

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

Final Minutes of Public Meeting March 7-9, 2006

Committee: EPI Suite Review Panel.

Date and Time: March 7-9, 2006 as announced in the Federal Register on February 1, 2006, 71FR21, Page 5317-5318.

Location: SAB Conference Suite, 3rd Floor, 1025 F Street Northwest, Washington D.C.

Purpose: The purpose of this meeting is for the Panel to reach consensus on the content of their response to the charge questions, to capture that consensus in writing, to brief the Agency on the major findings and conclusions, and respond to Agency questions.

Materials Available: In addition to the materials circulated before the February 22 and March 1 conference calls, the following materials were distributed before the meeting:

1. agenda
2. additional information on the uses of EPI Suite
3. additional information on other EPA models that estimate properties
4. additional information on data quality
5. additional information on chemical classes covered by EPI Suite
6. more information about other EPA models and the PBT profiler
7. information on how outputs from EPI Suite are used
8. information on false positives and false negatives
9. brief public comments from Gerry Wood and Layla Batarseh
10. collected individual independent responses to the charge questions by panelists as of March 6
11. collected preliminary integrated responses to the charge questions by the coordinators as of noon on March 7
12. information on the history of EPI Suite
13. EPI Suite Essay, by Thibodeaux
14. Materials from panelists Bennett, Diamond, Hopfinger, Murray, Reinert and Salvito distributed at the start of the meeting on March 8.
15. Materials from Parkerton and Thibodeaux distributed after lunch on March 8

Attendees: The sign-in sheets will be found in the FAC file for this meeting.

The following panelists were present for the meeting:

The chair, Dr. Michael J. McFarland, Associate Professor, Department of Civil and Environmental Engineering, Utah State University, Logan, UT, and members:

Dr. Deborah H. Bennett, Assistant Professor, Department of Public Health Sciences, University of California, Davis, Davis, CA

Dr. Robert L. Chinery, Research Scientist, Environmental Protection Bureau, New York State Department of Law, Albany, NY

Dr. Christina E. Cowan-Ellsberry, Professional Staff, Risk Science, Policy and Regulatory Sciences Department, The Procter & Gamble Company, Cincinnati, OH

Dr. Miriam L. Diamond, Professor, Department of Geography, University of Toronto, Toronto, Ontario, CANADA

Dr. William J. Doucette, Professor, Department of Civil and Environmental Engineering in the Utah Water Research Laboratory and, Center for Environmental Toxicology, Utah State University, Logan, UT

Dr. Anton J. Hopfinger, Research Professor, Deans Office Administration, University of New Mexico, NM.

Dr. Michael W. Murray, Staff Scientist, Great Lakes Field Office, National Wildlife Federation, Ann Arbor, MI

Dr. Thomas F. Parkerton, Advanced Sci Assoc, Toxicology & Environmental Sciences, ExxonMobil Biomedical Sciences, Annandale, NJ

Dr. Kevin H. Reinert, Principal Toxicologist, AMEC Earth and Environmental, Plymouth Meeting, PA

Dr. Daniel T. Salvito, Manager - Environmental Program, Research Institute for Fragrance Materials, Woodcliff Lake, NJ

Dr. Hans Sanderson, Director, Environmental Safety, International and Regulatory Affairs, Soap and Detergent Association, Washington, DC

Dr. Louis J. Thibodeaux, Jesse Coates Professor, Gordon A. & Mary Cain Department of Chemical Engineering, College of Engineering, Louisiana State University, Baton Rouge, LA

(Dr. David A. Dzombak, Professor, Department of Civil and Environmental Engineering, Carnegie-Mellon University, Pittsburgh, PA Drs. Dzombak and Salvito were not able to stay until the end of the call.)

The Director of the Science Advisory Board Staff Office, Vanessa Vu, and the Associate Director for Science, Anthony Maciorowski, and the Deputy Director Richard Albores, attended parts of the meeting, as did Ron Josephson. The DFO, Kathleen White, attended the full meeting.

Scientists and managers from EPA's Office of Pollution Prevention and Toxic Substances were present for part or all of the meeting. The acting director of the Office of Pollution Prevention and Toxics' Economics, Exposure and Technology Division Neal Patel attended as did Bob Boethling, Cathy Fehrenbacher, and Lawrence Bill Eckell of the Office of Pesticide Programs attended.

No members of the public were present on Monday.

The following individuals from the press were present: Cheryl Hogue

Summary The meeting went largely according to the agenda.

The Panel had discussed the charge and the views of individual panelists on the two conference calls preceding the face-to-face meeting. In preparation for this meeting panelists had written on the charge questions to which they were assigned (and sometimes other questions) and most coordinators prepared draft responses to the charge questions using the individual writings. More writing was done at the meeting and the DFO sent the collected writings to the Panel after the close of the meeting. This began a cycle of review and revision in preparation for the April 5, 2006 public conference call meeting.

The following is a chronological summary of the meeting.

1. Welcome, Roll Call, and Opening Remarks

Tuesday

SAB Associate Director for Science, Tony Maciorowski spoke of the importance of open, transparent expert review and thanked the Panel for their efforts. Mike McFarland also thanked the Panel for their efforts and observed that his review of the individual initial comments indicated there were no real areas of contention. Then he asked OPPT to begin their presentations.

Neil Patel, Associate Director of the Economics, Exposure and Technology Division, spoke of the importance of exposure and modeling to their work. He felt the initial individual comments revealed a lot of thoughtfulness. He plans to be at the meeting as much as he can and thanked Dr. Vu for providing this helpful review.

Bob Boethling gave a brief history of EPI Suite. It had its beginnings in the publication, in 1980, of the famous Lyman Handbook in an era when personal computers were rare and had much smaller capacities than today. A computerized method for boiling point was available. About 1986 they developed the first fragment based biodegradation probability program. In the early 1990s, EPA could see there was a second generation of computer programs developing and thought it would be useful to bring them under one umbrella, which they called the Shell Program. Biodegradation surveys were developed in the early 1990s. There was a lot of activity in the mid 1990s such as MPBD, KOWIN, Water Solubility, etc. The Windows operating system was becoming more common and SRC reprogrammed the DOS materials into Windows to create EPIWIN. BCFWIN, two biodegradation programs (BIOWIN 5 and 6), and two fugacity based models were developed in the late 1990s. The Water NT program, a fragment based approach to water solubility, was developed around 2000. The Government bought the patent around this same time and since has added a lot of convenience features. In sum, EPI Suite developed through an evolutionary process, not the implementation of a grand design.

Fehrenbacher asked Boethling to respond to the Panel's questions from the March 1 public conference call meeting. These had been addressed in a series of emails, but not presented orally with the opportunity for questions and discussion.

Boethling addressed uses of EPI Suite in OPPT. EPI Suite is used in the PMN process in new chemical reviews, particularly in developing the earliest view of hazard at the Structure Activity (SAT) meeting. Solubility, KOW, melting point, vapor pressure, boiling point, absorption through skin and GI tract, and a variety of human health endpoints are used at that meeting. The same properties are used for environmental assessment, plus some others in EPI Suite. The main quantitative use of EPI Suite is the output of KOW which leads into ECOSAR (which is not addressed in this review).

Fehrenbacher compiled information on how OPPT used the results of EPI Suite. An important exposure they use for new chemicals is the Exposure Fate Assessment Screening Tool (EFAST). This multi-media model has recently been redesigned to have a single input screen where the user would enter particular properties. Where measured data does not exist, they would likely use outputs of EPI Suite. After entering the inputs, the user chooses an assessment from a number of different assessments available to do and runs the calculations.

Fehrenbacher reviewed the steps and decisions in the PMN process. The first decision is made in a couple of weeks at the Focus Meeting. A submission comes in and is logged in. Most are Confidential Business Information. The chemists assess the chemistry, this usually takes two days. Then there is a hazard, environmental fate and transport assessment using EPI Suite. At the SAT meeting hazard and chemistry experts meet and develop some preliminary ratings. With a day or two of the SAT meeting, there is an occupational exposure and environmental release meeting. There is an assessment of consumer and general population exposure using the environmental release estimates for the general population exposure. There is also an economic and benefits assessment. After the exposure assessment (that largely comes out of EFAST), there is a Focus meeting. All of the groups that had input into assessing the chemical meet with senior managers to make preliminary decisions.

EPA only regulates 5-10% of the new chemicals. Where there are no concerns the chemical is dropped from further consideration. Sometimes they have a concern, but not enough to regulate and they send the company a letter asking them to take action to mitigate that concern. The Focus meeting might decide to conduct a more in depth review on some chemicals, perhaps to regulate using a 5E consent order.

There are some bright line criteria, none of which are solely based on EPI Suite.

