

**U.S. Environmental Protection Agency
Science Advisory Board**

Final Minutes of Public Meeting April 5, 2006

Committee: EPI Suite Review Panel.

Date and Time: April 5, 2006 from 2 - 4 Eastern Time as announced in the Federal Register Notice, published February 1, 2006. Volume 71, Number 21. Page 5317-5318

Location: By telephone only, run from 1025 F Street Northwest, Washington D.C.

Purpose: The purpose of this teleconference is to review and plan revisions to the Panel's draft report.

Materials Available: The following materials were distributed before the meeting:

1. agenda
2. an "interim" draft, March 10
3. a "second" draft, March 17
4. a "third" draft, March 24
5. email exchanges among panelists on the materials

Attendees: Because this was a conference call, there are no sign-in sheets. The following panelists participated in all, or most of, the teleconference: the chair, Dr. Michael J. McFarland, Dr. Deborah Bennett, Dr. Robert L. Chinery, Dr. William J. Doucette, Dr. David A. Dzombak, Dr. Anton J. Hopfinger, Dr. Michael W. Murray, Dr. Thomas F. Parkerton, Dr. Kevin H. Reinert, Dr. Daniel T. Salvito, Dr. Hans Sanderson, and Dr. Louis J. Thibodeaux. Dr. Diamond was not able to participate; Drs. Dzombak and Salvito were not able to stay until the end of the call.

Anthony Maciorowski, Associate Director for Science and Kathleen White, DFO of the SAB Staff Office were present as were Cathy Fehrenbacher and Bob Boethling of OPPTS/OPPT/EETD. Three members of the public were present: John Carbone, Ph.D., Senior Scientist, Toxicology Environmental Sciences, Toxicology Department, Rohm and Haas Company; David J. Kent, Keller and Heckman LLP; and Diana Graham, Ph.D., Keller and Heckman LLP

The DFO called roll, listed the comments received, referenced her email with extracts of the comments prepared in aid of the discussion, and turned the meeting over to the chair. McFarland saw no fatal flaws or show stoppers among the comments and thought there was over-arching agreement. Proper emphasis and priorities may need to be sorted out. The DFO asked for comments from the Panel on the draft.

Dzombak, who had been unable to attend the March 7-9 meeting, raised an issue he'd brought up on the March 1 call which appears in the body of the report and only indirectly in the executive summary, but not in the cover letter. He thought it would be helpful to provide the perspective that EPI Suite applies to about half the chemicals considered and OPPT uses different approaches for the others. He suggested this change in the cover letter:

We are pleased to inform you that the EPI Suite models, developed and made freely available by the Office of Pollution Prevention and Toxics, is based on combining sound science, user friendliness, transparency, and cost-effectiveness. The models are applied within the Agency and moreover are widely employed by both governmental and private organizations within the United States. **While the EPI Suite models are applicable to only about half of the new chemical applications submitted, for the categories of chemicals for which they apply EPI Suite estimates physical-chemical properties as well as the fate and transport of these chemicals with accuracy sufficient to support regulatory the screening applications.** Owing to its availability as freeware over the Internet, EPI Suite has an important role to play in assisting emerging industrial economies to develop in an environmentally defensive and sustainable manner.

He suggested this change for the Executive Summary.

The Panel considered the accuracy and validation of EPI Suite. **For the nonpolar organic compounds which are the focus of most of the EPI Suite tools, EPI Suite predicts** physical-chemical properties within an order of magnitude, which is normally sufficient for screening level regulatory assessments. While no model is ever completely validated, those within EPI Suite have been satisfactorily evaluated through the peer-reviewed scientific literature. Additionally, the physical-chemical properties (Q)SARs in EPI Suite generally satisfy the OECD Principles for (Q)SAR validation, a fact that supports its use as a screening level tool for regulatory decision-making.

The DFO raised this related change on page 59.

“EPI Suite does not cover all of the chemical categories that are considered in the PMN and P2 programs. EPA is aware of this and uses other approaches to evaluate these chemicals.”. The domains of the (Q)SARs do not provide adequate coverage of nanoparticles, surfactants, organometallics, inorganic compounds and some polymeric chemicals (and several other classes of chemicals).”

