modeling, the POD for convulsions was clearly described and correctly calculated. The panel also agreed the calculations of the HEDs for these studies was scientifically supported and clearly described. However, the panel did not agree with EPA's use of a BMR of 1% for benchmark dose modeling of Crouse et al. (2006) data for convulsions, as uncertainty increases with extrapolation of estimates at BMRs below the observable range of response data. The panel concluded a BMR of 5% based on Crouse et al. (2006) would be more consistent with the observed response at the Lowest-Observed-Adverse-Effect-Level (LOAEL) of 15%. While the panel agreed convulsion is a severe endpoint, and the proximity of dose-response for convulsions to dose-response for lethality is a valid source of uncertainty, this uncertainty should be addressed through uncertainty factors.

The panel found the calculation of the lower bound on the benchmark dose (BMDL) for convulsions to be appropriate and consistent with EPA's Benchmark Dose Guidance.

#3a(iv) – Uncertainty Factors for Nervous System Endpoints

The panel agreed with the application of an interspecies uncertainty factor of 3 to account for the toxicodynamics and residual toxicokinetic uncertainty in extrapolation from animal to human, a subchronic to chronic uncertainty factor of 1, a LOAEL to No-Observed-Adverse-Effect-Level (NOAEL) uncertainty factor of 1, and the uncertainty factor 10 to account for intra-human variability. However, the panel disagreed with the application of a database uncertainty factor of 3, and recommended EPA consider applying a UF_D of 10 to account for data gaps for developmental neurotoxicity, lack of incidence data for less severe effects, and the proximity of convulsive dose to lethality dose.

#3a(v) – Nervous System-specific Reference Dose

The panel did not find the organ/system-specific reference dose derived for nervous system effects scientifically supported and clearly characterized. The proposed RfD did not capture all of the potential adverse outcomes or their severity. The panel recommended the assessment use the NOAEL from Cholakis et al. (1980) as the primary basis for the derivation of the RfD.

The panel concluded their deliberation for the day and Dr. Wong recessed the meeting at approximately 5:30 pm.

TUESDAY, DECEMBER 13, 2016

Dr. Wong reconvened the meeting at 8:30 am. Dr. Ramos continued to lead the discussion on responses to charge questions.

#3c – Developmental and Reproductive System Effects

#3c(i) – Developmental and Reproductive System Hazard

The panel concluded that the available animal data did not support EPA's conclusion of suggestive evidence for male reproductive effects. The panel also concluded, based on the

data reviewed, that there was enough available evidence in animal studies indicating that RDX exposure did not represent a teratogenic hazard to humans. Additionally, the panel agreed that no conclusions could be drawn regarding other forms of developmental toxicity, which occurred only at maternally toxic dose levels. The panel also noted that other hazards to human reproductive and developmental outcomes were not adequately addressed. There is potential neurodevelopmental toxicity based on the reported mechanism of RDX inhibition of GABAergic neurons and the findings that RDX was present in the brain of developing rats and in milk during lactation when the dam was administered RDX during gestation.

#3c(ii) – Reproductive System-specific Toxicity Values

The panel concluded that after consideration of all presented evidence from the available studies, the selection of the Lish *et al.* (1984) study that described male reproductive system effects was not scientifically supported and clearly described. Effects observed at 24 months were the result of aging, and not the result of treatment.

#3c(iii) – Points of Departure for Reproductive System Endpoints

The panel did not support the use of Lish *et al.* (1984) for describing male reproductive system effects. Given that Lish *et al.* (1984) was the data source for dose-response modeling and subsequent derivation of the POD and HED, the panel was concerned about the validity of the derived POD and HED.

#3c(iv) – Uncertainty Factors Reproductive System Endpoints

The panel believed the UF_D should be endpoint-specific. However, the panel did not support the derivation of a RfD based on male reproductive system effects. Thus, the question of uncertainty factors, as applied to the POD, was extraneous.

#3c(v) – Reproductive System-specific Reference Dose

Since the selection of Lish *et al.* (1984) for representing the male reproductive effects was not scientifically supported, the panel concluded the RfD should not be calculated from the data provided in this study.

#3d – Other Noncancer Hazard

The panel found that other noncancer hazards were well described. However, dose-related effects on body weights and/or body weight gains should be addressed. In addition, neuro-inflammatory changes that may influence the conclusions about the immune system should be considered.

Break

#3e – Cancer

#3e(i) – Cancer Hazard

The panel agreed that the available human, animal, and mechanistic studies support the descriptor that there was “*suggestive evidence of carcinogenic potential for RDX*” and this descriptor applied to all routes of human exposure. The panel also identified several

limitations in the available studies, namely, the studies by Lish *et al.* (1984) and Levine *et al.* (1983).

#3e(ii) – Cancer-specific Toxicity Values

The panel found the draft assessment adequately explains the rationale for quantitative analysis considering the uncertainty of the data and the suggestive nature of the weight of evidence. The panel also found the selection of the Lish *et al.* (1984) study for this purpose is scientifically supported and clearly described.

#3e(iii) – Point of Departure for Cancer Endpoints

The panel found the approach for calculating the POD was not clearly described. The panel noted there was paucity of data on mode of action, so there was no support for the dose-response model form. Since the mode of action was unknown, the panel supported the default approach to use linear low-dose extrapolation in the RDX draft assessment, as recommended in EPA's 2005 cancer guidelines. There were concerns about the quality of the scientific support of the methodology used in the derivation of the point of departure. These concerns included the low incidence of liver tumors in female mice, and its impact on dose-response modeling.