Also, within the new chemicals program, they have developed categories of chemicals. Over the last twenty five years they have learned that they will require testing for certain kinds of chemicals. These are identified on their website and manufacturers know that, if they submit such a chemical, they will be expected to provide additional data. These are termed "category chemicals" and EPA pretty much knows how to deal with them. Nevertheless there are novel chemicals and others which are more challenging and take more time.

The Agency gets about 2000 notifications a year. At any given 2-3 hour Focus meeting as many as 25 chemicals could be considered. Some get shunted out early. Not every chemical gets the same amount of attention.

Thibodeaux had thought EPI Suite was a screening level model, but noted there is no real output from EPI Suite that leads to a decision. Rather, it seems to be a source of information on properties related to where the chemicals will go that become inputs to other models. You never use the output of EPI Suite in itself to make a decision, it always goes to something else. Boethling agreed Thibodeaux's assessment was fair.

Thibodeaux thinks EPI Suite is a data generating model that feeds into screening models. Boethling mentioned two models within EPI Suite that are used with human input to make decisions. Boethling says you could even question whether EPI Suite should be called a model.

Patel says there are no concerns or concerns If there are concerns, there is a broad spectrum of actions that can be taken. If there are health concerns, but there are few alternatives and the new chemical is an improvement, in some way, over them, that is a different situation than some others. Sometimes they require protective equipment for occupational purposes, as little as gloves to as much as a moon suit. EPA also considers other potential uses of the chemical and might specify limited production or limited uses. The Agency can also ban them chemical until more data is provided and assessed.

Diamond asked, "What happens when you want more data?" Fehrenbacher indicated that, because time is short, they usually call the manufacturer. If the new data exists and can be provided or can be generated quickly, it can be used in the original assessment. Otherwise it might be an iterative process. Patel reminded people that they have to act within 90 days to act, but if they need more data, they can ask for another 90 days, or even more.

Bennett asked whether the middle ground was getting more data. Fehrenbacher said that, if they make a determination that they need more testing, they have to issue a 5E consent order.

What is the chemistry assessment like? Boethling said the chemists look at the submitted structure to see if it makes sense, look in standard sources for additional data, look at the chemical category and the name.

Murray had read the 2005 GAO report and noted that the Agency only requires testing for very few chemicals (185 so far). Patel said EPA has evaluated something like 40 000 new chemicals with more and less data. EPA has used these submissions to add to its data base which makes it more confident in its predictions. If EPA feels very comfortable that the new chemical will behave very much like ones they know well, they probably will not regulate. However, they don't want to stifle innovation so for new chemicals they often couple some controls with a requirement for additional testing. Depending on the analysis of the new data, the controls may be continued or removed.

Sanderson asked about the conservatism in EPI Suite and in models that use data from EPI Suite, such as EFAST. Boethling said EPI Suite has best-fit models without in-built conservatism. The conservatism is in the process and in the models into which EPI Suite feeds. Fehrenbacher reported that, at the Focus meeting, part of the discussion is on the overall conservatism of the assessment. The experts level of comfort with the analyses influences how conservative they are in their decisions. Many factors are considered in making decisions on any particular chemicals.

Sanderson observed that OPPT does a tremendous amount of work and probably gets it right most of the time, but it would be interesting to look at a couple of cases where things did not work out well. Fehrenbacher said there have been cases, in the occupational setting, where EPA required controls and, when the manufacturer did actually workplace monitoring and submitted data to EPA that showed that EPA had been conservative. She is not aware of specific assessments where EPA's decisions resulted in an uncontrolled risk. There are also situations where models have not been sufficiently broad in coverage to allow EPA to consider all classes of chemicals equally well which presents difficulties in assessing certain kinds of chemicals, so EPA tends to be more conservative there.

McFarland followed up on Fehrenbacher's comments by asking what EPA is doing about nanoparticles. Fehrenbacher says they do not believe EPI Suite is appropriate for the assessment of nanoparticles. They are looking for better approaches and would welcome useful advice.

Diamond returned to the issue of conservatism. She says it is conservatism in the exposure models, but not in EPI Suite. Precision and accuracy may be better words for the evaluation of EPI Suite.

Chinery asked whether they were to look at EPI Suite only in the context of the PMN program, or more broadly. He was involved with OPPT when they needed to do a risk assessment for a particular situation where they used EPI Suite to provide input. He assumes EPA does this on a regular basis. Fehrenbacher would like the Panel to focus on EPI Suite as a screening level model in the PMN program, but they do use it to evaluate existing or commodity chemicals where data does not exist. For example, they might use EPI Suite to provide data on which to make a decision about requiring a company to provide some data. Boethling observed it is also used in different ways outside of EPA.

Parkerton asked how EPA decides when the individual EPI Suite modules do apply to a particular chemical, for example, isomeric mixtures. Boethling said the decisions are made by human experts. Parkerton thinks the use of experts results in questions of consistency.

Parkerton then asked about "PBT-ness" and whether it would drive a 5E regulatory decision. (PBT stands for Persistent, Bio-accumulative and Toxic.) Boethling responded that the Toxicity part comes from ECOSAR as interpreted by humans using bright line criteria. Fehrenbacher thinks it would be considered in a risk context. They also make exposure based decisions – if exposure will be substantial, they will require testing. There is a whole range of decisions they may make, but none of them are made on environmental transport and fate alone, they also look at economics, benefits, risk, etc.

Hopfinger asked two questions relating to human objectivity. He understands that the outputs from EPI Suite are used in a primary screening, another part of which includes human health endpoint related measures (such as irritation and skin sensitization). If those endpoints exist, are they used? If not, why haven't they been developed. Fehrenbacher responded that a separate division makes those assessments using separate models. Boethling asked about the benefit of including such models in EPI Suite, given that EPI Suite already includes a dermal penetration module which hardly anyone is aware of.

Hopfinger asked another question which may also be outside the EPI Suite model. He has heard many times that the decision makers compare an unknown chemical with a known one and wondered if there was some modeling underway to make this more consistent. Boethling says an analog identification program is under development, but they have not had a chance to evaluate it.

Murray returned to the question of conservatism. If EPA has required testing for only 185 chemicals out of 40 000, is that conservative? (He also gave a Section 6 example) Also, polymers have been excluded. Perhaps the overall process might not be conservative enough. Patel spoke of the HPV Challenge program where EPA identified about 3000 chemicals produced in million pound or more quantities to develop additional information on. Most of the information has been received and is being entered into a data base which will be available to everyone and, which, they hope, will be helpful in the new chemicals program.

Reinert pulled up a March 3 FR where 7 of 13 new chemicals are polymers. He thinks about 50% of the new chemicals are polymers and excluded. What about additional information? If manufacturers have it when they apply, they must submit it. But they may develop new data during the application process which they will provide if asked. Also, there are dozens of categories, which, if your new chemical contains, you know you will have to do additional testing.

Reinert asked about the charge and how the Agency will use the recommendations of the Panel. Patel said their overall goal is to improve what they have currently. Their understanding is that there is a variety of expertise on the Panel because of what they know and do, so the Panel can provide broad recommendations for what the Agency can do. Because of the information quality act it is in the Agency's interest to make the models as good as they can. Resources are limited, but their senior management has been supportive so far. He is looking for recommendations in two categories - one that they can do without major new resources, and the second being improvements that would require new resources. Boethling said all improvements require resources, but the low hanging fruit, like improving user interfaces, may be achieved with limited resources.

Fehrenbacher wants to make the best use of the Panel's expertise.

McFarland would like to talk about funding and the Office of Management and Budget's Program Assessment Rating Tool after the break. He would like the Panel to think about priorities because, when the Panel's report is given to the chartered SAB, they will be asked which are the most important. He wants the Panel to understand the financial and institutional pressures operating on the Agency.

At 10:45 the Panel took a break.

The meeting resumed at 11:05.

Diamond asked whether the outputs of STP and Level 3 are used as inputs to other models. The removal rate for sewage treatment affects stream concentrations; humans use this information to inform assessments. OPPT responded that these outputs are used in a general way to help OPPT to focus its resources; if something isn't getting into the air, there is no great need to spend resources there.

Bennett asked for clarification on what industry is required to provide. Fehrenbacher said this was a programmatic issue. In the new chemicals program, companies are required by law to provide the information they have at the time of notification. In the early stages of a PMN review, if EPA has a question or needs more information, they will call the company and ask for a clarification (if appropriate) or for additional information to be provided during the PMN process. In the existing chemicals program, unless there is a regulation in place, companies are not required to provide information. EPA has a number of voluntary programs, however, to which industry provides quite a bit of information. Patel noted Section 8 of TSCA requires that, if there is knowledge of an adverse effect, it must be provided to EPA. Patel said that the applicants must provide certain information, such as use, with their notification. The Agency might ask more about the manufacture and use of the new chemical, for example, to clarify routes of exposure and so forth.

