

**MINUTES FROM THE EPA SCIENCE ADVISORY BOARD**  
**Acrylamide Review Panel**  
**Public Face-to-Face Meeting**  
**March 10-11, 2008**

**PURPOSE:** The Acrylamide Review Panel of the EPA Science Advisory Board (SAB) met on March 10-11, 2008. The purpose of this meeting was to allow panel members to deliberate on the charge questions developed by the Agency on its draft IRIS review entitled, *Toxicological Review of Acrylamide*. The SAB Acrylamide Review Panel was being asked to comment on the scientific soundness of EPA's IRIS assessment. Attachment A is the Federal Register notice announcing the meetings (73 FR 22:6182-6183 February 1, 2008). A meeting agenda is included as Attachment B.

**LOCATION:** Melrose Hotel, Washington, DC.

**DATES:** MARCH 10 – 11, 2008.

**PARTICIPANTS:** The following individuals participated in this meeting: SAB Committee and Board Members - Drs. Deborah Cory-Slechta (Chair), Alfred Branen, Daniel Doerge, James Felton, Timothy Fennell, Penelope Fenner-Crisp, Jeffery Fisher, Sean Hays, Steven Heeringa, Richard LoPachin, Lorelei Mucci, Jerry M. Rice, Dale Sickles, Gina Solomon, Anne Swenney, Lauren Zeise. The Review Panel roster is included as Attachment C and a set of biographical sketches is included in Attachment D. SAB Staff - Dr. Sue Shallal and Resha Putzrath, Designated Federal Officers (DFO); EPA Presenters – Ila Cote, Rob Dewoskin Other Participants – Other EPA staff and members of the public were also present. A partial list of names is attached (Attachment E).

**MEETING SUMMARY:** The meeting deviated from the agenda (Attachment B) and took place over two days instead of the two and one-half days that were originally planned. A summary of the meeting follows.

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### **MARCH 10, 2008**

Convene the Meeting and Introductory Remarks – Dr. Suhair Shallal, Designated Federal Officer (DFO), opened the meeting at 9:05 AM after allowing time for panel members to take their seats. She presented background information on the SAB panel formation process and informed the audience that the SAB operates under the rules and regulations of FACA where all meetings, during which discussions and deliberations take place, are held in public. She also reminded the members of the panel and the audience that the background materials including the charge questions (Attachment F) can be found on the table at the entrance to the meeting room and on the SAB website.

Welcome - Dr. Cory-Slechta, the Chair of the Panel, reviewed the agenda and explained the purpose of the meeting. She stated that the meeting would begin with presentations from the Agency and panel members would be able to ask clarifying questions. She reminded panel members that she had assigned individuals as lead discussants for each topic of the charge questions. She explained that the lead discussants would be called upon to provide their comments and then other panel members would have an opportunity to add to them.

### **Agency Presentations**

Ila Cote of the EPA National Center for Environmental Assessment thanked the Panel members for their work on the Panel and she provided some background information on the Acrylamide IRIS assessment. Rob Dewoskin then followed with his presentation. Dr. Dewoskin presented an overview the Acrylamide IRIS assessment (Attachment G). He elaborated on the findings of the Agency's evaluation of the data. He then explained the conclusions reached in the draft IRIS assessment. He outlined the methods and the model that were used. He explained how the risk estimates were derived, as well as, the data sets, model assumptions, the adjustment factors used and the uncertainties associated with the modeling. Panel members had an opportunity to ask clarifying questions after the presentation period.

Presentations: Agency presentation may be found posted at

<http://yosemite.epa.gov/sab/sabproduct.nsf/MeetingCal/4C24E314EE7DB345852573C4007A1907?OpenDocument>

- SAB Review : IRIS Toxicological Review of Acrylamide

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### Public comments

Dr. Cory-Slechta then introduced the public commenters. There were 6 individuals who had registered to present public oral comments, Bob Fensterheim of the North American Polyelectrolyte Producers Association (NAPPA) and Dennis Marroni of SNF, Ernest E. McConnell of ToxPath Inc., Marvin A. Friedman, Senior Scientific Advisor, SNF S.A.S, Errol Zeiger and Annette Shipp of Environ Corp (Dr. Shipp did not attend and Dr. McConnell made the presentation on her behalf). As there was additional time available, Dr. Michael Dourson of TERA also presented his comments.