Sanderson agreed, noting that nanomaterials should also be identified on the list of categories not addressed by EPI Suite. He wondered whether EPI Suite did not evaluate some surfactants. Hopfinger clarified that you can predict inter-molecular properties of surfactants, but not some other important ones and these should be differentiated. He suggested that the text distinguish between them. Hopfinger and Dzombak agreed that the Panel should mention the nature of the approach – a mix of approaches are used based on professional judgement. Parkerton thinks the Agency has not defined a consistent approach to the other chemicals – a sort of best practices. Murray assumes there’s nothing on the scale of EPI Suite for these other chemicals. McFarland thinks this could be captured and said positively. Sanderson wants to be sure of the text that relating to the 50% -- is the Panel going to call out what is not included? He is concerned because surfactants is a very broad class, some can be assessed by EPI Suite and some cannot. McFarland agrees this is a very important point. Boethling agrees with Sanderson. Dzombak thinks that a goodly number of surfactants canNOT be addressed by EPI Suite and would like EPA to clarify where the shortcomings are with regard for surfactants. Boethling doesn’t think there’s a clear description. Salvito thinks this is an issue that could be identified, but not addressed in detail. Someone suggested qualifying that “certain chemicals are outside the domain of specific EPI Suite modules” There are even some modules that work for organo metallics. Doucette said Dzombak brought up an important point. There is another tack to take. If you look at the historical development you could say EPI Suite developed for non-polar, blah blah, but it’s use has expanded, but still cannot be used for about half the new chemicals. Boethling brought out the difference in the modules. Sanderson said, if we are going to call out sectors, it has big implications and hasn’t been thought out that well. McFarland agreed with Doucette’s approach.

Dzombak would like some mention of compounds not addressed, but agrees to modification. Overall, the idea that there is a significant fraction of the new chemicals submitted cannot be addressed is important. He would modify, but keep the specific examples – perhaps saying “some” or “certain”.

McFarland proposed taking Doucette’s suggestion and qualify the list of compounds. Sanderson disagrees about the value of adding the examples and there is a downside. The Panel has not conducted an in depth assessment of the truth of this statement. Doucette agrees that the Panel should not quantitate. Salvito suggested “suspect these may include some . . . “ Dzombak agrees that the 50% number was an estimate on the fly and the Panel is not in a position to verify it, so significant fraction would do. Murray spoke to Boethling’s comments on polymers. Boethling said EPA doesn’t use EPI Suite for polymers. Sanderson fears the impacts of loosey-

goosey language; that's not what science means to him. Either do it right or leave it out. McFarland summarized to use the Doucette approach, use "significant fraction", and identify compounds as suggested by Salvito. Sanderson reminded

Potential vettors: Doucette, McFarland, Salvito, Sanderson.

In Diamond's absence, the DFO read her comments on BAF and related ones from Cowan-Ellsberry on the prior draft and Doucette on the March 24 one.

BAF. I do see some language to clarify that inclusion of BAF was controversial. The text says that BAF is already being worked on for inclusion. That differs from the message I got from Bob Boethling so it leaves me confused as to how the BAF enters as such as strong discussion point.

The following text from the March 24 draft is inserted into Diamond's comments for ease in discussion) Page 16, line 36 to page 17, line 1

Bioaccumulation factors (BAFs). A module for BAFs is being incorporated into EPI Suite. One obvious challenge is the difficulty of conducting experimental studies for BAF as well as the wide range in field measured BAFs that can be obtained for a given chemical. **[NOTE THIS IS NOT A CONSENSUS STATEMENT AND WILL NEED TO BE RESOLVED. ANOTHER PANELIST SAYS, "I do support the continued research to develop better methods for estimating BCF and BAF, I do not belief that these are ready for incorporation into the EPI Suite, especially since there is no current method for estimating metabolism which is a required parameter. MM proposes, "However some panelists still recognize the value in deriving estimates for BAF, while encouraging the development of model experimental systems to provide additional data on this parameter."]**

This comment is from Doucette on March 24 draft, 1Cii page 43

Bioaccumulation factors (BAFs) (Note: not all panelist agreed on the current feasibility of a BAF prediction routine while others felt it reasonable to include a BAF prediction routine into EPI with the appropriate caveats)

Thibodeaux thinks BAF and BCF should be included, but doesn't think we are there yet. There is even some disagreement over whether these are properties or fate models. Boethling The revised EPI Suite model, which has not yet been released includes a BAF module.