Doucette said are the fugacity and treatment models stick out because all the other modules just provide an output. It appears the fugacity and treatment modules were stuck in to provide context, but why were they put in? Boethling responded that STP was added to address a perceived programmatic need. He doesn't really know why the fugacity models were added. Fehrenbacher said SRC added those before EPA bought the model from SRC. Boethling observed that, in the HPV program, the majority of the data for environmental partitioning comes from EPI Suite. He infers from this that the outside user community finds it useful and likes it. Therefore, we should hesitate to drop the module. Doucette said he was not concerned with dropping it as much as how easy it is to accept the model default parameters and get garbage.

Doucette thinks there are certain features that would make the model easier to use for people outside of EPA. What is EPA looking for? Fehrenbacher said EPA recognizes EPI Suite is very widely used. The website allows people to ask to be notified of updates. She gets about 3-5 of these notices a day for EPI Suite. The Agency would like the Panel to make recommendations that relate to new users.

Murray spoke to new chemical submissions and data. He observed very few applicants provide any physical chemical data. Where data is available, the data would be useful in improving EPI Suite. However, he assumes it cannot be used that way, because it would violate CBI. Boethling says this is largely true. CBI adds a lot of complications to adding to improving models. Patel thinks that if chemical specific data is claimed as CBI, they would not use it, but for other chemicals, they would. Fehrenbacher gave a hypothetical where, if EPA had enough information on a class of chemicals that would allow it to develop a new method or enhance a method and that was one of their priorities AND the bulk of the data was not in the public literature, they would try to work with the companies to make that information more widely available. Because the new chemicals program is based on new chemicals and new technology, CBI is important and they take it seriously. Boethling gave an example of a chemical where this is done. If industry's trust is breached, EPA is dead in the water.

Reinert said that, even if it is CBI, it could help EPA decide which chemical categories need to be watched more carefully and which need little extra scrutiny. Fehrenbacher says sometimes companies come in with additional data for the purpose of showing a category of chemicals is safer than perhaps EPA thought.

Chinery asked about fate testing. Boethling says most of the fate testing is biodegradation testing. EPA generally asks for a protocol before they go ahead with the testing. Patel aside there are a number of published standard protocols.

Parkerton is uncomfortable with the idea that you can type in a structure and get outputs to be used as inputs to models. He asked whether OPPT had asked which algorithms in EPI Suite are most important in deciding courses of action. If the Panel knew which were most important to EPA, it could focus its own efforts on the modules most important to EPA. Boethling and Fehrenbacher said EPA has not looked at that systematically. Fehrenbacher said it depends on the chemical and the situation. It would be hard to make generalizations even within the new chemical programs. Boethling agrees but added he did think he could say that removal was important. Both Fehrenbacher and Boethling agreed that it was important to know about new properties.

Doucette asked whether any of the CBI has been used to enhance the models. Boethling said that it was used to look at analogs, but not to improve the models.

Sanderson asked why ECOSAR was not included and when it will be reviewed, the GAO report, mixtures (and expert judgment tools available to assess them), how can EPA use the HPV data to improve the models, etc. Patel observed OPPT would like scientific review of all the major models reviewed, whether by SAB or some other route. There is also the question of whether a separate review to consider how they all work together. They work closely with OECD and consider what Europe and Canada do about new chemicals. OPPT shares their tools and models widely; and the data that can be shared. Fehrenbacher said the risk assessment division, a separate division, manages ECOSAR. She doesn't know whether it has been peer reviewed because it is in a separate division, but they can check.

Cowan-Ellsberry noted there is a lot of capability in the modules that isn't obvious when you run it conventionally. She asked whether some of the features are used often. Boethling replied that, in the new chemical context, EPI Suite is run by a contractor and he would have to ask them. She also asked whether the outputs can be fed back in.

Salvito agreed with Sanderson about ECOSAR. The Panel should at least acknowledge it because it is part of EPI Suite and it informs decision-making process internally and externally.

Also ECOSAR is the key part of the PBT Profiler. EPI Suite is data-filling because the applicants often don't provide all the information requested. He asked whether there had been any retrospective review of how well EPI Suites predictions matched measured data and whether there was a pattern to the disagreements. Boethling said no systematic review has been done.

Patel said they can check with the risk assessment division to see what the situation is with ECOSAR – has it been peer reviewed? Do they plan to have it peer reviewed?

Murray asked about how EPA uses the output of the fugacity model. Fehrenbacher said it is used qualitatively to decide where the chemical is likely to end up in the environment, but not quantitatively. Information on environmental release comes from the group that does the occupational exposure. EFAST is used for this.

Thibodeaux asked about the PBT outputs. It seems to him they are asking what the most important phase is to concentrate on for additional information. Boethling agreed.

Thibodeaux sees a big difference between how we perceive the algorithm based modules like KOW which predict physical chemical properties and the modules like vaporization, fugacity and STP which take the physical chemical properties to make predications. He can see some ways to improve them. Fehrenbacher said they would be interested in the Panel's recommendations for improvement. Boethling thinks EQC Level 3 is used more widely outside EPA than within it. Cowan-Ellsberry agreed and said STP is also used widely.

Parkerton thinks that, if the fate modules were included as separate modules, EPI Suite would be more transparent and would reduce the likelihood of unthinking use of inappropriate defaults. Boethling made an analogy to EFAST which has four “buttons” to force the user to be aware of what he or she is doing.

Doucette is also concerned with how to best operate the model. There are benefits to streamlining for the experienced user, whereas forcing users to go through the individual modules is more educational. He also spoke of some mistakes that are easy for new users to make. He thinks this is almost philosophical. Boethling observed that some parameters for the Level 3 module are adjustable. Doucette and Boethling had similar examples of mis-interpretation of the air results. Diamond thought that, as an intermediate step, EPI Suite could identify what is adjustable. Mass transfer and volumes are important but not obvious.

Fehrenbacher said the individual modules have been published, but this is the first review of EPI Suite.

McFarland would like the Agency to provide some information about resources related to EPI Suite. Patel said they don't have pre-determined levels of FTE because priorities change. FTE are constant, but responsibilities increase, such as nanomaterials. OPPT does not have significant resources for EPI Suite because resources are declining and responsibilities increasing. Fortunately, their senior management thinks sound science is important and wants all models peer reviewed. If there was a recommendation to do a major redesign of the model, budget limitations would make it difficult to implement.

Priorities are important. There are two kinds of priorities. One is for making better decisions. Another is cost effectiveness of the improvements and leveraging (getting the most improvement for the resources you do have to invest). Their Director, Charlie Auer, has never zeroed out a budget for tools and models. Boethling spoke of making greater use of good models developed externally, which is much cheaper and faster than developing them internally or by contract. Patel made a similar observation about data. Industry sometimes comes forward with data on their own to help improve the models because the models impact them.

McFarland thought there were two important issues. One is, in a time of declining budgets, what is falling off the table? The other is, if the Agency had an unexpected gift of \$0.5 million to spend on EPI Suite, where would they spend it? Fehrenbacher said their highest priorities are the things they are already working on. Making the model more transparent and helping inexperienced users learn to use the model appropriately would be high on her list. After that it would be adding new features. McFarland asked about leveraging with industry to get resources to improve EPI Suite. Fehrenbacher said credibility is an issue. No matter who develops the methodology, it would have to be reviewed from a quality control perspective and EPA would have to be convinced adding it to EPA would be an improvement. There are legal issues and some mechanisms, such as CRADAS, that allow the government to work together with industry on common issues.

Hopfinger addressed the issue of leveraging and the thought that 7 of 12 new chemicals are polymers, he wondered why EPA had not made use of fragment-based polymer models publicly available for 15 years. Boethling says he didn't know about the models. Fehrenbacher said the polymer exemption was written when EPA thought certain classes of polymers would not endanger human health or the environment. Because EPA thought the polymers are not generally of concern, looking for models that addressed them was not a priority.

Sanderson said four things have to be balanced: transparency, user friendliness, accuracy, and relative conservatism of the estimates. Although it would be easy to provide advice on accuracy, that would be expensive, and it is not the most important issue. He thinks transparency, user friendliness and conservatism are more important. Patel asked whether the Panel will prioritize their time this way, or the recommendations will be prioritized. McFarland thinks Sanderson has provided a first cut on criteria for how to prioritize the Panel's recommendations.

