Report of the Second Meeting of the Peer Consultation Pilot for HPV and EHPV Submissions

Meeting Held at:
U.S. EPA, Washington, DC
December 15-16, 2008

Peer Consultation Organized by:
Toxicology Excellence for Risk Assessment
(http://www.tera.org/peer/)

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Introduction

On December 15 and 16, 2008 a panel of experts scientists met in a pilot public peer consultation meeting to provide stakeholder comments on High Production Volume (HPV) and Extended HPV (EHPV) submissions. The meeting was held at the U.S. Environmental Protection Agency (EPA) headquarters in Washington, DC. Industry representatives were present in person or by teleconference to answer the panelists' questions. This report summarizes the key scientific questions and comments of the panel on ten submissions.

Approximately 40 chemicals have been selected by the American Chemistry Council (ACC) and EPA to undergo review in this pilot project. The submissions, including robust study summaries of available data and test plans describing available data and proposing additional studies as necessary, are being reviewed by the panel members at two 2-day in-person meetings being held before the end of 2008. The first meeting was held November 18-19, 2008 and this is the report of the second meeting.

The HPV peer consultation pilot project was designed to provide expert review of HPV chemical hazard robust study summaries and test plans prepared by industry sponsors under the HPV and EHPV Programs. Under these programs, companies and consortia voluntarily sponsor chemicals that are manufactured and/or imported in the U.S. in quantities of 1 million pounds or more annually. Sponsorship in the original HPV Challenge Program involved providing the EPA with a test plan and robust study summary, which was then posted on EPA's public website for 120 days, during which time interested stakeholders and EPA could post comments regarding the content of the test plans and robust study summaries. The industry sponsor was then free to incorporate or offer further explanation regarding the comments made. If the sponsor did not agree with comments made, the sponsor prepared and provided a rationale for the rejection. The American Chemistry Council (ACC), in cooperation with the broader chemical industry, the EPA, and the Physician's Committee for Responsible Medicine (PCRM), launched the HPV Peer Consultation Pilot in the fall of 2008.

The purpose of the pilot is to test a new approach to provide stakeholder and EPA input on the robust study summaries (RSS) and test plans (TP); especially for the EHPV Program. The pilot will use in-person meetings of a small panel of stakeholder and expert scientists. Panel meetings will be used to facilitate exchange of expert opinions on the technical soundness of the RSS/TPs to better inform the ultimate stakeholder comments on the RSS/TPs, as well as ensure completeness of comments for sponsor consideration. The goal of a revised program is to expedite the review process for both EPA and stakeholder comments and present opportunities for the different parties to discuss scientific and technical comments with one another.

Toxicology Excellence for Risk Assessment (*TERA*), an independent, non-profit scientific organization, designed the pilot process and convened and facilitated the technical peer consultation panel meeting. The chemical industry is providing the funding to *TERA* for this project. Additional details about the pilot program are available at http://www.tera.org/peer/hpv/hpvwelcome.htm.

The panel members included expert scientists from two organizations who provided comments on test plans submitted under the HPV Challenge program (i.e., PCRM and EPA). Panel members included: from EPA - Dr. Louis (Gino) Scarano (human health endpoints) and Mr. Larry Newsome (ecological/environmental endpoints) of the Office of Pollution Prevention and Toxics; from PCRM - Dr. Chad Sandusky; and Dr. Hazel (Skip) Matthews, who authored many of the comments submitted by Environmental Defense Fund on the original HPV Challenge submissions. A senior scientist from *TERA* (Dr. Michael L. Dourson) facilitated the panel meetings to ensure that all appropriate scientific issues were addressed. Also in attendance at the meeting was Dr. Nancy Beck of PCRM who assisted Dr. Sandusky, and on occasion provided clarifying information on behalf of PCRM. Dr. Andrew Maier of *TERA* took notes and drafted the meeting report.

A representative of the company or industry consortia that sponsored the submission was also present in person or on the phone to answer the panel members' questions. These representatives were also allowed to ask clarifying questions of the panel so that they could ensure their understanding of the panelist comments.

The meeting was open to the public and interested persons were allowed to attend in person or by teleconference. Interested persons were invited to submit technical comments prior to the meeting for panel members' consideration; however, no public comments were received. A complete listing of attendees is found in Appendix A.

The meeting agenda is found in Appendix B. The meeting began with a welcome by Dr. Andrew Maier of TERA. He described the background and purpose of the peer consultation pilot and the panel members introduced themselves briefly. Dr. Michael Dourson, the panel facilitator, then described how the meeting would be conducted and the ground rules. He noted that all panelists would have the opportunity to state their positions on the charge items, to ask one another clarifying questions, and to discuss the issues further. Because this was a peer consultation, no formal attempt would be made to reach panel consensus positions on the charge items. For each submission, the panel members were asked to share their comments and discuss the charge questions:

- Does the information[1] provided address the SIDS endpoints?
- If a category is presented, is the rationale for the category reasonably appropriate, and is the use of read-across scientifically defensible?

Industry sponsor representatives were asked to address the panel questions to the best of their ability, recognizing that the sponsor representative may not be able to provide an immediate answer to all questions. Sponsors were also permitted to ask the panel members clarifying questions to ensure their understanding of panel member comments. Observers were provided the opportunity to register to make brief technical comments (none did so). Dr. Dourson also noted that panel members were free to contact sponsors prior to the meeting to obtain further information or insight that could assist them in developing their opinions. The sponsors however, were asked not to initiate contact with the panel members regarding the submissions.

[1] Note that exposure and use information that is part of the HPV or EHPV submissions was not subject to review in this Pilot; however, panelists could use this information to help inform their opinions regarding the screening-level hazard needs.

Panel Discussions of Submissions

The summary below is intended to provide a synopsis of the key discussions and recommendations resulting from the peer consultation. Each panel member also submitted additional detailed comments related to the submissions that were discussed. These individual comments are found in Appendix C of this summary report.

1,4-Cyclohexanedicarboylic acid (CHDA) (CAS No. 1076-97-7)
Sponsor: Eastman Chemical Company
EHPV Submission
(http://www.regulations.gov/fdmspublic/component/main?main=DocketDetail&d=EPA-HQ-OPPT-2006-1020)

The sponsor began the discussion with an introduction to the submission.

Discussion on Physical and Chemical Property Endpoints

- The panelists made several comments related to physical and chemical property endpoints. One panelist commented that the melting point and boiling point are helpful in evaluating other endpoints, and thus, empirical data for these end points are very desirable. This panelist suggested that the sponsors verify that such data are not available and recommended searching for the data from material safety data sheet (MSDS) databases, which often contain such basic information. In response to a sponsor clarification regarding the acceptability of model estimates for such endpoints, the panelist indicated that the current TP approach would not be adequate for boiling point and vapor pressure. Another panelist commented on the presentation of some endpoints. This panelist noted that the RSS can be viewed more easily in HPVIS (www.epa.gov/hpvis) using the standard report query. The panelist indicated that the partition coefficient description was a little unclear. The RSS indicated that this endpoint was estimated, but it appeared that an experiment was conducted. Also the reason for a range of values to be presented was unclear. Presumably this was because of the properties of the isomers. Based on clarifications from the sponsor the panelist indicated that the entries were sufficient.

Discussion of Environmental Fate Endpoints

- The panelists agreed with the test plan recommendations regarding the environmental fate endpoints.

Discussion of Ecotoxicity Endpoints

- The panelists agreed with the test plan recommendations regarding the ecotoxicity endpoints.

Discussion of Mammalian Toxicity Endpoints

- The panelists agreed with the test plan recommendations regarding the mammalian toxicity endpoints. The panelists commented on the use of data for dimethyl-1,4-

cyclohexanedicarboxylate (DMCD) for read-across and in particular the documentation of its metabolism to CHDA and methanol. One panel member commented that between the available data for the two chemicals, DMCD and CHDA, it appeared that all the endpoints were adequately covered. The panel member thought that it is highly likely that DMCD would be hydrolyzed to CHDA by esterases. This has been confirmed in studies of similar compounds, but not DMCD. The panel member expressed reservation regarding the use of DMCD data for read-across until DMCD metabolism to CMCD has been confirmed. Another panel member added that the Heck and Tyl (1985) abstract did not seem to inform the metabolism issue and the Barber et al. (1994) article which showed that alcohol formation from diethylhexyl terephthalate and diethylhexyl phthalate hydrolysis was quite different and does not clarify which metabolic path DMCD would follow. A panelist commented that there would likely be differences in the toxicity of the two chemicals because of the ester versus acid moiety, but if anything, the ester (DMCD) being used for read-across would be more toxic, since it would be more likely to be absorbed. This panelist also noted that metabolism of DMCD would generate methanol, and thus, the sponsor might consider adding toxicity data on methanol to the TP. However, the panel discussed that the effect of methanol seen in the animal toxicology data would only be a high dose acute affect that would not be relevant for an assessment at environmentally-relevant doses. Based on this consideration the panel members did not feel methanol data should be added. The panel members all agreed that there were no data gaps related to the mammalian toxicity endpoints, but recommended that the sponsors provide additional data on metabolism of DMCD, if available, and requested development of the data if it is not available.