Doucette asked the panel what they thought of including BAF as a model instead of a property? Chinery asked Boethling how the revisions dealt with BAF. Boethling says it's just a couple of lines after BCFWIN. Parkerton shares Cowan-Ellsberry's concern that Frank's model is calibrated on Kow. The concern is that BCFWIN is trained on lots of empirical data. To the extent that it reflects chemicals susceptible to metabolism BCFWIN will predict well for chemicals in that domain. But a BAF model that followed would only work for a subset of those chemicals. The results will be confusing

Boethling said that BCFWIN started out thinking about metabolism in fish, but, the correction factors are really empirically derived and do not relate to metabolism. In the March 24 draft someone raised the example of PFOA and stated this compound would be missed by BCF. He ran it through the new, as yet un-released model of BAF, and it did identify PFOA as a chemical of concern. (This was section 1Bi and the example is from Parkerton) Sanderson reminded the Panel that they have not reviewed the BAF module which Boethling mentions. He thinks a good BAF module would be good to have, but it has to be good. Boethling sees no evidence that the Goebels model does not meet the criteria Sanderson mentioned; the question is how it is parameterized. He wondered if it could be added and caveated. Sanderson spoke of the indifference of regulators to caveats in large runs.

Thibodeaux thinks that, if we can't decide if it is a model or not the solution may be to say very little about it, just that it was being developed and the Panel didn't look at it. Sanderson thinks they could add that a good model would be very valuable, while a bad or inconsistent model would be a problem.

There was more discussion. Doucette said it was clearly a science need, but the algorithms need to be developed with which to predict metabolism; then that could be used. Putting in the qualifiers doesn't change the fact that people who don't know much will use the models anyway and make decisions with it. But he thinks it should be included with the caveats. The potential for mis-use is of concern. Thibodeaux recommended a workshop. Frank's model is very simple and there is a certain amount of distrust of it. Sanderson notes that these tools are for regulatory decision-making, not academics. He cannot endorse a tool that he thinks is inherently inaccurate, even with the caveats. We need a really good molecule. This is one of three criteria chemicals will be regulated on in the future. A bad model could compromise the quality of the whole suite.

Murray would support the inclusion of a BAF module into EPI Suite, even as a pilot, and improve predictive capacities. If there is not a majority, the panel should point out that this is an area where EPI Suite is not conservative and could potentially under protect.

McFarland agrees that the Panel may not reach consensus on this issue on this call. He would like to get individuals with divergent views to craft language that will give the reader a feeling for the varied positions held by the panelists. The team would be: Cowan-Ellsberry, Diamond or Doucette, McFarland, Murray, Parkerton, and Thibodeaux will craft language that reflects the varied panel views.

The DFO read Diamond's second suggestion,

There is new language having as a high priority a module to estimate mass transfer coefficients. I recall the discussion on MTC, but it was a point of lesser importance and certainly not "high priority". I think this recommendation requires further discussion before entering the report as "fait accompli" as it now stands. There are many parts of the fate model that require more work, not just mass transfer coefficients!

Thibodeaux disagrees with Diamond; MTC is needed. He thinks it would be good for people to have a place to go to do get MTC's. He won't push the point. Hopfinger had question 1Ai, which addresses what should be added to the Suite later. He thought there was a consensus that they would put in MTC as a priority. Salvito agrees with Hopfinger and both agree that it has a place on the laundry list. Murray referred to page 14 line 13 where it appears as a high priority need. The problem there just isn't good information on MTCs between phases and there's a lot of variability. Not much work has been done to determine the rates. Thibodeaux doesn't go to EPI Suite for an MTC. If you want EPI Suite to be a general tool for property estimations, this would be a good one to add.

Bennett agrees that line 13 does overstate it. Hopfinger said that's Thibodeaux's wording. If Thibodeaux would be willing to soften "high priority" to "significant need" it would meet the spirit of Hopfinger's concerns.