Doucette asked what the budget was to maintain EPI Suite as it currently is. Patel said there is no line item to maintain EPI Suite. They do have line items for several things; EPI Suite falls into the one called Tools and Models. Then the office decides priorities within that line item. Fehrenbacher said that they have done some work on transparency and user friendliness, but have never looked at doing a major overhaul of EPI Suite. If EPI Suite is intended to be a screening level tool and it predicts within an order of magnitude, is that good enough that it can be used without further improvement to accuracy? If not, then the Panel might want to consider other

After lunch the Panel will discuss preliminary charge questions. No one has requested an opportunity to provide oral public comment.

When the Panel returned from lunch Bennett agreed to take on Dzombak's assignment as a coordinator for question 1Aiii. (Dr. Dzombak became ill just before the face-to-face meeting and was unable to attend.)

McFarland observed there were no members of the public who had asked to provide oral comments at the meeting. He asked the Panel whether they thought it would be helpful to discuss the public comments provided by the Chamber of Commerce. Bennett felt these should be discussed as related issues were raised in the discussion of the responses to the charge. Salvito spoke of the need to consider the sub-models in EPI Suite separately. McFarland thought he heard that they should proceed to discuss the responses to the charge and address the Chamber of Commerce comments as they were relevant to the questions. The DFO read the two other public comments (Wood and Batarseh) to the Panel. These had been emailed to the Panel earlier.

Parkerton asked about whether the data FDA collected was known to and useful to EPA. Maciorowski said the new chemical, commodity chemical, and pharmaceutical worlds are very different. They may use the same tools, but the regulatory worlds are very different and present barriers to sharing information.

Hopfinger, who comes from the world of pharmaceuticals, observed that lots of people would like to mine data at FDA. FDA likes to look at logP, others are interested in blood-brain barrier, skin penetration, etc. That overlaps with EPA's interest, but much doesn't.

Doucette had worked a year at E.I.Lilly and said that much of the data they generated was the same that would interest EPA.

Sanderson said that the Chamber of Commerce made it clear that they represent a huge industry and we should not appear arrogant. So it should be clear that their comments were considered. McFarland agreed the Panel should not be dismissive, particularly in the areas of accuracy and uncertainty.

2. Discussion of Preliminary Responses to the Charge Questions

McFarland suggested that the coordinators summarize, then there will be some discussion. This discussion is captured below with the *General charge to the Science Advisory Board* used to organize the discussion.

The Agency is primarily interested in the SAB's review of the supporting science, functionality, and appropriate use of EPI Suite. While SAB should feel free to comment broadly, specific responses to the following technical questions would be welcomed.

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?

Hopfinger said there was unanimity among those who had provided written responses that no property should be dropped. The more difficult question is what should be added. Most of those who wrote thought that aquatic transport and fate was well covered, but air and soil were not. However, models that could fill that need were not identified. Chinery said there are models that address the terrestrial food chain much like bioconcentration does for fish. Root and plant uptake may relate to KOW. There is additional information on uptake through food to cows and how that is transferred into beef and dairy products.

Cowan-Ellsberry said, based on this morning's discussion, it might be good to separate the models into those that provide p-chem properties from when those properties are passed on to models that affect fate. For a lot of bioaccumulation and similar models, we have to consider metabolism. Parkerton thinks PKA is low hanging fruit that should be added.

Hopfinger reflected that the discussion has gone from properties to environmental media. McFarland talked about setting priorities by what EPI Suite needs today, and long term. Doucette mentioned linking the properties to the models and not all those models have to be EPA sanctioned. McFarland thinks it would be defensible to consider the models EPA uses that take their inputs from EPI Suite and use that information to set priorities.

Fehrenbacher thought it would be helpful to focus first on exposure.

Cowan-Ellsberry thinks that, because EPI Suite is so widely used, they should be sure whatever is in it is very sound. This might mean refraining from adding other properties which are not as well predicted. Perhaps EPI Suite fills a role within the toolbox and then define its domain.

Thibodeaux asked whether EPI Suite should be updated to include other sorts of materials such as metals, surfactants, particles, etc. Boethling takes it as a given that EPI Suite is and should remain a structure-based program. As long as the methods can operate with the same input, there is not reason (other than resources) not to include them.

Diamond says that you could set priorities based on science or on regulatory needs. What does OPPT find lacking in its new chemical reviews. Boethling finds metabolism and bioaccumulation missing. McFarland asked, if nothing changed in EPI Suite, what would be the regulatory implications. Fehrenbacher says she is concerned about nanomaterials because they do not have appropriate tools to evaluate them. Salvito asked of the Agency is asked for more endpoints or is mapping the chemicals more important.

Sanderson came back to priorities. He's not sure if short, medium and long range recommendations are that helpful. He thinks the focus should be on the near-term.

It might look bad if the Panel put down two pages of endpoints EPA should be looking for even if it was unrealistic. Fehrenbacher thinks the more hazard driven properties are outside the scope of EPI Suite because they are addressed by a different division and her unit lacks the expertise to undertake them. Chinery agrees that the Panel should restrict their recommendations to properties for which an appropriate database exists.

Parkerton appreciates that, but still had two questions about hazard. He was concerned with photo-enhanced toxicity and other endpoints as well as properties like flammability and explosivity which present physical hazards. Boethling said the chemistry branch looks at the physical hazards and they had not considered whether they should be in EPI Suite. He doubts SAR tools are used to assess those endpoints.

Murray thought they should consider what goes into ECOSAR and what comes out of it and how wildlife toxicity is not included. Diamond mentioned other impacts, like life cycle assessment and building data sets.

Hopfinger said that he heard the Panel wants to set priorities. There appear to be two forms, the most immediate of which would be a ranking of those properties most often used as inputs to second programs, especially exposure programs, (he would need some input for that) and second the physical-chemical properties which could be added. Doucette thinks we could do that right now using the list.

Parkerton thinks some of the proposed enhancements will be more helpful than others, given the state of the science. Cowan-Ellsberry and Parkerton will help Hopfinger with this charge question.

ii. Are there additional sets of existing measured data which should be included in upgrades to EPI Suite? Are there specific measurements with the potential to improve EPI Suite estimates so much that an effort should be made to collect them?

Thibodeaux, the coordinator for this question, is still somewhat confused. The key words are “additional sets of existing measured data” There’s a lot of existing data; how do we set priorities for it? Parkerton raised the HPV data set. Sanderson noted that the HPV program was intended to bring out all the data the companies had that wasn’t in the published literature. This program will cause a lot of data to surface that would not otherwise.

Doucette thinks this question relates closely to the prior one. When you have the list of properties, you can answer the question about whether or not there is a data set to support it.

Parkerton had a critical review done of 600 chemicals in a training set for BCF; 50 of them were taken out based on quality or irrelevance. Then they looked at the primary literature for new data (including the MIDI BCF) to update the training set. He thinks there is a real opportunity to improve BCFWIN using new data. He thinks there is more concern about the biological endpoints than the chemical ones.

Cowan-Ellsberry said Parkerton's example points out the need to go back through some of the modules to see how good the data are and whether there is new data that could be added to the training set. Boethling observed that the more specific the recommendation the more useful. A recommendation that says "Look at data quality" is less helpful than one that says, "Look at data quality, beginning with . . ."

Reinert spoke of a regular scan of the literature for useful data.

Returning to 1Aii, Murray asked whether they would ever suggest data collection by EPA. EPA might have to use an ICR.

Thibodeaux spoke of the two kinds of models within EPI Suite, those that property algorithms and those fate models that use them. Most of the Panel's discussion has been on the p-chem algorithms. Should we continue that way, make one pass on the p-chem modules, then return to the other modules. There was general agreement on this two path approach – algorithms first, then models. Although some of the interface issues will overlap, the written responses will also honor this separation.

iii. Are there other capabilities that should be included in upgrades to EPI Suite? The Agency is especially interested in the SAB's views on uncertainty analysis and if/how information on how good the estimates are can be conveyed to users.

1Aiii was addressed by Bennett. (See her comments in handout of March 8 a.m.) She thought the Panel should narrow the topic to their views on uncertainty, how it can be presented, and whether it can be improved. Some of the comments in the individual responses could then be moved to other areas. She thought there were other points outside the scope of this question. For example, Murray spoke about using a close analog when available. This could go elsewhere, too.

She found four areas within uncertainty to discuss.

1. Evaluating the level of uncertainty about measured and predicted values by looking in a systematic way. Diamond notes there's a lot of overlap between 1Ai and 1Aiii. Hopfinger says that when he thinks about uncertainty, he thinks statistically. There are two issues – how good is the model and how suitable the model is for the particular chemical.
2. Is it telling you properly when you should or should not use the model?