Discussion of Other Considerations

- Several panel members commented on issues related to the potential for releases into the environment. One panel member commented that it appears that there is minimal potential for environmental release. A panelist asked whether the sponsor had claimed the material as a closed system intermediate (CSI). The sponsor clarified that they are the only company that manufactures the material and that a specific technical definition had not been claimed regarding CSI status, although the material is handled in closed systems. A second panelist asked whether there was potential for releases in wastewater. The sponsor responded that the product is sold to make polymers so there may be some release from customers' sites, but likely in only very small amounts. They also noted that wastewater containing CHDA is a very small fraction of the wastewater going through their secondary biological treatment plant. The sponsor was also asked to clarify the statement in the exposure summary regarding FDA approval and whether this was based on assessment of potential migration from food packaging materials and how it relates to the claim that the material in not found in consumer products. The sponsor noted that the polymer was approved based on evaluation of extraction and exposure potential.

Trifluoromethane (CAS No. 75-46-7)
Sponsor: E. I. du Pont de Nemours & Company, Inc.
Original HPV Submission (www.epa.gov/hpvis)

In opening comments regarding this submission the sponsor summarized that the material is very stable, is used in refrigeration and etching, and fire suppression in confined spaces. The material has a low order of toxicity. The high volatility and low solubility of the material make water solubility testing difficult. Overall the sponsor felt that data requirements for each of the SIDS endpoints had been covered. Prior to the discussion of this chemical Panelist Sandusky disclosed he had a prior meeting with the sponsor and that PCRM had submitted previously written comments supporting this test plan.

Discussion on Physical and Chemical Property Endpoints

- The panelists agreed with the test plan recommendations regarding the physical and chemical property endpoints.

Discussion of Environmental Fate Endpoints

- The panelists agreed with the test plan recommendations regarding the environmental fate endpoints.

Discussion of Ecotoxicity Endpoints

- Table 2 in the Robust Study Summary summarized the ecotoxicity data. The meeting facilitator noted that the table is unclear as to which endpoints have measured data or estimated data for data from surrogates. The sponsor clarified that algal toxicity is the only endpoint without measured data. A second panelist indicated that in absence of measured data for the algal toxicity endpoint the sponsors needs to provide data from a surrogate chemical to support the QSAR estimate, since confidence in the prediction for this compound is marginal. The sponsor noted that for the analog HFC-134a there are data for the fish and daphnia toxicity endpoints. The sponsor also mentioned that there were algal toxicity data for HCFC-123, which would likely represent a worst case surrogate for HFC-23. No measured data are available for the test material itself and collecting such data is difficult due to its volatility. A panel member suggested that the sponsor's surrogate chemical is the worst case. The TP should note this. Other panel members had no additional comments.

Discussion of Mammalian Toxicity Endpoints

- The panelists agreed with the test plan recommendations regarding the mammalian toxicity endpoints. The panel members agreed with the submission that there were no outstanding data gaps. One panelist commented that bridging from histopathology data in repeat-dose studies is sufficient to fill the data requirements for reproductive toxicity. A second panelist agreed that the material is fairly inert, but recommended that the sponsor provide some information in the TP on the possibility for suffocation from use in fire extinguishing applications. The sponsor indicated that this is not likely to be a significant issue because in such applications there is a pre-discharge alarm and 5-minute period before release of the material into the space. Moreover, the design requirements are such that the material reaches a concentration to serve in fire protection, but not to such a degree that there would be a risk of oxygen deprivation. However, since release in a confined space is a possible scenario, the comment is appropriate and this information can be made clear in the TP as well as the MSDS.

Discussion of Other Considerations

- A panelist commented that according to the test plan the chemical is being phased out and on this basis it is not a good candidate for additional testing. Given this production status another panel member asked about the potential for exposures related to transportation and disposal. The sponsor indicated that the material is transported (mostly in 100 pound cylinders) as compressed gas/liquid and also stored in this form. Excess material is destroyed by incineration.

Residual oils (petroleum), oxidized (CAS No. 64742-99-0)
Sponsor: Lubrizol Corporation
EHPV Submission
(http://www.regulations.gov/fdmspublic/component/main?main=DocketDetail&d=EPA-HQ-OPPT-2006-1020)

The sponsor introduced the submission indicating that the current test material is similar to the Petroleum Oxidates and Derivatives thereof Category and this EHPV submission fits in nicely with previous category submission.

Discussion of Category

- All the panelists agreed that it is appropriate to include this new petroleum oxidate substance into the existing category Petroleum Oxidates and Derivatives thereof).

Discussion on Physical and Chemical Property Endpoints

- The panelists agreed with the test plan recommendations regarding the physical and chemical property endpoints.

Discussion of Environmental Fate Endpoints

- The panelists agreed with the test plan recommendations regarding the environmental fate endpoints. The panel members agreed with the need to conduct a biodegradation study.

Discussion of Ecotoxicity Endpoints

- The panelists agreed with the test plan recommendations regarding the proposed testing for the ecotoxicity endpoints, but also discussed viability of using a read-across approach as an alternative. One panelist noted that test data are available for some endpoints for a potential surrogate (CAS No. 64742-98-9). Another panelist asked whether a rationale could be developed for using testing data for other category members CAS No. 64742-98-9 (a subcategory 1 chemical) and CAS No. 68603-11-2 (a subcategory 2 chemical). If in every case the aquatic toxicity is greater for subcategory 1 is there any reason to assume worst case and use the subcategory 1 chemical for read-across? This panelist also asked if it is possible to have any low molecular weight components in the test material that might help to identify additional surrogates. Such data would provide a worst-case read-across approach if the sponsor did not want to propose testing. The sponsor clarified that there are probably some smaller molecular weight chemical species present. If read-across were to be used the aquatic toxicity of the test material is more likely to

resemble that of CAS No. 68603-11-2, than the other options. However, the sponsor indicated that they were not proposing the read-across approach because the physical and chemical properties for those compounds in the category that do have ecotoxicity endpoint data are very different (e.g., the water solubility is very different) and these potential surrogates would not provide an adequate representation for the test material.

Another panelist added that they supported the idea of using read-across, although it is understandable that the sponsor might not want to read-across from the most water soluble materials. This panelist also noted that a data gap for chronic reproduction in daphnia would remain and so testing for that endpoint would still be recommended. This panelist further indicated that since the test plan material is very lipophilic, if the sponsor pursues additional testing they would need to follow the guidance for difficult to test materials. Several suggestions regarding the testing strategy were provided. The panelist recommended conducting range finding study up to the water solubility limit to determine where to start testing, rather than relying on loading rates. The panelist also suggested that a tiered testing approach be employed. Such an approach would rely on an acute fish test using a suitable carrier (not a surfactant) if needed to get the material into solution to a concentration of up to 100 mg/L. If no effects were observed in this acute fish test to the water solubility limit then the panelist suggested not doing the algal and invertebrate acute studies, rather go straight to a chronic daphnid (21-day) test. This panel member also noted that the sponsors could contact the EPA if they would like additional review of testing protocols.