Diamond's third point was,

The Exec Summary (which is well written!) does not have much info on fate models but rather focuses on PaR (I like your new acronyms). Needed are some points about expressing uncertainty, clarifying default input values, transparency in carry-over of p-chem properties to fate models, option of changing default values, expansion of suite of models to include fugacity versions of marine and urban systems and inclusion of vegetation in current multi-media model.

Doucette suggested that the idea did not come across as strongly. Hopfinger agreed with Doucette. He thought 1Ai addressed it. Bennett said there is no para representing that in the Executive Summary. McFarland asked Doucette to craft some sentences on decoupling (not a laundry list) for the Executive Summary.

Diamond's final comment was, "As you've noted in one of your comments, the document needs to be edited to distinguish between PaR and FaT." Doucette had suggested property estimated modules or routines and fate or transport models. Boethling liked a variation on what Doucette had said – chemical property relationships, reactivity modules (AOP, HYDRO, BIOWIN), and fate models. Murray said Boethling's suggestion made sense, but since the report is written in two categories, it would be a chore.

Doucette said we could compromise by putting property estimation modules (chemical property relationships and reactivity modules). Sanderson would just call them all (Q)SARS and call the others Fate models. It would be easier for an international audience. Thibodeaux thought (Q)SARS is narrow. Sanderson asked about the common language, but there doesn't seem to be one, and he can live with Doucette's formulation.

Doucette will provide a few introductory sentences or a paragraph.

Hopfinger referred to P 11, lines 22-40, which read:

1. Supporting Science

A. Comprehensiveness

- i. Are there additional properties which should be included in upgrades to EPI Suite for its various specified uses (PMN, P2)? (An example might be Characteristic Travel Distance.) Can any be dropped?**

In summary, EPA should **[panelists disagree over should or could in this case. USE "SHOULD" OR THIS ENTIRE ANSWER HAS NO MEANING]** consider reviewing data quality, adding new data to the training sets for each of the property estimation modules and reviewing the appropriateness of applying newer statistical models to the data sets. EPA could add prediction of the following properties: pKa; the influence of pKa on physical chemical properties as appropriate; temperature dependent estimates of the physical chemical properties; metabolism in bioconcentration models, and transport coefficients **[is this the mass transport coefficient? YES]** in fate models... The Panel has made recommendations for additional properties and models EPA could add in the long-term. Specific criteria for setting the priorities are provided below. The DERMWIN model could be moved to a more appropriate suite of programs provided such a home can be found and the availability of the model not lost.

Hopfinger said the use of "should" is a generic issue in the report. There was agreement it should be "should" here. Boethling spoke of a regulatory gradation of terms. Shall has the force of law, should means you damn well better do it, could is still an endorsement. The Panel should use should where it feels very very strongly. Salvito said there was, at the time, a universal decision to make everything could, unless should was absolutely necessary.

There was discussion of Page 14 line 48 to page 15 line 6, which reads:

The EPI Suite tools are, for the most part, applicable only to nonpolar organic compounds of relatively low molecular weight. Inorganic compounds, metallo-organic compounds, polar organic compounds, polymers, and surfactants cannot be addressed by most of the EPI Suite tools. Therefore, it is recommended that some of these chemical class deficiencies be considered in future planning. Polymers are the largest class of chemicals submitted to the EPA for which property estimation capabilities are not currently available in the EPI Suite.

Hence, the longer-range development of EPI Suite could [**should? I THINK YES, BUT...OTHERS SAY NO??**]include polymer property QSPR models. Commercial software packages are available for predicting polymer properties. That is, the data, methodology and theory to estimate several “standard” properties of linear polymers are available. Among the “standard” physico-chemical [algorithm] properties of linear polymers, the following are suggested for expansion of the EPI Suite.

Hopfinger thinks stay with could. No disagreement. Murray spoke of the earlier discussion led by Dzombak and said he could live with should because it is longer range. Sanderson agreed with Murray but thinks it is hard to make the calls relative to the limited resources. He would be happy with either. McFarland thinks the Panel is comfortable with could.

Hopfinger brought up a housekeeping item about acronyms: avoid them, define them, use them freely, add a glossary. McFarland agrees that a glossary has been needed. Agreement DFO will add a glossary if the Panel will help. Murray agrees that terms should be defined when first used. DFO will highlight issues where there is a difference of opinion.