3. If the model isn't a good fit, what should the user do?
4. How it should show you all the measured values if one than more exists?
5. While it is difficult to estimate the uncertainty, perhaps a range can be developed which could be propagated through the other models.

McFarland thinks uncertainty is open ended because you can think of model uncertainty parameter uncertainty. But is uncertainty analysis critical in a screening tool? He thinks not. Therefore we should explore what kind of uncertainty the Agency was looking for. Boethling said the question was a very general one. He cited petitions from the Chamber of Commerce under the Data Quality Act.

Doucette said the property algorithms are not designed to be conservative and aren't. The idea of conservativeness has to be separated from uncertainty. Surely the model can't be more accurate than the measured value.

Diamond doesn't think the notion of conservatism comes into the fate models because there is no reality to them, they are just illustrations.

Bennett suggested using error propagation to get a range, such as "we expect between 10 and 15% to be in the air." Diamond distinguished between variability and uncertainty.

McFarland wanted to see if there was a consensus on how EPA should capture model and parameter uncertainty and how uncertainty should be depicted.

Parkerton believes the most important thing is to determine, for each module, whether the training set is suitable for the molecule. Applicability first, then uncertainty. Chinery asked if this can be modeled. Boethling says there are multiple ways to do it and much controversy. Everyone agrees domain is important but there is little agreement on how to address it.

Cowan-Ellsberry agrees there is no consensus in the international community on how to determine whether or not a chemical falls into a particular domain. Since there is no consensus we need to flag it as an issue and state that there is no agreed upon way to address it.

Cowan-Ellsberry has found that the worst predictions occur where fragments are missing. Some recommendation about this issue is important as an interim solution.

Salvito agrees lack of fragments is important because it influences KOW which is used in many other models. One way to approach the domain is to say the kinds of chemicals used to build the model, something like what is used in Lyman. When you talk about the physical property modules the uncertainty analysis is different. You can give a confidence interval for the modules and compare them to other approaches. It is more difficult for the fate models.

Murray says for chemicals that fall outside of the training set, there is a difference in his mind between 10% above and three orders of magnitude

Chinery hears two approaches

1. Go get the frags
2. Continue to follow the discussion in the domain area and, when consensus is reached, employ it

Doucette spoke of estimated values outside the range of measured values. It could be right, but should be flagged.

Sanderson thinks uncertainty analysis should be quantitative wherever possible. Expert judgment will change with the experts and many are set to retire. McFarland said this raised the question of propagating the uncertainty through the model. Bennett thinks the Panel should recommend the Agency do just that. McFarland asked if you could justify Monte Carlo approaches, Bennett thought not. Diamond thought the HELP sections could be more forthcoming. Sensitivity could be addressed in the HELP section as well. Doucette observed that people use it unthinkingly, which is why he recommends ranges. Diamond says this would have to apply to mass transfer coefficients. Thibodeaux isn't sure about this, but he does agree with Doucette about having a range. Parkerton doesn't think that it is trivial to assess uncertainty of parameters. Variability isn't random, KOW variability goes up with KOW. Hopfinger says they routinely use residuals of fit for air analyses. There are standard statistical approaches to these problems.

Diamond thinks there are methods. McKay and MacLeod have some simpler approaches suitable for screening level. Parkerton says the first estimate of uncertainty is looking at the underlying experimental measurements. So, just characterizing that helps the users.

Doucette says the training set has been selectively culled of numbers that some expert thinks were not appropriate so there is only one value for each parameter. He thinks you lose a feel for the data that way. A recommendation could be enhancement of the phys-prop file.

Hopfinger said the issue could be approached another way. For some of the priority endpoints, you could use consensus modeling where you go to multiple models and see if you get similar answers.

Agreement was not reached by 4:20.

B. Method accuracy and validation

i. Is the accuracy of the modules in the EPI Suite sufficient for its various specified uses?

Reinert summarized using his individual comments (p 13 - 18). (His updated text was distributed March 8, in the morning.)

Murray observed that Reinert said the outputs could be overestimated or conservative, but Boethling said they were best fit. Reinert agreed that the physical property estimates are not conservative. Murray doesn't think the Panel should say the estimates are inherently conservative unless we believe it is and provide a basis for that conclusion.

Diamond is not comfortable with the discussion of conservatism, but she is interested in uncertainty, confidence limits and bias.

Chinery went into the HELP screens for BIOWIN and couldn't find some of the information Reinert found. Reinert got it from the HELP files the Agency forwarded. If it isn't there, it should be.

STP has some conservatism because the default is to assume no treatment.

Parkerton observed that the validation is not necessarily tied to a particular version and EPI Suite has evolved over time. Boethling said most likely the evaluation was done on the original version.

ii. Have the modules been adequately validated, and have they been published in the peer-reviewed technical literature or elsewhere?

Diamond summarized for 1Bii. (She provided revised text March 8 in the morning.) She began with the difficulty of words like evaluate, validate, etc. Chinery used OECD's five characteristics for deciding whether or not a QSAR was valid. He feels much what was in this section - like a discussion of domain - has already been discussed. The only additional issue was the use of predicted KOW values to predict, for example, water solubilities. Boethling thinks it was done for one or more modules, but not all and he doesn't know if it is in the EPI Suite drop down HELP module.

Hopfinger mentioned two additional measures of fit: Q Squared and Random Scrambling R-Squared. Diamond will add them if Hopfinger will provide a few sentences.

Parkerton brought up an interface issue. Where there is experimental data for some, but not all, chemicals in a related series, you may get some odd outputs that could lead to some strange decisions. Boethling asked, "How would you fix that?" Parkerton spoke to the training set and Boethling to lack of user training. Diamond also spoke to the "User Beware" issue. They joked about annoying pop-ups and noises to awaken the user to the difficulties.

The fate models cannot truly be validated and this needs to be conveyed. Also, STPs have improved since the original model was developed.

1Biii. Are some modules more accurate/better validated than others, and if so, which need more work?

Salvito thinks a lot of this has already been addressed in the earlier discussion of accuracy and validation. (His revised text was distributed March 8 in the morning). He asked, "When you think of the modules, does it matter which are better than the others or that each is the best currently available?"

Doucette thinks the KOC module is getting pretty dated and he's not a big fan of KOC anyway. A lot of the data weren't generated properly, either. It is still the most widely used model and it works reasonably well. KOC is not a very constant constant. Boethling asked how else they would approach soils.

1Biv. To the extent that modules work together to generate estimates, do they do so correctly?

Salvito said, basically, yes.

There was a brief discussion of the organization of the report, the inclusion of different points of views in responses, the need for priorities and the criteria therefore. etc.

Wednesday

The meeting did not start until 9:15 because the DFO needed to make copies of six inputs that had been written overnight and there were copier problems.

With the exception of Dr. Dzombak, all panelists were present. Cathy Fehrenbacher of OPPT was present. Kathleen White of the SAB staff was present as DFO. Steve Gibb, Chief Editor of the Risk Policy Report, attended. There were no other attendees.

The Panel began by revisiting the issue of uncertainty. Panelists may have different ideas about uncertainty and, if consensus cannot be achieved, then the varying views need to be presented in the report. Bennett led the discussion. There was agreement that EPI Suite is not conservative, but accurate. Estimates for compounds within the domain there is less uncertainty than for compounds outside of the training set. However there is no consensus within the scientific community at this time on how to determine domain. The Agency could run a workshop on this.

The Panel discussed measures the Agency could employ as a stop gap measure. The Agency could consider whether a significant number of fragments are missing. This might be more important for the fragment based models within EPI Suite than for the property model. Cowan-Ellsberry suggested that EPA list what is NOT in the training set and provide a flag to the user when the user is outside the training set.

Doucette suggested that the CBI information be used to improve the model even though that information cannot be shared. Murray and Sanderson believe that would make the use of the model problematic as the information with which to falsify/review it would not be available. Bennett will craft compromise language.

Bennett raised four more issues: partitioning coefficients, half lives, bioconcentration factor, models.

For partitioning, we know larger KOWs have more uncertainty than smaller ones. Possibilities include developing compound specific uncertainties. Another is to provide general range and present it in the output and a third is to provide ranges in the HELP files, but not in the outputs. Doucette said KOWs for very water soluble compounds also have more uncertainty. He struggles with whether the training set provides a statistically basis for setting the uncertainties. Salvito hears Doucette as advocating the second option as ideal, but the third as more practical. Salvito doesn't see what providing uncertainty for a model output means. Parkerton says if it outside the training set you can't calculate uncertainty anyway. Diamond thinks the single number has just as much meaning as the number with confidence levels but the confidence levels help you with subsequent analysis. Sanderson doesn't think the bands will change the output of the screening so we are just creating numbers for no reason and perhaps even obscuring what's going on. He thinks the Agency's efforts to improve EPI Suite would be better used elsewhere.