Discussion of Mammalian Toxicity Endpoints

- Although the panelists agreed with the test plan recommendations regarding the mammalian toxicity endpoints, they discussed the value of the proposed combined repeated-dose and reproductive/developmental toxicity screening test. One panel member questioned the proposed use of dermal administration as the dose route for this study. Based on a clarification that the sponsors had not done any testing to evaluate potential dose ranges, the panelist was concerned that unless a material is toxic and is well-absorbed then such studies will not provide a robust quantitative estimate of the effect level. Such studies are technically difficult due to run-off of the applied liquid if a large surface area is required to apply an effective dose. This panelist suggested under such circumstances the typical endpoint testing recommendations may not apply if it is not practical to get reasonable data out of the traditional methods of testing. The sponsor agreed with these comments on the difficulties in conducting such dermal studies. However, an alternative approach using oral dosing would present other issues because the oral route does not match the typical human exposure route (which might be raised by others in the risk assessment context) and when dosing orally, secondary effects due to gasto-intestinal tract irritation, and laxative effects hamper the interpretation of such studies. Two panel members agreed with this concern and did not support substituting an oral study for the proposed dermal study.

  A second panelist suggested that the sponsor consider evaluating dermal absorption using an *in vitro* test system or modeling approach. If there is little or no absorption then the proposed *in vivo* toxicity study would not be useful. This panel member added that for another HPV test plan (commercial hydroxyl ethyl piperizine) EPA found it acceptable to

model dermal absorption and based on evidence for the lack of absorption EPA supported the decision not to do required testing. The panelist provided a copy of a poster presentation on the application of this approach (see Appendix D). Another panel member asked if there was a specific cut point for absorption that would support the conclusion that testing would not be needed. A panel member clarified that the prior submission noted as an example of such an approach found essentially no absorption. The panel members were not aware of guidance on this specific point, rather the determination would depend on the degree of absorption and whether sufficient absorption could occur to have a reasonable possibility to identify toxicity from an in vivo study. The panelist also suggested that the sponsor review the materials from workshop proceedings by the Institute of In Vitro Sciences, which provided technical guidance on the issue of conducting *in vitro* studies (Raabe et al., 2005) and also noted that there is an OECD protocol for dermal absorption that could be considered. The sponsor noted that a modeling approach may be difficult since the test material is a complex mixture, but perhaps an *in vitro* test system could be used. The panel members agreed that given the discussion on the dermal exposure issue the approach to evaluate skin absorption is reasonable. One panel member indicated that they would also review the prior EPA comments on applications of this approach.

While the panel members considered the approach based on evaluating dermal absorption as reasonable, the panel also noted the availability of a repeat-dose oral study for one of the category chemicals (CAS No. 64742-98-9) which identified a NOAEL at the limit does of 1000 mg/kg-day. The sponsor further noted that this is a lower MW component and might represent a worst-case scenario. A panel member agreed that these data might be used for read-across, but that this particular material is the only member of subcategory 1 in the broader category and thus might be somewhat different from the test material. However, this panel member also noted that oral testing with the lower molecular weight material could be used to make the argument that the likely most bioavailable member of this category showed no toxicity, which would further support the argument that no testing is needed. A second panel member indicated that a good argument could likely be built on the basis for the absorption issues, but did not oppose bringing in this read-across approach.

Discussion of Other Considerations

- The panel discussed the proposed timing of the additional testing. The test plan noted "that to avoid duplicate animal testing, and limit vertebrate animal testing as far as possible, the timetable of proposed testing is on hold until 2010 wherein data sharing with other European manufacturers and importers of this substance will be accomplished through Substance Information Exchange Forum (SIEF) under REACH." The sponsor clarified that this statement should not be read to imply that the EHPV Program is not also a high priority. A panel member reaffirmed support for waiting for the REACH timeline before proceeding with animal testing as noted in the preliminary comments. Another panel member noted the possibility that other manufacturers will have data that can fill some of the endpoints, but this will not be known until the REACH process for this material unfolds.

C4-6 Isopentene Rich-Ether Fraction (IRF) Stream (CAS No. 108083-43-8)
Sponsor: ExxonMobil Chemical Company
Original HPV Submission (www.epa.gov/hpvis)

The sponsor noted that following a brief review of the premeeting comments from the panel, they did not foresee significant problems in addressing the questions and issues raised. Some of the premeeting comments applied to both the current submission as well as of the C3-5 Butene-Isobutylene-Rich-Ether BIR) Stream (the next item on the meeting agenda). The sponsor provided responses to several of the premeeting comments in the opening remarks and these responses are reflected in the context of the endpoint topics described below.

Discussion on Physical and Chemical Property Endpoints

- A panelist stated that it can be problematic to represent the physical and chemical property endpoints for complex mixtures based on data for individual constituents. The sponsor commented that using constituent data is one of the better approaches for his materials since for endpoints such as partition coefficient, boiling point, and melting point the characteristics of a complex stream are a range of values depending on the constituents. The sponsor noted that for the vapor pressure one could argue to use measured data for the mixture and such data could be submitted. This panelist clarified that in the current Chemical Assessment and Management Program (ChAMP), risk-based prioritizations (RBP) are being developed from submitted HPV Challenge data. In the context of conducting the RBPs, EPA has decided that it is not appropriate to use individual major constituent data to represent the physical and chemical property endpoints for complex mixtures, since the actual values will always be a range. Rather the following general summary statement has been used in such situations - "These complex mixtures will not have a well-defined molecular weight, melting point, boiling point or vapor pressure, log Kow, or water solubility." As a result, the panelist suggested that the sponsor present the RSS as data entries for the material stream, rather than as RSS for the individual constituent chemicals. In response to comments from another panel member and the responses by the sponsor on alternative approaches, the panel member further indicated that it is reasonable to identify the lowest and highest value based on all significant constituents for each endpoint and represent the physical and chemical endpoints as the range of these values. This approach is different from picking a few primary constituents and using their individual properties as representative of the mixture. For example, in Table 2 on Page 8 of the TP, the sponsor could eliminate the individual values from major or representative constituents and just present the range of values for the mixture. Other panel member had no additional recommendations related to these endpoints.

Discussion of Environmental Fate Endpoints

- The panel also discussed the issue of using representative mixture components in the context of filling data requirements for the environmental fate endpoints. The sponsor indicted that one needs to know the main constituents of the mixture for endpoints like fugacity, atmospheric oxidation potential, and hydrolysis. Such endpoints are difficult to characterize for the mixture as a whole. Some endpoints are calculated and there is no other way to address, other than to use constituents since the models require a specific

chemical structure. The sponsor noted that biodegradation is an exception, since it can be evaluated on a stream basis. However, the sponsor noted that the biodegradability is fairly low for the methoxy ethers in this stream– so based on the existing data the stream is best characterized as poorly degradable. A panelist agreed that for biodegredation it would be better to look at the stream and constituent representation is less informative. This panelist felt that assessments of photodegradation and fugacity for the mixture would not be informative and for the RBP process a general statement indicating this conclusion has been used. Other panel members added that fugacity modeling based on the individual components would be appropriate since fugacity is chemical specific and in the environment the mixture would begin to follow the characteristics of the individual components.

Discussion of Ecotoxicity Endpoints

- The panel discussed the use of QSAR modeling for ecotoxicity endpoints presented in the TP. A panelist asked the sponsor to comment on whether they felt the ECOSAR modeling was adequate. The sponsor noted that in this case constituent data can be used to characterize the stream for aquatic toxicity. Although the C4-C6 materials are more complex because they have saturated and unsaturated fractions, but in looking at the stream as a whole the saturated C7 is the predominant driver for toxicity in the aquatic environment. Based on review of the premeeting comments from the panel the sponsor also added that some chronic testing might be appropriate. The sponsor suggested using the Target Lipid Model (e.g., McGrath et al., 2004). Recent analyses for methyl-tert-butyl ether (MTBE) derived a predicted no-effect concentration (PNEC) of 18.1 ug/L MTBE while the Target Lipid Model estimated a PNEC of 20.7 ug/L. This model would be proposed instead of chronic aquatic toxicity testing.

  Regarding QSAR modeling performance, a panelist noted that in reviewing Tables 5, 6 and 7 in the TP that tert-amyl-methyl ether (TAME) has significant measured data, but for n-heptane and cyclohexene measured data were only available for one endpoint to compare the measured and model estimated values. This panel member stated that current EPA practice for individual chemicals is to require testing data for the material itself. If no data are available, then data for a surrogate chemical must be provided in addition to QSAR modeling to waive the testing requirement. In this case heptanes and cyclohexene would likely be the most toxic constituents and QSAR estimates as well as data for surrogate chemicals for these two components need to be presented to waive testing. With regard to the use of n-heptane to represent the other 5 constituents of the heptanes fraction, a panelist indicated that n-heptane would have higher aquatic toxicity than the branched heptanes – so data for this constituent was conservative. Since the underlying models have robust data sets it might be possible to pick an analog from the training set and include that data in the TP justification. The panelist further suggested that if data are not available for heptanes then the sponsor might consider using data for hexane with the caveat that it is a lower-end estimate or using octane with the caveat that it is a higher-end estimate. Another panel member noted that additional data had been identified by People for the Ethical Treatment of Animals (PETA) and suggested the sponsor review this additional information for inclusion in the TP. In response to these recommendations the sponsor noted that they did provide some data that showed that the

QSAR models agree with the available data when looking at the group of data as a whole. Nevertheless, they would seek additional data based on the panel member comments. The sponsor indicated that they did not include surrogates for the primary constituents in the TP submission since the models appeared to do well and such data would complicate the test plan.