All public comments provided in writing may be found posted at

<http://yosemite.epa.gov/sab/sabproduct.nsf/MeetingCal/4C24E314EE7DB345852573C4007A1907?OpenDocument>

- Comments from Dr. Ernest E. McConnell, ToxPath Inc.
- Comments from Dr. Marvin A. Friedman, Senior Scientific Advisor, SNF S.A.S
- Comments from Dr. Errol Zeiger
- Comments from Dr. Annette Shipp, Environ Corp
- Comments from Dr. Michael Dourson of TERA
- Comments from North American Polyelectrolyte Producers Association (NAPPA)

### Discussion of Charge Questions

Dr. Cory-Slechta thanked the public commenters. The lead responders for each question were asked to present their comments. Other panel members then provided their insight. Charge question assignments are listed in the table below:

NON-CANCER ISSUES	CANCER ISSUES	PBTK MODELING
Chapters 4 and 5		Chapters 2 and 3
Charge Questions 1-7 and 13-17	Charge Questions 18-26	Charge Questions 8-12
Brannen	Doerge	Fennell
Fenner-Crisp	Felton	Fisher
LoPachin	Mucci	Hays
Solomon	Rice	Heeringa
Sickles	Zeise	
Sweeney		

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The charge memo, containing the charge questions, has been appended to these minutes. A summary of the highlights of the discussion that ensued over the next two days follows:

Presentations: All presentations by panel members may be found posted at

<http://yosemite.epa.gov/sab/sabproduct.nsf/MeetingCal/4C24E314EE7DB345852573C4007A1907?OpenDocument>

- Presentation by Dr. Dale Sickles
- Presentation by Mr. Sean Hays
- Presentation by Dr. Lauren Zeise

## NON-CANCER ISSUES

### **Selection of Studies and Endpoints for the Oral Reference Dose (RfD)**

Drs. Brannen, Fenner-Crisp, LoPachin, Solomon, Sickles and Sweeney were asked to focus on the responses to Questions 1-7 and they lead the discussion for this section.

1. The Panel agreed that the selection of neurotoxicity is the most appropriate choice for the most sensitive non-cancer endpoint based upon the available animal and human data. Panel members also believed that the heritable germ cell mutations are very important health effects and needed further discussion in the IRIS document. They also suggested that more studies to understand their impact.
2. The Panel provided additional information on the discussion of mode of action (MOA) for acrylamide-induced neurotoxicity. It was suggested that the MOA discussion be grouped in one section of the assessment. Panel members also wanted the discussion regarding the effects of Acrylamide versus Glycidamide to be expanded. There was an extended discussion of neurotoxicity by Drs. Lopachin and Sickles. Panel members suggested that both MOAs be presented in the report for the Agency's consideration.

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3. The Panel agreed that the qualitative discussion of acrylamide's heritable germ cell effects is clear, transparently and objectively described, and reflective of the current science. Panel members believed that more studies using lower doses were needed.

### **Derivation of the Reference Dose (RfD)**

4. The Panel agreed that the selection of the Friedman et al., (1995) and Johnson et al., (1986) studies as co-principal studies has been scientifically justified. However, Panel members had some concerns, including: They believed that both studies have problems associated with them since they were designed as carcinogenicity studies and neurotoxicity evaluations were done later. An uncertainty factor may need to be added to account for the data gap. Both human and animal data should be used. More data will be available from the NCTR study when it is completed.
5. The Panel agreed that the choice of benchmark dose methods and the response level used in the derivation of the RfD are reasonable. Panel members believed that more justification for using the BMDL5 level was needed.
6. The Panel agreed that the selection of the uncertainty factors (other than the interspecies uncertainty factor) applied to the point of departure (POD) for the derivation of the RfD is appropriate. Some members suggested that a data gap uncertainty factor was needed.
7. When asked to provide any other comments on the derivation of the RfD and on the discussion of uncertainties in the RfD, panel members suggested that a common mechanism of action analysis may be performed for type 2 alkenes, of which acrylamide, is a member.