Bennett and Thibodeaux proposed that, for things within EPI Suite, such as STP, we know that above and below certain vapor points the compound will be found either primarily in air or water. While this would not be quantitative uncertainty throughout, it would address whether or not the compound is close to one of these margins. There would be more uncertainty when the compound was close to one of the margins. Diamond said KOW goes into other models. Therefore, she thinks putting intervals on that are based on use is unwise. Bennett thinks the approach could be employed for other uses. Doucette suggested that for those models EPA operates it could be done with flags. Parkerton's fundamental concern about uncertainty analysis is that it is typically incomplete. You have model prediction error and measurement or data error. Today, when we calculate uncertainty we only consider model error and ignore data error. To do the analysis properly you have to propagate both model and data error, which are not independent. Diamond said the fate models can't be verified anyway – they are abstractions. Parkerton was talking about QSPR models.

McFarland thinks Doucette may have articulated a healthy compromise. Murray reflected on Bennett's proposal. If you ran EPI Suite for chemicals we already know the behavior of, you could see if the results made sense in terms of what action might be taken.

McFarland asked Parkerton to write up his position with the pluses and minuses of including quantitative uncertainty analysis. Bennett will present her view as well.

Boethling asked for an example, as specific as possible, of what kind of statement you would make, taking existing information already in EPI Suite HELP files (not chemical specific), and make the statement the Panel envisions. Parkerton responded, "50% of the data are less than a factor of 2, 20% are less than . . .". Salvito observed that this model is being used in a very large batch scale to consider thousands of chemicals at once. The errors will get lost in this paper. Doucette says it is more helpful to people looking at a small set of chemicals of a single type.

McFarland wants to defer discussion of mis-use of the model until uncertainty has been settled.

Bennett also thought it could be set up so that the user could select whether or not to have the ranges as part of the output.

At 10:10 the Panel discussed the breadth of users and potential misuse. McFarland asked EPA whether, in their development and refinement of EPI Suite – which was done for EPA’s uses – it had taken into account the needs of other US regulatory agencies or even international bodies. The model is being used globally now. Fehrenbacher said they have received requests from other governments who want to give them the source code so they can take EPI Suite and turn it into the model they would like to use in their country and EPA has not done that. As the panel read in Layla Batarseh’s comment, EPA gets requests from other federal agencies for help using EPI Suite for their uses. Even if EPA tried to incorporate caveats, it is possible that others would not benefit from them because their use is so much different from the intended use of EPI Suite.

EPA has focused on the intended use of EPI Suite for EPA’s purposes and make the model as transparent as possible, including up front “user beware” notices.

Cowan-Ellsberry doesn’t think the Panel’s concerns are outside the spirit of what EPA said. The model is used widely throughout the world and it is clear EPA is careful about what they put out. The problems have been when people have used the model stupidly. She thinks that propagating uncertainty will actually mislead naïve users into believing there’s more certainty to the model than there is.

Cowan-Ellsberry has had problems with non-EPA regulators all over the world who do not seem to recognize – although OPPT does – the classes of compounds for which EPI Suite does not generate good predictions.

Fehrenbacher gave examples of where they had kept EPI Suite as a stand alone tool instead of linking it so that people can’t just press a button and get an answer without thought.

Doucette developed a software tool for the Air Force and it is IMPOSSIBLE to keep people from mis-using models, but you can provide more guidance. For example, you could force them to go to the data first, before generating any estimates.

There was discussion over whether to get rid of batch mode because it is easy to misuse, or keep it because of its utility.

Salvito said, if you put boundaries around a number, colleagues in other countries who are more precautionary, will take the worst value even though the real uncertainty comes from other issues, such as the failure to consider metabolism.

Absolutely, the measured values should be used where they exist.

McFarland questions whether or not European uses should have any influence on EPI Suite. Fehrenbacher observed that, while they have some stewardship responsibilities, EPI Suite must meet EPA's needs, and if it is helpful to others, great. Boethling asked how Europe's needs differ from EPA's.

Boethling says EPA runs EPI Suite mostly in individual mode.

Bennett and Doucette think that, if the properties were bracketed with an error bar, there would be a tendency of Europeans to pick the value that most reflected their policies. Chinery asked whether all EPA users are trained and have a sense of the uncertainties? Fehrenbacher said OPPT's users are trained, understand uncertainty, and have experts down the hall that they can call on. He thinks most other Agency users are trained and know who to call if they have questions. However, they have not sponsored EPA Training classes on EPI Suite. But they have provided basic training in EPI Suite through the Sustainable Futures program.

Sanderson is still struggling with accuracy and its importance. He understands why scientists value it, but sees EPI Suite as primarily a decision-making tool that assists EPA and industry. It is important that the HELP files be updated considering global use and including explicit discussion of uncertainty and accuracy. He does not think EPA should have to work about the European REACH effort. The most important thing is to keep the HELP Files updated for current uses.

Murray thinks that, if the Panel thinks something is too onerous, it should say so.

At 10:30 the Panel returned to the discussion of its responses to the charge questions

C. Estimation Methods and Alternates

i. Are the estimation methods in EPI Suite up-to-date and generally accepted by the scientific community for its various specified uses?

Sanderson led the discussion. Up-to-date, scientific community, and scientific community are the ambiguous words. He thought EPI Suite was up-to-date enough. The scientific community is split between general users and regulators with different traditions on transparency, etc. The OECD gives EPI Suite a high reliability score in its assessment, believing that, in many cases, it is better than a measured value because there are so many poorly measured values. The models have been peer-reviewed and are well understood. Hypothesis-generation and evaluation are the primary uses. He provided points that have to be considered in QSAR models and also discussed the OECD criteria for the use of models. For screening processes, speed and transparency EPI Suite is very good.

He included two quick case studies. The first is a comparison of SPARC and EPI Suite on the water solubility of certain alcohols. While SPARC did a little better at the extremes, it has other limitations, including poor transparency, so EPI Suite is preferred.

It just means you need to get data for the tails. The second compared EPI Suite with experimental values for hydrolysis which gave errors of half a log, which is fine. He doesn't think EPA should go to SPARC to gain these small improvements in accuracy.

Chinery thought a summary assessment of the various tools could be included. He mentioned the difficulties of the use of these models for nanomaterials. He acknowledged the global responsibilities EPA has for these tools. He thinks, on the whole, it is better that so many individuals and institutions have access to these models.

From a scientific and regulatory perspectives the tools balance the five criteria of transparency, accuracy, uncertainty, feasibility, and .

Hopfinger took the "up-to-date" statement pretty literally. They aren't. Simple regression methods don't maximize the amount of information you can extract from a data base. Statistical methods for this have improved in the last decade. When you talk about an order of magnitude or less for screening models, you can do better with categorically models than with a more general model. You might want to use a logistical model for fitting. This would be state-of-the-art for getting the most bang for your buck. It might not be practical, but it would be state of the art. McFarland asked whether the Panel agreed EPA should consider more up-to-date statistical methods. Doucette and Diamond thought such a recommendation would be in harmony with what had already been said. Murray asked for a couple of references where the new statistical approaches had been applied for similar problems.

Cowan-Ellsberry mentioned DERMWIN because the Panel has not discussed this. Sanderson will revise to reflect

ii. Are there other estimation methods which should be considered in upgrading EPI Suite?

Doucette finds this issue ties into many discussions. Are there any other methods to predict properties already in EPI Suite? There is no consensus other than there should be a reference to the other alternatives. But the overall idea is consensus modeling – if multiple models predict similar values you are more confident in the results. Are there any methods to predict properties not now in EPI Suite? (PKA, ionizable, acid-base, temperature dependence, and additions already planned such as anaerobic biodeg . . . ; also ones mentioned yesterday for terrestrial and air, etc.)

Doucette would like the material on other properties to be included in his answer as well.

2. Functionality (Program documentation; user interface; convenience features)

A. *How convenient is the software and does it have all the necessary features?*

Murray says EPI Suite still feels like a DOS program and it could be modified to have more of a windows feel in terms of moving around. He can suggest some minor improvements to the operational settings. Doucette would still feel better about isolating the fate models from the phys-prop. To him these are totally separate issues. Salvito thought this could get around the batch issue. You could run the physprop in batch mode, but you would have to think before you put it into the fate models. Cowan-Ellsberry and Bennett think it would be nice to be able to access the individual models from the interface.

B. Are there places where EPI Suite user's guide (and other program documentation) does not clearly explain EPI's design and use? How can these be improved?