McFarland asked if there were additional comments that panel members had.

Sanderson commented on 1B, principal four, “EPA could calculate the 95% Confidence Intervals for the coefficient of determinations (R^2) and report these values in the user’s manuals. This information will allow users to assess the precision of estimates and the potential uncertainty in the results of risk assessments using the QSAR results. “

Sanderson thinks a few worst-case studies could determine whether these have any significant impact on the results and, if not, forget the uncertainty. If it doesn’t change the outcome of the decision-making, why introduce it?

Bennett suggested saying there was disagreement and refer the reader to the uncertainty section. Sanderson would like to see the worst-case analyses included, even if it was in the uncertainty section. There are trade-offs which Bennett thinks are addressed in the uncertainty section.

Doucette thinks uncertainty will help non-EPA users.

Murray finds he is confused by the paragraphs now that he looks at them. More specifics are needed on what standard deviation is being discussed in the second paragraph. It's good to express quantitative uncertainty when you can.

It is not a deal-breaker for Sanderson. Bennett agrees there should be a reference to the uncertainty section. Chinery said he wrote the section Sanderson mentioned before Bennett wrote the section on uncertainty.

There is agreement on referring the reader to the uncertainty section. Chinery thinks they may as well delete. Sanderson says that leaving it in means the Panel is making a recommendation. Another voice thinks that the uncertainty section is well nuanced. Sanderson would like to drop, "EPA could calculate"

Bennett will write up and send to White.

DFO mentioned Reinert edit on page 27, " (see later example Regarding perfluorodecanoic acid and fish BSF).," in light of earlier discussion. Sanderson thinks the Panel should stay away from this example. Reinert doesn't care whether it is in or not. Parkerton doesn't think it critical. The point can be made generically.

McFarland hears consensus among the panelists to remove that example.

Reinert suggests, given today's example, removing the language he has on BCF a few pages earlier (his page 28).

Parkerton spoke about his question on page 29, "In answering this question the Panel needs to be mindful of what is meant by "adequately validated". Oreskes et al. (1994) define validated as establishing the "truth". Models that approximate experimental (e.g., determination of physical-chemical properties) and the environmental systems (e.g., Level III and STP fugacity models) can not be validated in the strict sense. For experimentally determined physical-chemical properties, against which QSARs are compared, true values may only be approached, given limitations in all measurement methods; for a given parameter, the "true" value may be a function of the measurement method used. Environmental systems that are modeled are "open ended" and as such, can not be validated. Rather, Oreskes et al. (1994) recommend the use of the term "evaluate" rather than "validate" to convey the process of establishing consistency of model results with measured data (phys-chem properties) or that the processes are mechanistically sound and parameter values have been found to be reasonable (fate models). Oreskes et al. (1994) comment that models can be verified, which refers to establishing that model mathematics and code are correct.

A panelist, who does not disagree with the above, asked whether this comment contradicts earlier points. Specifically, the comment that models can never be verified only determine that their mathematics and code are correct seems counter to the discussion of uncertainty analysis,

doman mapping, and data review. Doesn't that all go beyond code and equations. What is the Panel's view?]"

Boethling likes the OECD term "Corroborate" and says it would be a good idea for the Panel to use internally consistent definitions.

Parkerton thinks the language goes beyond that in saying, 'the environmental systems (e.g., Level III and STP fugacity models) can not be validated in the strict sense". Panelist seem to agree with this language. Validations trials can be done, but the model can't be validated.

Neither McFarland and Parkerton understand the paragraph as written. McFarland would be happy taking it out.

A proposal was made to, take out the paragraph and substitute "corroborate" for "validate" throughout. Sanderson asked if they can change the charge questions to corroborate. McFarland said they can say what they understand that validate means corroborate. Murray noted there is also language on page 33 that says "we can't evaluate them". The Panel should revisit the text on page 33 as well. Bennett noted it is harder to evaluate the fate models and Murray agreed.