Lunch

Charge Question #4 – Dose-Response Analysis

#4a – Oral Reference Dose for Effects other than Cancer

The panel found that EPA clearly described the process and choices made to derive the oral RfD. However, the panel concluded that the scientific support for the proposed oral RfD was weak, as it did not take into account confirmed convulsions in exposed pregnant female animals at the much lower dose of 2 mg/kg-day in Cholakis *et al.* (1980). The panel observed that while there was tighter dose spacing and a cleaner model fit from Crouse *et al.* (2006), the lower NOAEL/LOAEL from Cholakis study should not be disregarded. The panel recommended that the NOAEL of 0.2 mg/kg-day from the Cholakis study should be used as the POD for the derivation of an RfD. This option eliminated the problem with the choice of an appropriate BMR from Crouse *et al.* (2006).

#4b – Inhalation Reference Concentration for Effects other than Cancer

The panel believed it was reasonable to not derive an RfC since neither inhalation pharmacokinetics nor inhalation toxicity studies were available. Thus, route-to-route extrapolation of pharmacokinetics could not be supported.

#4c – Oral Slope Factor for Cancer

The panel commented that the derivation of the oral slope factor was not clearly described. The panel also concluded that proper justification for only considering the multi-stage dose-response models was not provided. The panel stated that the design and use of the MS COMBO model should be clearly explained and that a better explanation for the procedure should be provided. The panel was concerned that the female liver cancer concurrent controls were low compared to available historical control rates, and that the highest dose in Lish *et al.* (1984) was above the maximum tolerated dose. Therefore, they suggested that

the POD may be calculated by excluding the highest dose level. This would change the POD and in turn change the oral slope factor.

#4d – Inhalation Unit Risk for Cancer

The panel agreed that the available data do not support an inhalation unit risk since there are no toxicokinetic data for inhalation of RDX, and there has not been an inhalation cancer study of RDX conducted.

Break

Charge Question #5 – Executive Summary

The panel observed that the current executive summary adequately summarizes the findings and conclusions in the draft assessment. The panel noted that, as the EPA makes changes and revises the assessment, the executive summary should also be revised to reflect those changes.

The meeting recessed at approximately 5:30 p.m. until the next morning. The writing teams for various charge question met to prepare summary slides for presentation.

WEDNESDAY, DECEMBER 14, 2016

Dr. Wong reconvened the meeting at 9:00 am, and introduced SAB's Acting Deputy Director, Khanna Johnston, to the panel. Dr. Ramos asked the leaders of all writing teams to present their summary slides for panel discussion. The summary slides for the draft responses to the charge questions were revised based on panel discussion and can be found at the link below:

[https://yosemite.epa.gov/sab/sabproduct.nsf/C135EEC114F42976852580A30063EBAA/\\$File/Compilation+of+Summary+Slides+1-9-17.pdf](https://yosemite.epa.gov/sab/sabproduct.nsf/C135EEC114F42976852580A30063EBAA/$File/Compilation+of+Summary+Slides+1-9-17.pdf)

Brief Clarifying Comments

Samantha Jones of EPA's IRIS program thanked the panel for their participation on this review. She stated that she looked forward to seeing the panel's report.

Next Steps

Dr. Wong informed the panel of the follow-up action items for preparing the draft panel report. Lead writers were asked to revise the summary slides and send them to their team members for consensus before sending the slides to the DFO. The revised summary slides were due on Tuesday, December 20, 2016. Panel members who wanted to revise their preliminary comments should send their revised individual comments to the DFO by Wednesday, December 21, 2016. The written responses to the charge questions were due on Friday, January 20, 2017. Lead discussants were asked to initiate the write-up and circulate the responses to team members for consensus before sending to the DFO. Dr.

Wong then reminded panel members that the follow-up public teleconferences to deliberate on the draft panel report were scheduled for April 13 and 17, 2017 from 1:00 p.m. to 4:00 p.m., EST.

Dr. Wong thanked the Panel and adjourned the meeting at approximately 1:00 pm.

On Behalf of the Committee,
Respectfully Submitted,

_____/s/
Diana Wong, Ph.D.
Designated Federal Officer

Certified as True:

_____/s/
Kenneth S. Ramos, MD, Ph.D.
Chair, SAB CAAC-RDX Review Panel

NOTE AND DISCLAIMER: The minutes of this public meeting reflect diverse ideas and suggestions offered by committee members during the course of deliberations within the meeting. Such ideas, suggestions, and deliberations do not necessarily reflect definitive consensus advice from the panel members. The reader is cautioned to not rely on the minutes represent final, approved, consensus advice and recommendations offered to the Agency. Such advice and recommendations may be found in the final advisories, commentaries, letters, or reports prepared and transmitted to the EPA Administrator following the public meetings.

Attachment A. Other Attendees

a. List of persons who attended the meeting in person:

Name	Affiliation
Desmond Bannon	DOD
Lou D'Amico	EPA
Todd Blessinger	EPA
Melissa Branigan	EPA
Shaunta Hill	EPA
Vince Cogliano	EPA
Tom Carpenter	EPA
Susan Reith	EPA
Dahnish Shams	EPA
Sue Shallal	EPA
Samantha Jones	EPA
Edward Ohanian	EPA
Gina Perovich	EPA
Maria Hegstad	Inside EPA

b. List of Persons who Registered to Attend the Meeting by Calling-In:

Ravi Subramaniam	EPA
Vicki Soto	EPA
Christine Cai	EPA
Channa Keshava	EPA
Jim Kim	OMB
Abraham Lustgarten	ProPubica
Maria Spassova	EPA