### **Use of a PBPK Model in the Derivation of the RfD and the Inhalation Reference Concentration (RfC)**

Drs. Fennell, Fisher, Hays and Heeringa were asked to focus on the responses to Questions 8 – 12 and they lead the discussion for this section.

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8. The Panel believed that the documentation for the recalibrated Kirman et al. (2003) PBTK model development, evaluation, and use in the assessment was not sufficient to determine if the model was adequately developed and adequate for its intended use in the assessment. Panel members suggested that there are more recent data available for use in developing the PBTK model. Dr. Hays offered a comparison of modeled results and measured data (see table, available at URL listed below). A panel member also suggested that a PBPK model may not be necessary and the use of AUC would suffice.
9. No, the Young et al. (2007) PBTK model was not adequately discussed in the assessment. More recent data should be used to recalibrate the Kirman et al model.

## **MARCH 11, 2008 (DAY 2)**

Dr. Sue Shallal was not able to continue as DFO due to illness; therefore, Dr. Resha Putzrath stepped in as DFO for the duration of the meeting.

The panel continued the discussion of the PBPK modeling and Charge Question #9.

The Panel was concerned about the fact that the model was not adequately described. There is new data that was not used in the development of the model. Also it was noted that a complex PBPK model may not be necessary; others felt that since there are data available it should be used.

10. Using the PBPK model may be justified over the use of a default factor. Data is limited; therefore, it is difficult to know what value to assign to it.
11. The Panel noted that there are limited data available for the derivation of an RfC. Inhalation studies are difficult to do. Using the PBPK model appears to be appropriate.
12. No further comments on the derivation of the RfC and on the discussion of uncertainties in the RfC.

**Margin of Exposure (MOE) Analysis**

Drs. Brannen, Fenner-Crisp, LoPachin, Solomon, Sickles and Sweeney were asked to focus on the responses to Questions 13-17 and they lead the discussion for this section.

13. To facilitate a MOE evaluation by EPA's Regional or Program offices, or by other end users of the assessment, Panel members supported the idea of including a table and discussed the content of such a table to include, e.g., RfD, RfC, NOAEL, LOAEL, BMD at 1%, 5% and 10% levels, etc.

**Quantitating Heritable Germ Cell Effects**

14. Some concern about the lack of data on heritable germ cell (HGC) effects was expressed, however the description of the methods used for quantifying HGC effects was thought to be important. Panel members believed that a more robust discussion of the uncertainties was needed.
15. Panel members noted that heritable germ cell effects may occur at doses lower than those seen for neurotoxicity. More studies are needed using lower doses.
16. The Panel agreed with the Agency's conclusions that exposure to acrylamide in animals leads to heritable gene mutations and that these results indicate that HGC effects may also pose a hazard to humans. In addition, the Panel supported the Agency's conclusions that the available data are not adequate to conduct a robust assessment of this endpoint at this time.
17. Heritable germ cell effects were thought to be very important. The Panel was concerned about the lack of a suitable data set for dose response assessment for acrylamide-induced heritable germ cell effects. Most studies reported have been conducted in mice using relatively high doses. The extension of the physiologically-based pharmacokinetic modeling approach to include the mouse should be a priority. Studies to examine the dose response for heritable genetic effects, and the effect of long-term exposure to acrylamide are needed. The

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mode of action of acrylamide and glycidamide in the induction of heritable genetic effects is unknown. The DNA adducts of glycidamide may play a role.

### **Carcinogenicity of Acrylamide**

Drs. Doerge, Felton, Mucci, Rice and Zeise were asked to focus on the responses to Questions 18-26 and they lead the discussion for this section.