Discussion of Mammalian Toxicity Endpoints

- The panelists agreed with the test plan recommendations regarding the mammalian toxicity endpoints. A panelist noted that in contrast to physical and chemical endpoints and environmental fate endpoints one can make a better argument for assessing mammalian toxicity endpoints for complex mixtures based on significant constituents. This panelist did clarify that in reality some of the individual chemicals are representative of categories of constituents, and therefore, the selected key constituents for which data were provided represent something close to half of the stream mixture rather than up to approximately 90% as indicated by the sponsors. The panel discussed the choice of n-heptane as a representative of the heptanes fraction. A panelist commented that he was satisfied by this choice, since the other heptanes would not be likely to be metabolized in such a was as to remove the methyl groups. Therefore, data developed for n-heptane should be representative of that for other members of the group. The sponsors added that n-heptane was selected since it was one of the higher percentage components in this fraction and had toxicity data available. In response to a follow-up question, the sponsor indicated there were very little data for any of the other chemicals to determine if n-heptane would be more or less toxic than the other chemicals in that fraction. One panelist indicated that in premeeting comments a suggestion had been made to evaluate the potential toxicity of the members of the heptanes fraction using an SAR approach followed by a potential screening toxicity study. However, this panelist noted greater comfort in the selection of n-heptane following the panel discussions due to the rationale regarding differences in branched versus straight-chained molecules, the apparent effort to identify data for other heptanes, and the observation that for ecotoxicity endpoints n-heptane appears the most toxic of the constituents. These lines of evidence should be described in the TP as a justification for selecting representative chemicals for different fractions (or bins). A panelist summarized the availability of data for mammalian toxicity endpoints and concluded that the test plan recommendations are appropriate. Other panelists agreed with this conclusion. This panel member noted that additional data had been identified by PETA (Brown-Woodman et. al., 1995) for developmental toxicity. Only an abstract was available for review, but this study might be added if the full study is available and is found to add to the data set.

Discussion of Other Considerations

- The panel also discussed whether the TP should provide an indication of the potential for odors to be present in water contaminated with the material. One panelist asked whether the nuisance odor properties should be mentioned in the TP. A second panelist commented that the TP is a source of information to the public it might be worth adding this information. The sponsor was asked if data exist on the taste and odor threshold for this material or its major constituents and whether the MSDS provides such information. The sponsor noted that this consideration of including the odor threshold information was

a good point, but in preparing the documents thought this was outside the scope of the HPV Program, which focuses on hazard data. The document content was limited to data regarding HPV endpoints. The sponsor also noted that the only use of the test plan material is as a feedstock, and it would not expected to be released to public, although the material is a transported isolated intermediate.

C3-5 Butene-Isobutylene-Rich-Ether (BIR) Stream (CAS No. 102479-87-8)
Sponsor: ExxonMobil Chemical Company
Original HPV Submission (www.epa.gov/hpvis)

In opening discussion regarding this submission the panel members noted that several of the general issues in assessing mixtures raised in the context of the prior discussion also apply to this stream. Detailed discussion of the underlying issues are described above for C4-6 Isopentene Rich-Ether Fraction (IRF) Stream (CAS No. 108083-43-8).

Discussion on Physical and Chemical Property Endpoints

- The panelists agreed with the test plan recommendations regarding the physical and chemical property endpoints, although a panel member noted the issue of appropriate representation of mixtures as ranges. The panelist did note that in this case a greater rationale exists for using representative compounds, since the bulk of the material is limited to MTBE and TAME.

Discussion of Environmental Fate Endpoints

- The panelists agreed with the test plan recommendations regarding the environmental fate endpoints, although a panel member noted the issue of appropriate representation of mixtures.

Discussion of Ecotoxicity Endpoints

- The panelists agreed with the test plan recommendations regarding the ecotoxicity endpoints and had no additional recommendations.

Discussion of Mammalian Toxicity Endpoints

- The panelists agreed with the test plan recommendations regarding the mammalian toxicity endpoints. A panelist summarized that in this case the toxicity is represented by primarily two compounds – mostly MTBE and TAME. The material would have low toxicity with significant data in IUCLID for each compound. A second panel member noted that there is a current IRIS assessment for MTBE that might provide additional data.

Discussion of Other Considerations

- A panelist indicated that as for the C4-6 Isopentene Rich-Ether Fraction (IRF) Stream the TP should include data related to nuisance odor. A second panelist added that the HPV Challenge is meant to provide for a minimum data set and does not preclude including other information. The addition of this information is reasonable even though

it may not be required. Panel members indicated that the test plan was well done, although a few typographical errors were noted. One panelist indicated that the CAS No. entry appeared to have an error. Another panelist noted on page 15 of the TP a concentration for acute inhalation toxicity of 8.5 mg/L did not appear to match the value in the RSS.

1,3-Propanediol (CAS No. 504-63-2)
Sponsor: ACC 1,3-Propanediol Panel
EHPV Submission
(http://www.regulations.gov/fdmspublic/component/main?main=DocketDetail&d=EPA-HQ-OPPT-2006-1020)

The sponsor opened the discussion with a brief introduction of the submission.

Discussion on Physical and Chemical Property Endpoints

- The panelists agreed with the test plan recommendations regarding the physical and chemical property endpoints. One panelist commented that the RSS descriptions of some endpoints were short on detail and questioned whether reliance on data from the compilation by Daubert and Danner 1989) was adequate. However, another panel member confirmed that this reference is considered by EPA as sufficiently robust for the HPV Challenge Program endpoints.

Discussion of Environmental Fate Endpoints

- The panelists agreed with the test plan recommendations regarding the environmental fate endpoints.

Discussion of Ecotoxicity Endpoints

- The panelists agreed with the test plan recommendations regarding the ecotoxicity endpoints.

Discussion of Mammalian Toxicity Endpoints

- The panelists agreed with the test plan recommendations regarding the mammalian toxicity endpoints. A panelist indicated that there were no problems with that test plan and agreed with the use of a weight-of- evidence approach to meet reproductive endpoint data requirements. The sponsor noted that in premeeting comments there were questions about one of the toxicity studies and provided some clarification. The sponsor noted that there was additional evaluation of sperm parameters in the subchronic study (Gingell et al. 2000) because a prior *in vitro* study indicated that 1,3-propanediol led to DNA cross-linking in testes homogenates and postulated that this may occur *in vivo*. It was suggested that this rationale be added to the TP. A panelist also asked that the sponsors clarify the extent of the evaluation of the ovaries in the subchronic study, since this endpoint was not mentioned in the section on fertility endpoints in the RSS but was mentioned in the section on repeat-dose toxicity. Moreover, the panelist felt that the subchronic study should be referenced in the fertility section of the RSS and more information related to reproductive endpoints from this study should be added.

A panelist added that it would be useful to include toxicokinetic data to the submission. Such data help in the interpretation of the toxicity findings even though toxicokinetics is not one of the endpoints required for the HPV challenge. The sponsor indicated that to their knowledge no significant metabolic studies had been done since the material was not found to be particularly toxic, and therefore, no compelling need exists to do such studies. The panelist agreed that new studies would not be justified and suggested that the addition of toxicokinetics information should only be for any studies that are currently available.

Discussion of Other Considerations

- A panelist asked for clarification regarding the potential for exposure during use of the material for deicing of aircraft, as well as the potential for exposure from use in personal care products. The sponsors noted that Shell Chemical is no longer selling this material into the deicing market, but for DuPont this is a current application. The sponsors also noted that the material is being sold in the Indian market and additional data may become available.