Cowan-Ellsberry thinks the documentation is quite good; the problem is people don't use it. Because much of the information is repeated in the different guides, it tends to dilute the information unique to each module. She thinks there may be better ways to present the information. The introductory paragraph can be further improved. The whole guide needs to be available in a way where it can all be downloaded at once. Parkerton suggested a blurb on common mistakes. Hopfinger knows of commercial models which are regularly updated and could be used as templates for how to reformat the EPI Suite HELP section(s).

There was a brief recess for lunch. When the Panel returned, Cathy Fehrenbacher said a few words about ECOSAR. Parkerton will draft a few sentences for the report about why the Panel did not review ECOSAR

C. Are there aspects of the user interface (i.e., the initial, structure/data entry screen; and the results screens) that need to be corrected, redesigned, or otherwise improved? Do the results screens display all the desired information?

Bennett led the discussion. She was a new user and others in her group were more experienced. The biggest issues are:

- the Panel's preference for having multiple measured points and references in EPI Suite
- some questions about structure
- results should have similar notation
- the default should be the full display option because you learn a lot from it
 - Diamond thinks this will be tedious for experienced users.
 - Salvito thinks this could be solved with a settings feature
 - Doucette says this results from its DOS history and evolutionary development. This might not be the best place to spend money.
- nice to have the option of putting output into EXCEL

D. Currently one enters EPI Suite using SMILES and CAS; are there other ways to describe the structure (e.g., ability to input a structure by drawing it), that should be added?

Hopfinger led the discussion. (see handout of March 8 a.m.) The bottom line is that the three contributors felt the SMILES and CAS are adequate to query chemical structures, so there is no urgent need to add input options. However, most chemists would prefer to draw in a structure. Also, the casual user can easily forget some of the SMILES notation rules whereas they are more likely to remember their organic chemistry.

Chem-draw allows you to draw the structure and transform it into SMILES so it can be entered into EPI Suite. It doesn't make sense for EPA to develop it's own program to do this, especially if later it goes into the 3-D area and will need something like Chem-draw.

A convenience option could be a master label for a congeneric series of compounds. Another option would help you see which parts of a molecule are responsible for a particular property; this would involve some visualization software.

Salvito asked about INEX numbers and other descriptors but there was no interest in it. He asked Parkerton about CAS numbers for mixtures. Parkerton said it would be nice if the Agency was assured that the chemical evaluated represented the mixture. Sanderson thinks it would be nice to get SMILES updated because when you get to larger CAS numbers you run out of SMILES numbers. There are ways around this, but they don't work very well.

Hopfinger says that, if polymers get more consideration, there's some thing better than SMILES.

McFarland asked whether the Panel wanted to say anything about polymers. Hopfinger will address in 1Ai. Diamond thought we should return to this after the Panel finishes its first run through of all the charge questions.

E. The EPI Suite has many convenience features, such as the ability to accept batch wise entry of chemical structures, and automatic display of measured values for some (but not all) properties. Are there other features that could enhance convenience and overall utility for users?

Murray (see handout of March 8 a.m.) emphasized these suggestions were for convenience. He noted that the GAO report and the SMILES disagree by a factor of three on the number of chemicals in the old chemical inventory.

Doucette spoke of the convenience of drop down menus with things like unit conversion options.

F. *Are property estimates expressed in appropriate units?*

Salvito responded yes but would like more attention to correct and consistent use of significant digits. Diamond had other comments, mostly relating to BIOWIN, that may be moved from here.

G. *Is adequate information on accuracy/validation conveyed to the user by the program documentation and/or the program itself?*

Parkerton thinks much of this was covered in earlier discussions. His thoughts were distributed in writing on mid-day March 8. The basic answer is yes, but not always in a consistent and transparent manner.

There was some further discussion with Doucette will capture and send to Thibodeaux

3. *Appropriate Use*

A. *Currently Identified Uses: review of PMNs, P2 decisions, predicting physical/chemical properties and environmental fate and transport properties for HPV Challenge chemicals, to begin the assessment of exposure, and other routine OPPT uses. It is important to understand that EPI Suite is intended to be used in the absence of measured data and not take their place.*

i. *Is the science incorporated into EPI Suite adequate for each of these current uses?*

ii. *If not, what improvements are needed to make EPI Suite adequate and what alternate approach could be used in the interim?*

Chinery led the discussion. The science in EPI Suite is acceptable for current uses: risk based priority setting, lower tiers of risk assessment, and setting priorities for testing. The order of magnitude estimates are appropriate for the uses identified. He could separate the answer into QSAR and other models, but it wouldn't change the answer.

Reinert sent something to Thibodeaux on 1Aii and perhaps 1Bi identifying other alternative methods that would allow some comparison. There is nothing that should be dropped, but things could be added. It's used well inside EPA, its when others shove tens of thousands of chemicals into it and makes decisions on the input that it's inappropriate.

There was more discussion of polymers. Some are exempt and some are not. Those that are not exempt are carefully considered.

Thibodeaux asked about mining and minerals in the context of HPV. Fehrenbacher said that, within OPPT, another group normally looks at metals and her group provides them with increasing support. There is more likely to be measured data for metals.

Sanderson said that metals are among the HPV documents. If you want to learn about metals and HPV, you should look at the recent zinc document. Salvito asked how OPPT would assess an organo metallic; Boethling responded mostly like an organic. Parkerton talked about considering where the domain of the model needs to be improved by providing new experimental data. McFarland would like this captured in 3A – the business of chemicals outside the domain.

Hopfinger said there are commercial packages for organo metallic property predictions. Compounds between 500 and 3000 of molecular weight used to be a no-man's land. More chemicals are coming out in this range now. Boethling says they limit EPI Suite to things which have molecular weights of 500 or less.

B. Potential Additional Uses

Cowan-Ellsberry led the discussion. She identified broad areas of potential additional uses.

Nanomaterials were discussed. Salvito suggested taking another look at DERMWIN if nano is an issue. Doucette says the current emphasis is workplace exposure to nanoparticles. Salvito says EPI Suite deals with chemistry, but the unique part of nanoparticles is their physics. Chinery thinks nano should be discussed in Hopfinger's 1Ai which prioritizes new modules. Sanderson understands the drive to get nano into EPI Suite, but if you can't get metals and polymers into EPI Suite, it is a long stretch to get nanoparticles into EPI Suite. The Panel needs to be careful here. Salvito suggested their might be a separate nano toolbox so that EPI Suite could answer the chemical questions and another tool address the physics of nanomaterials. Reinert indicated that regulators don't know how to approach nanomaterials yet. This is definitely something for the future. It's not that there isn't a real need to understand nanomaterials, it's just not possible to move it ahead right now. Sanderson noted that, the EPA /ORD/SPC September 5, 2005 white paper on nanomaterials explicitly said nanomaterials should be run through EPI Suite.

Sanderson sees global applications as the primary are of new use. EPI Suite can make a substantial contribution to sustainability on a worldwide scale -- if EPI Suite is made available in other languages.

Murray thinks EPI Suite could be used to reduce testing. If you look at the chemical data available, you might want to choose one test rather than another. Parkerton said this is called partition-driven effects testing.

Salvito mentioned the use of EPI Suite to reduce testing in the HPV challenge testing.

The Panel took a break from 2:20 to 2:40.

When they returned, the Panel discussed the possibility of revising their sections at a writing session this afternoon, giving the materials to the DFO to integrate, copy and distribute. Panelists agreed in principle, but if the discussion went on too long, there would not be enough time to do this.

Discussion began on 1Ai and a possible recommendation to move DERMWIN out of EPI Suite because OPPT doesn't use it or maintain it. If it can be moved elsewhere where it will still be publicly available, it should be, but it would be better to keep it in EPI Suite than lose it. Boethling said, from his view, exposure ends at the skin. However some external users might find it convenient to have it there. Fehrenbacher said they would still be responsible for maintaining it. She said they can consider whether or not it is a viable Agency model. Parkerton knows of at least one alternative model. Murray asked if OSHA was doing its own exposure models; Fehrenbacher responded that OSHA doesn't make much use of models.

Hopfinger divided up the priority setting for existing and new properties into algorithm estimated properties and fate models.

Bennett considers vapor pressure and solubility as among the properties which should be improved; vapor pressure is more important for indoor exposure which is relevant to occupational exposure. Boethling said that the preferred way to get Henry's Law is from measured values of vapor pressure & water solubility.

Besides use of the output in other models, criteria for setting priorities include short and long term (Sanderson), uncertainty in the QSAR and degree of external validation (Chinery), and the fraction of chemical submissions that fall outside the model domains (Parkerton).

Doucette says we should consider the importance of the parameter AND the state of the art for estimating it. KOW is twenty years old has thousands of chemicals in the training set.