18. Yes, the rationale and justification for the cancer designation for acrylamide has been clearly described. The conclusion that acrylamide is a likely human carcinogen is scientifically supportable in accordance with the EPA Cancer Guidelines.
19. Yes, the weight of the available evidence supports a mutagenic mode of carcinogenic action, primarily for the acrylamide epoxide metabolite, glycidamide (GA). The rationale for this MOA has been clearly and objectively presented, and is it reflective of the current science.
20. There is little significant biological support for alternative MOAs for tumor formation, or for alternative MOAs to be considered to occur in conjunction with a mutagenic MOA. The hormonal disruption MOAs proposed for acrylamide as tissue-specific alternatives to a DNA-reactive MOA are highly speculative, are supported by at most limited evidence
21. The two chronic bioassay studies in F344 rats are the main studies to consider in dose response analysis. Overall the document does a good job discussing these studies, but the rationale for using only the Friedman *et al.* study for derivation of the oral slope factor is not sufficient. The strengths and limitations of both studies should be discussed in greater depth. The Panel does not agree with the Agency's conclusion that the Friedman *et al.* study is "superior" and "larger and better designed" and recommends that both studies be subjected to modeling for the purposes of deriving oral slope factors. The two studies may have fairly similar oral slope factors. At a minimum, estimates for the second study should also be presented to clarify the impact of study selection in the uncertainty discussion.

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22. The use of the Weibull-in-time multistage-in-dose analysis is a reasonable and scientifically justifiable way to take into account the early mortality in the high dose group in the male study.
23. The Panel agreed that using the AUC for glycidamide is the best choice for estimating the human equivalent concentration to derive the oral slope factor. The Panel agreed with the conclusion that glycidamide is the more mutagenic metabolite based on experimental studies. The documentation in the report regarding the correlation between levels of DNA adducts and extent of mutations *in vivo* was good. The metabolic conversion of acrylamide to glycidamide also supports the MOA.
24. The Panel agreed that there are insufficient cancer inhalation data to derive an inhalation unit risk (IUR). The Panel suggested that the PBTK model can be used in a route-to-route extrapolation of the dose-response relationship from the oral data, and to estimate the human equivalent concentration for inhalation exposure to acrylamide.
25. The Panel agreed with the recommendation to use the age-dependent adjustment factors (ADAFs) is based on the determination of a mutagenic MOA for carcinogenicity.
26. The Panel concluded that the development of the inhalation unit risk based on HEC accounts for the toxicokinetic but not toxicodynamic interspecies differences. The discussion of uncertainties is good, but human variability could be addressed in greater length. Sensitive populations should be address and discussed to a much greater extent.

The meeting adjourned at the end of day 2 after all charge questions were discussed. Panel members were instructed to provide written responses which reflect the comments and concerns of the panel as discussed at the meeting. Dr. Cory-Slechta reminded panel members of their assignments and reiterated that all members will have an opportunity to comment on the responses to any of the charge questions as the draft report is developed. She asked panel members to provide their revised comments by April 1, 2008.

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Finally, Dr. Putzrath reminded panel members to include both Dr. Shallal and Dr. Cory-Slechta as recipients on any correspondence with other panel members.

The meeting adjourned without the need for a third day of discussions as had been originally planned.

Respectfully Submitted:

**/Signed/**

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Dr. Suhair Shallal  
Designated Federal Officer,  
EPA SAB Acrylamide Review Panel

I certify that these minutes are accurate to the best of my knowledge:

**/Signed/**

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Dr. Deborah Cory-Slechta  
Chair, EPA SAB Acrylamide 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 not to rely on the minutes to 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.

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All attachments are available in hardcopy upon request

<u>Attachment A</u>	Federal Register notice (73 FR 22:6182-6183 February 1, 2008)
<u>Attachment B</u>	Meeting agenda- March 10-12, 2008
<u>Attachment C</u>	Consultative Panel roster
<u>Attachment D</u>	Biographical sketches
<u>Attachment E</u>	List of participants
<u>Attachment F</u>	Charge Questions
<u>Attachment G</u>	powerpoint presentation by Rob Dewoskin 3-10-08