Quarternary TEA esters, C16-18 & C18 unsaturated methosulfate (CAS No. 157905-74-3)
Sponsor: Evonik Goldschmidt Corporation and Stepan Company
EHPV Submission
(http://www.regulations.gov/fdmspublic/component/main?main=DocketDetail&d=EPA-HQ-OPPT-2006-1020)

The sponsor representative indicated that issues that could be addressed during the panel deliberations would be handled, while some others would need to be taken back to the sponsoring companies for further consideration. There is an EU consortium being formed and new testing results are being included in a risk assessment document that is in progress (likely to be published in 2009). The document has not yet been made public and the data are not available for release. A panel member asked the sponsor whether the risk document was being developed for – OECD, REACH, HPV, or another initiative. The sponsor noted that the document is planned as an independent toxicity summary that is being developed for a class of quarternary compounds. Based on this, the panelist inquired as to the peer review process that would be involved, but the sponsor was not aware of this detail.

Discussion on Physical and Chemical Property Endpoints

- The panelists agreed with the test plan recommendations regarding the physical and chemical property endpoints. One panelist noted that the data summaries look good. However, the reported water solubility is very high and the levels reported are likely due to the chemical being dispersible rather than soluble in water. This panelist recommended that the sponsor verify which is the case and revise the language in the TP accordingly.

Discussion of Environmental Fate Endpoints

- The panelists agreed with the test plan recommendations regarding the environmental fate endpoints.

Discussion of Ecotoxicity Endpoints

- The panelists agreed with the test plan recommendations regarding the ecotoxicity endpoints for fish and invertebrates. A panel member questioned the robustness of the algal toxicity data. This panelist commented that the hydrolysis data are not consistent with the algal toxicity report. In the algal test 92% of the material was removed, which generates questions about hydrolysis in algal media since in general there should not be this much breakdown of the test material. Moreover, for this class of compound a greater degree of toxicity would be expected, one would expect toxicity at less than 1 mg/L. In light of these discrepancies the panelist suggested comparing this algal endpoint point finding to other surrogate chemicals.

Discussion of Mammalian Toxicity Endpoints

- The sponsor noted that current testing data for a related material is being done that will address the data for reproductive and developmental toxicity for the current submission. The identity of the surrogate is not available, and the data will not be available until the release of the ongoing risk assessment document. The sponsors noted that the new data will lead to a substantial revision to the TP related to these endpoints. A panelist noted that this clarifies the sponsors' intent for filling the current data gaps related to these endpoints, although the timeline for having these data is uncertain, and the panel members cannot judge the adequacy of such data until it becomes available.

Discussion of Other Considerations

- The panel discussed additional enhancements to the current TP. Panel members noted that the material is classified as Unknown, of Variable Composition, or of Biological Origin (UVCB). Nevertheless it would be helpful if the TP included a representative chemical structure. The panel members also suggested that a summary table be included in the TP that provides the type of data being used to fulfill the testing requirement and the test recommendation for each endpoint. Another panel member questioned the description of the CAS numbers in the TP and indicated that the second CAS No. noted in the TP (CAS No. 919995-81-2) was not available in ChemID Plus and was perhaps the EINECS number. A panel member suggested that the TP also include data on production volumes. However, the sponsor commented that with only two producers such information could not be added due to confidential business information (CBI) concerns, since adding the information would lead to exact knowledge of the production volume of each manufacturer.

Fatty Acids, Coco, 2-Sulfoethyl Esters, Sodium Salts (Sodium Cocoyl Isethionate or SCI) (CAS No. 61789-32-0)
Sponsor: Sodium Ethyl Sulfonates Coalition
Original HPV Submission (www.epa.gov/hpvis)

The sponsor opened the discussion with a brief introduction of the submission.

Discussion on Physical and Chemical Property Endpoints

- A panel member noted that the physical and chemical property endpoints were estimated. The data for these endpoints should be enhanced using measured values, even if the data are obtained from secondary sources. The sponsor commented that there are additional data for certain parameters that they have recently gained access to as part of the REACH process and none of the new data differs greatly from the estimates presented in the TP. As additional information becomes available it will be provided. The test material (SCI) as well as a related material SI (Ethanesulfonic Acid, 2-Hydroxy-, Monosodium Salt) have been preregistered under REACH so there may be additional studies that are needed for EU registration. A panelist asked if the available or planned data include a water solubility test. The sponsor noted the availability of some data, but these data were difficult to interpret. Thus the sponsors are in the process of conducting additional tests for water solubility. The values in Table 1 for water solubility are older information. There are technical difficulties in collecting data for this endpoint due to the nature of the test material. A second panelist commented that he appreciated the effort by the sponsors to do physical and chemical property testing and update the submission. This panelist noted that the EPISuite model gives incorrect results for salts and surfactants because the model makes the assumption that there is a covalent bond to the sodium ion. .

Discussion of Environmental Fate Endpoints

- The panelists agreed with the test plan recommendations regarding the environmental fate endpoints. No additional comments related to these endpoints were made by the panel.

Discussion of Ecotoxicity Endpoints

- A panel member commented that it was not clear whether the ecotoxicity tests values were reported for the concentration of the test material itself or for a concentration equivalent of the active ingredient after correcting for the percentage of active ingredient in the test material. Either is acceptable, as long as it is clear.

  The panel discussed that for aquatic toxicity testing, OECD and EPA generally view effect levels above 100 mg/L as of low concern, but some of the testing results were presented as greater than a concentration below the value of 100 mg/L. For example in Table 4 of the test plan a 48-hour EC50 for daphnia was reported as >32 mg/L for SCI. A panelist noted that the testing as reported does not give a definitive value for invertebrates in this regard and this endpoint should be retested. The sponsor indicated that the results indicate that no toxicity was seen at the highest level tested and higher concentrations were not evaluated because of difficulty in getting material into solution. In some of these studies precipitation in test solutions was observed. The sponsor also stated that it is not possible to reach a level of 100 mg/L in aquatic tests without the use of a solvent, and that no aquatic toxicity is observed up to the limits of water solubility. Analytical chemistry data were not available at the time the studies were done and results from that period are often reported as nominal concentrations. Based on this consideration a panel member reiterated the need for accurate water solubility testing to help in evaluating whether the daphnia testing was done at the limit of water solubility.

The panelist suggested that the sponsors consider retesting with a carrier. Alternatively, the sponsor could enhance their argument for this endpoint using data for a surrogate chemical, since related materials containing C13 to C14 chains should have been able to have been tested with no precipitation using a proper carrier. This panelist did confirm that although the invertebrate data were less than desirable (since they only tested up to 32 mg/L for SCI) if the water solubility is found to be less that this concentration then the sponsor will not need to do retesting. Other panelist agreed. One panelist noted that in this study it may have been that 32 mg/L was the highest concentration that could be tested, but the study did not fully document this limitation in solubility. Another panelist added that it appears from the robust summary that the authors did a range finding and found precipitates at 100 mg/L and then lowered the tested concentration to 32 mg/L. The panel recommended that the extent to which water solubility limitations affected the aquatic toxicity effect level estimates should be made clearer in the TP.

Discussion of Mammalian Toxicity Endpoints

- The panelists noted agreement with the test plan recommendations for all of the mammalian toxicity endpoints, except for reproductive and developmental toxicity. The panel members noted that it is incumbent on the sponsor to justify the decision for no additional testing if they are proposing existing data as sufficient to fill a data gap. For these two endpoints the panel members provided recommendations for additional lines of evidence to consider in making the argument for waiving testing, as well as recommendations for testing approaches, if additional testing were ultimately determined to be needed. One panelist noted that the sponsors presented an argument based on a history of safe use of the material and low toxicity in 28-day repeat-dose studies. This panelist indicated that the history of safe use argument is not sufficient. The reviewer also commented that the availability of two 28-day studies might strengthen the argument, but using repeat-dose studies to address reproductive toxicity usually requires a 90-day study to ensure that the full spermatogenic cycle is considered. Moreover, the panelist pointed out the absence of data for developmental toxicity.