Thibodeaux's question is which data sets need to be updated (Parkerton mentioned three, including BCF)

Bennett suggested making two cuts. Parkerton asked if it would be appropriate just to list the criteria for setting priorities rather than setting them. Doucette says log KOW is just an intermediate calculation; it doesn't fundamentally represent something that is going on in the environment. Sanderson thinks it is extremely important.

Diamond says we can't do absolute ranking, so we should provide a series of rankings Agreement is to just provide the criteria.

There was a long rambling discussion. Diamond and Murray discussed the relative value of BAF and BCF in a screening context. She would prefer to see more emphasis on PKA, a view with which Cowan-Ellsberry appears to agree. Are we making mistakes with BCF at the screening level. Parkerton thinks it is more important to exploit the good quality of data in the literature for BCF than adding a BAF that can't be parameterized.

Hopfinger feels the discussion blurred the distinction Thibodeaux had proposed between the algorithms that estimate properties and the fate models. Doucette spoke about fundamental properties. There seemed to be agreement on what he was saying and Hopfinger says that, if we are tossing out the concept of important properties, Doucette's concerns do not fit in 1Ai. Doucette will provide language to Thibodeaux.

At 3:50, discussion shifted to 1Aii with Thibodeaux leading the discussion. The current text does not say much about vegetation, marine, etc. Issues arose about whether things had been published and updated. HELP files could be published in peer reviewed journals; Boethling thinks this would be difficult as it is not new work. Doucette says it could be presented as a review. Sanderson thinks it is new.

Bennett proposed writing on the pluses and minuses of propagating error through fugacity. Diamond summarized this as three options. Thibodeaux and Bennett had reached some agreement. Doucette thinks if you separate the property algorithms from the fate models, the problem is simpler.

Loose ends – decoupling of the models could go into functionality. Murray has this in 2E. Parkerton spoke of what was in and out of scope; this should be in the introduction. He will draft it and talk about how informed and engaged OPPT staff were. McFarland spoke of the positive things about the model – saving on animal testing, etc. Salvito, Diamond, Parkerton, and Cowan-Ellsberry will write on this.

The panelists worked until about 6:30 after which the chair and DFO integrated the test into a single document which was emailed to the Panel in the evening.

Thursday

The full panel (less Dr. Dzombak who was sick) convened at 9:00 a.m. Kathleen White of the SAB Staff Office was present as DFO. Cathy Fehrenbacher and Bob Boethling of OPPT were present. No members of the public or press were present. After the Panel briefly considered the draft, they decided to write short summary responses to each charge question which will be helpful in establishing consensus, making the report more understandable to the reader, and in the preparation of the Executive Summary. Drs. Bennett and Parkerton made further revisions to the section on uncertainty in 1Aiii and Dr. Murray provided brief edits.

SAB Staff Office Director, Dr. Vu was able to attend from about 10:30 to 11:00. At 10:45 the Panel used the multi-media projector to put up the conclusions. The charge question coordinators undertook to make edits as the conclusion to their charge question was discussed. The revised text was displayed for all to agree on. After agreement was reached on one conclusion, the Panel moved on to the next.

Parkerton suggested some of Reinert's material be moved to an appendix, to which he agreed. Sanderson suggested the same for 1ci. There was general agreement that the responses to the charge questions should be limited to about 2 pages with the remaining material moved to appendices.

At 1:00 Neil Patel, Cathy Fehrenbacher and Bob Boethling were present along with the whole Panel, Kathleen White, DFO, of the SAB Staff Office, and Cheryl Hogue of Chemical and Engineering News.

McFarland opened the summary briefing by recognizing the Agency's development of EPI Suite as a valuable, easy to use, readily available tool appropriate for screening. Overall the Panel strongly supports not just the development and maintenance but also the further advancement of EPI Suite. Using the conclusions developed by the Panel before lunch, he summarized the Panel's responses to the charge questions. The Panel had an opportunity to correct or expand on his statement but no one felt they needed to say anything.

At 1:30, Neil Patel of the Agency responded. He really appreciates their work and mentioned certain areas in particular. He spoke of the importance (and expense) of belonging to larger organizations like ANSI. They will provide more information on ECOSAR. Overall they appreciate the Panel's work. He, Cathy, and Bob will sit down with more senior management and more of the staff to share what they have learned.

Fehrenbacher said it was a pleasure working with the Panel and hoped OPPT had provided the information they needed. The Panel was thoughtful and on task and understood both resource limitations and the directions in which the Agency would like to go. She had a few comments on the draft reports which was distributed this morning where the language is not, perhaps, consistent with the conclusions articulated and revised this morning.

1. The discussion of uncertainty on page 14, line 8-9. It is correct, but the decision to quantify uncertainty is made on a case by case basis, varying by program and need. The Panel may wish to clarify what it means by explicit acknowledgement of uncertainty and consider the Agency guidance if this statement remains in the report.

2. On page 18, line 28 “no formal . . . or models occur,” is not quite correct. There may not be a set formal process and schedule, but the scientists are continuously looking for data and to make improvements. Scanning is part of their jobs but how much time and resources they have for this is limited.

3. On page 20, line 3 “Based on this model prediction . . . is not a concern.” She’s not sure one of their assessors would reach that conclusion, although someone outside the Agency, who is less experienced, might. Parkerton said they could say novice or inexperienced.

4. On page 20, line 31 she would like a clarification, “Data should be verified from primary sources whenever feasible.” She wasn’t sure of the context because they use the databases within EPI Suite as quick pointers, but they would go to the primary references for their assessments. Reinert said sometimes tables of data propagate errors. It takes a lot of time to check this, but when it’s possible, it is good to check. Secondary and tertiary sources can get it wrong. Parkerton also thought, if there were future updates of the model, that would provide an opportunity to provide a more rigorous process for selecting data and improving the training sets. Especially as you move to new endpoints. Parkerton or Reinert will reframe in this more positive way.

Fehrenbacher reminded the Panel that they do have QA/QC procedures in place for both assessments and software.

5. On page 35 line 2 “The OECD HPV . . .” Sanderson clarified there are two OECD assessments underway on similar topics.

6. The Science Policy Council White Paper on nano does not recommend EPI Suite, but mentions EFAST explicitly. OPPT will look into this.

She then provided updated information on ECOSAR. Vince Napholz said ECOSAR was peer reviewed 5 times – in 1989 by contractors, 1994? EU EPA . . . , two articles (a book chapter and journal article) by Kaiser, Environment Canada, and a Netherlands Laboratory reviewed for OECD.. Fehrenbacher will email details to White. Sanderson is aware of the ones she mentioned. The more thorough assessments were late 80s to mid 90s. He thought a more dedicated review that repeats the mid-90s assessment would be valuable. Salvito thought there had not been an assessment of ECOSAR in the context of overall chemical assessment

Boethling echoed Fehrenbacher, noting that the quality of work, being on point, and attention to detail, is exactly what they were looking for in a peer review. He has nothing to add to or criticize about the main points. There are a lot of practical things there. He would like to have someone look over the document in a holistic way. There seems to be some internal inconsistencies concerning conservatism and potential false negatives and false positives. Domain may be another area that could stand a look. On page 12 "for compounds . . . all such data should be presented" is fine in principle, but if there are 100 values, it is asking a lot. McFarland will look for this.

The DFO will take what she has today and send out on Friday.

Parkerton suggested individual coordinators make their sections as pithy as possible with people providing inputs to the relevant coordinator, including what could go into an appendix.

Vu reminded the coordinators to CC the DFO on materials they sent to each other.

The Agency would like to receive both what goes to the Panel March 10 and their revisions which will be due March 17. Coordinators will have final version by March 24. The Agency will comment on the same draft the coordinators will revised and the DFO will prepare boilerplate.

Boethling will comment on the March 24 version, not the earlier one.

McFarland thanked the Agency and hoped that the Panel's work would help OPPT retain support for EPI Suite even at OMB PART review.

Parkerton observed there might be some merit in saying that the, "Allocation of resources . . . is not commensurate with the value." Vu responded that the Panel could absolutely say this. It is a general recommendation which would be very appropriate in the letter to the Administrator.

Thibodeaux said the Panel was proud to be part of this important effort and hoped they could help move it to the next level.

At 2:15 Sanderson said the should also stress the significant contribution EPI Suite makes to sustainability and the emerging economies.

The meeting adjourned at 2:20.

Respectfully Submitted:

/s/

Ms. Kathleen White
Designated Federal Official

Certified as True:

/s/

Dr. Michael McFarland, Chair
EPI Suite Review Panel

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

1. Federal Register Notice
2. Agenda for the meeting
3. Workgroup roster and biosketches
4. Comments prepared by individual workgroup members in advance
of the meeting
5. Email approving minutes