Hopfinger had to leave

Sanderson had an issue with this sentence on page 24, "EPA may benefit from better defining the levels of error (Type I or II) would be acceptable for its uses of the program." It would be great to have the estimates, but it might be a lot for EPA to generate them. Murray noted nothing was said about minimizing false negatives. He suggested, "minimizing false negatives provides better confidence . . ." McFarland liked Murray's language and he will send to DFO.

Sanderson noted the references from E-FAST and ECOSAR were dropped from the next para. Even though we didn't analyze or discuss them, he thinks they should be mentioned. Reinert thinks removing them was Cowan-Ellsberry's idea, but he would be happy having them back in. Sanderson said a parenthetical could be added stating that the Panel did not review these models. Bennett suggested a footnote. Bennett will craft the footnote.

Sanderson suggests that the Panel make the Executive Summary more readable.

OPPT provided comments at 3:00. Fehrenbacher brought out two points

1. Page 26 line 1 "OPPT indicates that there is no formal periodic review or verification of current data and models or acquisition of new data or models." This is not factually correct and could be misconstrued. She would suggest rewording it to something like, "OPPT periodically reviews and updates the data currently in the model and also considers acquisition of new data or models to enhance EPI Suite. The Panel recommends that comparisons with new data be conducted annually instead of on an *ad hoc* basis."

Doucette had to leave before the Agency got to their second comment. McFarland said he hoped that the Panel could approve the report contingent on resolution of these smaller issues. Doucette is comfortable with that. He asked for an email reminder of his assignments.

2. Page 41 line 25

“Caution should be exercised if/when (Q)SPRS for nanomaterial under TSCA are developed and/or potentially applied under EPI Suite nanotech materials.” It is an awkward sentence. It is fine to recommend that caution be exercised if one wants to use EPI Suite to evaluate nanomaterials. However “under EPI Suite nanotech materials” makes no sense, end at EPI Suite.

Line 25 “E-FAST has been mentioned as a tool for exposure assessments of nanomaterials.” In correct. This is not what the white paper says. Could it just be deleted? It is fine to include a statement about nanomaterials an E-FAST, just be sure it is accurate. McFarland confirmed Panel agrees to remove the sentence.

At 3:15 Boethling mentioned some technical clarifications that are not show stoppers. He has a lengthy list which he would like to submit in writing, they are just clarifications and corrections. A number of these were already discussed on this conference call.

--He heard discussion of false positives and false negatives and doesn't understand the relevance. Bennett thought that was weird, too. Sanderson agrees. Someone mentioned the false positives and false negatives in the context of PBT decision-making OUTSIDE of EPI Suite. Boethling said the false negatives and positives really applies to the assessments, not to the EPI Suite itself. Murray spoke to the importance of the implications incorrect model output have for decision-making. Bennett offered to add a few sentences up front reflecting this discussion. Over and under estimation might be better terms.

--He spoke of discussion of the compartment dimensions, which are hardwired in the models. They are not adjustable. If the Panel thinks they should be, they should say so.

Bennett suggested we send to the Panel and the section coordinators make the appropriate changes. McFarland and Panel agreed.

At 3:25 McFarland went to next steps. He asked the Panel whether they would approve the report in principle, pending the crafting of new language on the following issues

1. The cover letter, Executive Summary, and page 59 will be edited as proposed by Doucette and the evolution of EPI Suite noting there are categories of materials that the tool does not work well for. The language will get worked out by the team.
2. Salvito will decide how the panel will address the BAF model

3. Then Doucette will add language to the on the two kinds of models
4. Doucette will write a sentence or two on property estimating routines v re activity v fate

Goal is to have all changes to White by April 11 so she can send out draft #4 by April 14. (DFO is on leave April 6-10, has to work on sustainability April 11-14, and on nitrogen for the next two weeks) These revisions will be crafted, circulated, and then worked on by the group. The full panel will have an opportunity to review the full report before it is sent to the chartered SAB.

Respectfully Submitted:

Certified as True:

/s/

/s/

 Ms. Kathleen White
 Designated Federal Official

 Dr. Michael McFarland, Chair
 EPI Suite Review Panel

Attachments will be found at the SAB website and/or the FACA file

1. Federal Register Notice
2. Agenda for the meeting
3. Workgroup roster
4. Materials distributed in advance of the teleconference
5. Email approving minutes