  As an alternative argument to those presented by the sponsors, the panel members suggested evaluating whether there is a significant systemic dose from skin contact if dermal exposure is the focus of the assessment based on exposure patterns. If the potential for dermal absorption is sufficiently low, this consideration could be used in making the argument for waiving further testing. A secondary prong of the argument could then be the history of safe use. The sponsor indicated that there are dermal absorption data, but this might not have been apparent in the IUCLID since it was placed in Section 5.10 (other relevant data). A panelist indicated that this was the appropriate section for such information. An *in vitro* human skin study is available as well as an *in vivo* toxicokinetics study in rats. The data indicate dermal penetration was less than 0.1 to 0.3%. A panelist noted that the document concludes that the material has low to moderate dermal absorption, and based on the available kinetic data this panelist suggested developing a systemic dose estimate for humans based on a worst-case exposure scenario and then comparing this to the systemic dose from the 28-day study which was negative at the limit dose. A second panelist also agreed this might be a useful argument, but the approach is not cut and dry, since there is some indication of

absorption, even though it might be limited. This panelist suggested that the authors could use a parallelogram approach to estimate human systemic absorption potential since *in vitro* human, *in vitro* rat, and *in vivo* rat data are available. A third panelist agreed that the degree of dermal penetration is a key point. If such studies show just a trace of absorption then there would be less of a concern for a chemical such as this one. This panelist commented that virtually any dermal study will give only qualitative estimates of effect levels. The sponsor indicated that they would be comfortable with this approach of extrapolating from the applied dose levels to estimate internal doses and they have experience in evaluating consumer exposure scenarios to estimate internal doses taking into account skin penetration data. A panelist agreed that with the presumption that systemic absorption would likely be low for consumers, but for the ChAMP occupational exposures are also considered and doses under workplace scenarios can be different.

A panelist also identified complications that would need to be considered, when using the dermal absorption data to enhance the TP rationale regarding further testing. This panelist pointed out that the dermal study was done with the dodecyl material versus the cocoyl material, and the data would be viewed as read-across to the current submission. Moreover, there is a range of concentrations in the test materials that might make the comparison of doses more complex. The panelist felt unsure as to whether the dosages could be meaningfully clarified if the starting material contains a wide range of SCI (from 15 to 90%). The sponsor noted that many exposures are tested using finished product, so the doses of SCI component vary. The sponsor asked whether it would help to clarify dosing issues if in the document the doses were presented as the amount of active ingredient that was applied. Panel members indicated that such information would provide clarification. In addition, while the comparison of internal doses to the 28-day repeat-dose study could be presented, the approach would not address the normal use of a 90-day study for filling the data requirement for reproductive effects or the absence of a developmental toxicity study. The panelist thought another approach would be to build an argument for combining the test data for SCI and SI. This would be useful since they are added together in product formulations and SCI has more data. If this approach is adopted and testing is planned, then a reproductive and developmental toxicity study should be done for SI and used for read-across to SCI, as discussed in greater detail in the SI summary below. A study conducted by the oral route would be sufficient. The sponsor commented that since the material will be going through the REACH process some additional studies may be needed. If a decision was made that another study was needed, the data would not be available before the end of 2009, so the sponsors would need to see how this fits into the schedule for REACH as well.

A panelist also asked for clarification from the sponsors as to the degree to which they relied on QSAR models in arriving at conclusions regarding mammalian toxicity. The panelist noted that two models appear to have been used - DEREK and TIMES. This panelist noted that an International Life Sciences Institute (ILSI) workshop report evaluated available programs for assessing reproductive and developmental toxicity and concluded there are significant challenges in their application (Birth Defects Research [Part A], 2004, [70]: pp. 902-911). The sponsor noted that they run several systems and

look at the results together. Conclusions are reached based on the overall weight-of-evidence and the QSAR models are really done more for completeness. In response to a panelist suggestion, the sponsor indicated they could add a paragraph describing the QSAR models (in particular TIMES since the panel was less familiar with this model) and include the model outputs in the submission package.

Ethanesulfonic Acid, 2-Hydroxy-, Monosodium Salt (Sodium Isethionate or SI) (CAS No. 1562-00-1)
Sponsor: Sodium Ethyl Sulfonates Coalition
Original HPV Submission (www.epa.gov/hpvis)

Sponsors opened the discussion with an introduction to the submission. The sponsor also noted that SI is a starting material for making SCI (Fatty Acids, Coco, 2-Sulfoethyl Esters, Sodium Salts). In addition, SI is added as an ingredient in final consumer product to stabilize SCI. Thus, in the context of consumer uses, exposure is to both SI and SCI.

Discussion on Physical and Chemical Property Endpoints

- The panelists agreed with the test plan recommendations regarding the physical and chemical property endpoints. A panelist noted that most endpoints were measured except for vapor pressure. The panelist recommended enhancing the descriptions where possible.

Discussion of Environmental Fate Endpoints

- The panelists agreed with the test plan recommendations regarding the environmental fate endpoints.

Discussion of Ecotoxicity Endpoints

- The panelists agreed with the test plan recommendations regarding the ecotoxicity endpoints. A panel member thought that the TP and RSS were adequate and the conclusions were reasonable. This panelist added that for the ecotoxicity endpoints combining the data for SCI and SI into a single TP would not be recommended. A second panelist agreed with this comment. Past submissions for related material were combined for ease of review, but in this case it would be appropriate to just refer to the TPs for SCI and SI as appropriate, since the data were not being combined for all endpoints.

Discussion of Mammalian Toxicity Endpoints

- The panelists noted that some of the issues related to this submission are cross-cutting with those of SCI. Although some of the same issues apply, one panelist noted that there are less data available for SI. There are acute toxicity data and data for gene mutations, but no data for chromosome aberrations, no repeat-dose toxicity studies, and no data for reproductive and developmental toxicity. The QSAR models DEREK and TIMES were included as part of justification for no further testing. As noted for SCI a panelist suggested providing additional description of the use of these models and the model outputs in the submission. Panelists also asked if there were any other data that might

become available for the material or surrogates that could be used to address the endpoints in the submission. The sponsor noted that they had completed a comprehensive literature search on both SI and SCI, as well as on closely related isethionates, and no additional relevant data were identified. A panelist noted that a SIEF call will be coming and perhaps there will be an opportunity for other data to be developed that might address data gaps in this submission.

A panelist felt there were sufficient data gaps that should be filled with testing. The panelist felt that the chromosome aberrations data for SCI could be read-across to SI. Additional testing for SI for other endpoints could be used to fill the data gaps for SCI as noted above. Based on the current data gaps an OECD 422 study was suggested to fill the data gaps for both chemicals. Another panelist commented that the TP was well done, but supported the idea of the proposed repeat-dose study that also evaluates reproductive and developmental endpoints such as an OECD 422 study. This panelist suggested testing the commercial product. A third panel member agreed that if a study were to be done, then an OECD 422 would be most appropriate. This panelist agreed with the idea of testing SI and bridging back to SCI and also indicated a preference for an oral dosing study, but noted that the sponsor would need to present a rationale for extrapolating the findings across dose routes. The sponsor commented that other experts might suggest testing with SCI and bridging to SI based on an argument analogous to the concept of testing the parent material since the exposure will automatically generate exposure to any breakdown products (or metabolites). One panelist could see the logic of testing the parent since essentially this would be tantamount to testing both chemicals. A second panelist added that in this case the recommendation to test SI, rather than SCI, is driven by the fact that there are less data available for SI, and there may not be a need to test all aspects of toxicity if some information is available for each compound that supports using read-across between the two chemicals. However, this panelist could support testing of SCI or SI, with read-across to the other. The panel members agreed that the key point is that if testing moves forward, an OECD 422 is most appropriate, and the study design should address the considerations of dosing route (oral versus dermal) and the nature of the test material (commercial product, SCI or SI).

Although the panel discussion focused on potential for additional testing a panel member also suggested evaluating whether the data would support a testing waiver based on limited dermal absorption as discussed for the SCI submission. This panelist noted that the TP indicates skin penetration is limited, but this statement only references a personnel communication from Unilever. The panelist asked for clarification of the available data regarding skin absorption for SI and asked if absorption for SCI could be used for estimating dermal absorption potential of SI. The panelist noted that the extent of the of dermal absorption data for SI in the IUCLID, was less than was available in the IUCLID section 5.10 for SCI. A panelist commented that any dermal kinetics study that is done should radiolabel the SI moiety, since there is good understanding of the kinetics of fatty acids. It is likely that if SCI is absorbed, the SI portion of the molecule will be hydrolyzed from the fatty acid. Therefore, since the fate of fatty acids is well understood, placing the label in the SI portion of the molecule would provide information on the fate of that portion of the molecule.

p-Toluenesulfonic Acid (CAS No. 104-15-4)
Sponsor: p-Toluenesulfonic Acid Coalition
Original HPV Submission (www.epa.gov/hpvis)

The sponsor opened the discussion by providing a brief history of this submission. The material was an orphan chemical and not sponsored under the initial HPV Challenge Program, but was subsequently adopted by the sponsor group for the EHPV Program. The sponsor also noted that they had reviewed the preliminary comments from the panel members, which appeared to be consistent with their recommendations for no new testing for this chemical.

Discussion on Physical and Chemical Property Endpoints

- The panelists agreed with the test plan recommendations regarding the physical and chemical property endpoints. One panelist noted that the description of some endpoints should be enhanced since the RSS did not specify if they were measured or estimated. A panelist noted that these endpoints appeared to be measured based on the descriptions in the product MSDS. The sponsor noted that the presentation reflected a limitation of the IUCLID document that was available as a source of data summaries for the current submission and they were not sure of the procedures related to the editing rights for the IUCLID document.

Discussion of Environmental Fate Endpoints

- The panelists agreed with the test plan recommendations regarding the environmental fate endpoints.

Discussion of Ecotoxicity Endpoints

- The panelists agreed with the test plan recommendations regarding the ecotoxicity endpoints. A panelist indicated that the test plan was done well and that base set of testing had been completed. Another panel member commented on the description of which endpoints were based on read-across data. Data were provided for the test material as well as a proposed surrogate, benzenesulphonic acid. The TP indicates that for algal toxicity the surrogate was used for read-across, but it was less clear if surrogate data were being used for the daphnid toxicity endpoint. The panelist suggested that the TP should make more clear which endpoints were based on read-across to benzenesulphonic acid.

Discussion of Mammalian Toxicity Endpoints

- The panelists agreed with the test plan recommendations regarding the mammalian toxicity endpoints. A panelist had submitted comments in agreement with the test plan recommendation of no further testing regarding the mammalian toxicity endpoints. The panelist further noted that there is a data gap for reproductive and developmental toxicity. One repeat-dose study was available, but a full description was not provided in the RSS. Nevertheless, due to the corrosive nature of the material, additional testing would not be useful since any such data would be confounded by corrosive effects. This panelist also suggested that the TP make clear the purpose of including the data for benzenesulphonic acid, since the data for this chemical were provided in a table, but a sentence in the TP states that the data were not being used as read-across to fill the endpoint requirements.

A second panelist indicated that there is support for the use of data from benzenesulphonic acid because the sulphonic acid moiety is the primary driver for toxicity and any difference between the benzene and the toluene moiety would be insignificant given the level of corrosivity.

Discussion of Other Considerations

- In a discussion of the potential for exposure, a panel member suggested that the TP include a statement that there are no consumer exposures and the material is not found in consumer products. The sponsor confirmed that the material is used primarily as a catalyst and would not be present in consumer products.

Revisit of November 2008 Meeting Submissions

Lubrizol Corporation sponsored a number of submissions that were discussed during the November 18 and 19, 2008 Peer Consultation. The sponsor provided written responses to the draft Peer Consultation report. The sponsor requested thoughts from the panel on these responses. The panel facilitator noted the panel would not be providing formal agreement or non-agreement with the responses, since there had been only limited time to review the comments. However, the panel agreed that they were comfortable providing clarification or indicating that further evaluation would be needed before a clarification could be given. In some cases the written responses provided by Lubrizol were of a clarifying nature that were noted, but not further discussed during the December meeting. Such clarifying comments are not described here as they are available in the written attachment from the sponsor. In a few cases the written responses from the sponsor generated additional panel discussion. These discussions are summarized below for the various November submissions.

Benzenamine, N-phenyl-, (tripropenyl) derivatives (CAS No. 68608-79-7)

- The panelists discussed the clarification related to the potential for bioaccumulation. The panelist noted that the sponsor had clarified the issue of data availability. However, they questioned the value of including the interpretation of such data based on the referenced methodology from the Texas Natural Resource Conservation Commission. One panel member indicated that he was not familiar with this guidance document and could not comment on its justification. A panelist commented that the second part of the sponsor's written response is an interpretive question and not necessary for this submission.

Dithiophosphate Alkyl Ester Category

- For this submission the panel members discussed the response from the sponsor regarding the rationale for using the zinc containing material as a surrogate for the non-zinc materials in this category. One panel member felt that the additional justification from the sponsors was not satisfactory and that the characteristics of the zinc-containing material would be different – the significant difference in molecular weight was noted. Moreover, the claim that the zinc-containing material will not biodegrade to the mono acid would be an argument that it is *not* an acceptable surrogate.. Another potential difference in chemical properties that might occur is the degree to which the acid moiety

is free to react in the zinc-containing material. This panelist recommended that a biodegradation test be conducted. Another panel member agreed that the zinc-containing material is substantially different from the material covered in this TP, but could agree to the read-across approach, if the conclusion is that the material will not biodegrade. A panelist indicated that the sponsor could request additional EPA review from appropriate experts on this issue. This panelist felt that the sponsor may be correct that the material would not be biodegradable, but thought it would be to their benefit to test the material, since they were making the conservative assumption that it would not biodegrade. Another panelist asked the sponsors to clarify whether the zinc salt will undergo aerobic attack or hydrolysis. The sponsor noted that they are reporting that this is the case and that the zinc salt does not degrade back to the dithiophosphate alky ester. The panelist suggested that the TP should clarify this point and provide additional supporting information. In addition, the panelist asked whether the zinc salt would break down in water. The sponsor indicated they would need to check on these issues. The sponsor indicated disagreement with these concerns related to read-across for biodegradation, based on their opinion that the molecular weight difference would not be relevant to this endpoint and that the submission is indicating the materials are not biodegradable, so the read-across issue would seem less of a concern since a conservative approach had been taken.

A limited discussion of other issues also occurred. One panelist indicated that the sponsors seem to have addressed some of the issues on corrosivity. Another panelist reserved judgment on the closed system intermediate claim, although the new paragraph looks good. The new text was significantly different from the information in the 2003 submission for this category, which was rejected by EPA. A panelist offered to take the revised wording to the EPA staff who review these.

Heptanoic Acid, mixed esters with pentaerythritol (CAS No. 68441-94-1)

- The panel discussed the suggestions related to alternative read-across surrogates and the potential reactivity of the suggested analog with the carboxylic acid group (CAS No. 68130-55-2). The sponsor provided a response to the suggestions regarding alternative read-across surrogates and accepted the panel member suggestion for the mammalian toxicity endpoint by removing CAS# 68130-55-0 from the read-across list for repeated dose systemic toxicity, and only bridging to CAS# 67762-53-2, which give a NOAEL estimate of 2000 mg/kg-day. With regard to the read-across for acute invertebrate toxicity the sponsor suggested retaining the read-across to the surrogate with the carboxylic acid group, but also suggested an additional chemical from the category for read-across (identified as Figure D in the sponsor response to the November Meeting Report). One panel member indicated a need to evaluate more closely the newly suggested surrogates.

Octanoic Acid, 1.1'-(2,2-dimethyl-1,3-propanediyl) ester (CAS No. 31335-74-7)

- A panelist noted that as recommended in the November Meeting report the sponsors provided additional references related to the potential for enzymatic hydrolysis of the test material. The panelist indicated that he would need additional time to review these

references. Two panel members also noted that some of the cited references might be difficult to obtain. In addition, a panelist indicated that for some prior submissions EPA has asked for bench analysis of hydrolysis to enhance this type of theoretical argument. A panelist indicated agreement with the sponsor's approach of attempting to make the argument, but agreed with another panelist that it might be easier to do the study.

Soybean oil, sulfurized (CAS No. 68152-90-9)

- The panel discussed the further descriptions of the testing protocols for ecotoxicity endpoints provided in the sponsor response. A panelist noted that the main point is that due to such lipophilic nature of the material no further testing would be needed, but when using WAFs it is best to describe as much as possible the approach used. The panel members said that they would need to evaluate more complete methodology descriptions before judging whether the additional details provided were adequate.

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Appendix A – List of Attendees

Attendees

Panel Members

Dr. Skip Matthews
Matthews Toxicology Consulting Company

Dr. Chad Sandusky
Physicians Committee for Responsible Medicine

Dr. Louis (Gino) Scarana
U.S. Environmental Protection Agency

Facilitator

Dr. Michael Dourson
Toxicology Excellence for Risk Assessment (*TERA)*

Attendees

Dr. Ammie N. Bachman
ExxonMobil Biomedical Sciences, Inc.

Dr. Nancy Beck
Physicians Committee for Responsible Medicine

*Mr. Philip Benes
Nease Corporation

*Ms. Leigh A. Belcher, M.S., D.A.B.T.
DuPont Haskell Global Centers for Health & Environmental Science

*Ms. Susan Blevins
Exxon Mobil

Mr. Richard Davi
ExxonMobil Biomedical Sciences, Inc.

Dr. James Deyo
Eastman Chemical Company

*Eliot Deag
Unilever

*Ms. Carol A. Fairbrother
ExxonMobil Chemical Co.

*Mr. Robert Foster
NOTOX B.V.

Ms. Christina Franz
American Chemistry Council

*Dr. Ralph Gingell
Shell Oil Company

*Dr. Gary W. Jepson
DuPont

*Dr. David J. Kent
Keller and Heckman, LLP

*Ms. Kathy Kiibler
Shell Oil Company

Dr. Wendy H. Koch
Epona Associates, LLC

*Dr. Yafan Li
The Lubrizol Corporation

Dr. Andrew Maier
Toxicology Excellence for Risk Assessment (*TERA*)

Mr. David Mallon
Unilever

Mr. Jack Murray
p-Toluene Sulfonic Acid Coalition

Mr. Larry Newsome
U.S. Environmental Protection Agency

Ms. Pat Rizzuto
BNA

*Dr. Steven Signs
The Lubrizol Corporation

Dr. Douglas Winkelmann
ExxonMobil Biomedical Sciences, Inc.

*Participating via Conference Cal

Appendix B – Meeting Agenda

AGENDA
Peer Consultation Pilot of HPV and EHPV Submissions

Monday, December 15, 2008

7:30 Registration

8:00 Meeting Convenes[2]

Welcome, Description of Pilot, and Introductions: Dr. Andrew Maier, *TERA*
Meeting Process: Dr. Michael Dourson, Facilitator, *TERA*
For each submission, the panel members will share their comments and discuss the charge questions:

- *Is the information provided adequate to support the conclusions for each relevant SIDS endpoint?*
- *If a category is presented, is the rationale for the category reasonably appropriate, and is the use of read across scientifically defensible?*

The panel members and sponsor representatives may ask one another clarifying technical questions. Observers may provide brief technical comments (2-3 minutes maximum), if they have pre-registered to do so.

8:30 Panel Discussion of Submissions

- 1,4 Cyclohexanedicarboylic acid
  Sponsor: Eastman Kodak
- Trifluoromethane
  Sponsor: DuPont
- Residual oils, oxidized
  Sponsor: Lubrizol
- Revisit/Follow up to Lubrizol November Submission discussions

12:00 Lunch (attendees on own for lunch)

1:00 Submission Discussions Resume

- C4-6 IRF Stream
  Sponsor: Exxon Mobil
- C3-5 BIR Stream
  Sponsor: Exxon Mobil
- 1,3-Propanediol
  Sponsor: ACC 1,3 Propanediol Panel
- Quaternary TEA
  Sponsor: Evonick Goldschmidt and Stepan Chemical

5:00 Meeting Adjourns

[2] The facilitator will call for mid-morning and mid-afternoon breaks at appropriate times.

Tuesday, December 16, 2008

8:30 Meeting Reconvenes

Panel Discussion of Submissions

- Na Caocyl Isethionate (SCI)
  Sponsor: Sodium Ethyl Sulfonates Coalition (SESC)
- Na Isethionate (SI)
  Sponsor: Sodium Ethyl Sulfonates Coalition (SESC)

12:00 Lunch (attendees on own for lunch)

1:00 Submission Discussions Resume

- p-Toluenesulfonic acid
  Sponsor: para Toluenesulfonic Acid Coalition
- Revisit earlier submissions as necessary

5:00 Meeting Adjourns

Appendix C – Pre-meeting Comments of Panel Members

NOTE: This appendix contains the preliminary comments prepared by the individual panel members prior to the meeting. Note that these issues and questions were discussed by the panel and the reader is referred to the body of the meeting report for a summary of the discussions.

Pre-meeting Comments on December 2008 HPV Pilot Submissions

Dr. Chad Sandusky, PCRM

Chemical	Comments
1,4-Cyclohexanedicarboxylic Acid	▪ Existing data satisfies all SIDS endpoints, except for reproductive and developmental toxicity, which are met with data from an analog/metabolite. As has been noted in previous stakeholder comments by Environmental Defense and PETA, the manufacturer may want to consider inclusion of data for methanol as an additional metabolite/analog to further strengthen the weight of evidence approach used here. ▪ Some clarification is in order regarding exposure potential. The plan mentions that CHDA is approved by FDA for use in food packaging but also states that CHDA is not used directly in any consumer products. The plan suggests that exposure potential is low because CHDA is manufactured in a closed system at one site involving less than 25 workers and an estimated 50-75 downstream users, but it also states that there is some release of CHDA in wastewater. ▪ CHDA has been detected in wastewater and while toxicity to fish and daphnia is quite low, there is higher toxicity to algae, which may be of concern. ▪ In previous HPV submissions, analogue DMCD was used to support CHDA and the reverse is being applied here. Previous reviews by EPA (2003) and AP agreed with this approach.
Trifluoromethane	▪ All SIDS endpoints are met with data from HFC-23 and supported by data from the analog HFC-32 ▪ Use of histopathology data on reproductive organs from a repeat dose study is appropriate for addressing reproductive toxicity. ▪ Likelihood of exposure is low because HFC-23 is handled in closed, pressurized systems so there is no direct contact with workers. Additionally, the manufacturer limits environmental release of this chemical because it is a greenhouse gas with high global warming potential. ▪ In addition to the low inherent toxicity and low likelihood of exposure, production of the chemical is purportedly being phased out, further obviating the utility of additional testing. ▪ Phys/chem, environmental fate and aquatic toxicity endpoints (read across for algal inhibition) have been addressed.
Residual Oils (Petroleum Oxidates and Derivatives)	▪ The Lubrizol Corporation has made a sound argument that the physiochemical properties of oxidized residual oils (CAS# 64742-99-0) warrant their categorization with and comparison to subcategory 2 petroleum oxidates and derivatives.

	▪ Based on these similarities, the Lubrizol Corporation has made a case for extrapolating mammalian acute toxicity information of subcategory 2 members to CAS# 64742-99-0 in place of additional animal testing. ▪ Could Lubrizol also make the case for extrapolating from the subcategory 1 chemical (CAS # 64742-98-9) to meet the acute fish toxicity and repeat dose/repro dev endpoints? The study on the single subcategory 1 chemical (CAS # 64742-98-9) would represent the worst case conservative estimate for these 2 endpoints. Comparison of the single LC50 in fish on the 1 of 8 subcategory 2 chemical (CAS 3 68603-11-2; lower molecular weight and higher bioavailability?) suggests this may be the case. ▪ Most of the RSS on key studies were not in the submission. ▪ It is not clear that testing before 2010 is appropriate pending additional information from other manufacturers. The meaning of this statement is unclear. ▪ Finally a dermal OECD 422 is proposed. In some cases it would seem appropriate to assess potential dermal percutaneous absorption before conducting in vivo dermal testing. If there is little or no dermal PA, then systemic toxicity via dermal exposure would not be anticipated and testing by this route may be waived.
C4-6 Isopentene Rich-Ether Fraction Stream	▪ ExxonMobil Chemical Company proposes to use data from representative constituents from the methoxypentanes and heptanes along with cyclohexene to fill all SIDS endpoints. Specifically, there are mammalian SIDS data available for TAME (addressing the methoxypentane olefins comprising 43 – 6-% of the stream) and cyclohexane (addressing the C6 cyclic olefins comprising 6 – 9% of the stream) but only a repeat dose study for heptanes (comprising 18 – 24% of the stream). Are the additional data identified in Peta original April 12, 2008 (Brown-Woodman et. al., 1995) useful in addressing the developmental endpoint for the heptanes? ▪ Although fish toxicity data are not available for n-heptane, measured n-heptane data are available for a freshwater invertebrate species. The measured n-heptane data compares favorably with data calculated by the ECOSAR model, and ECOSAR is considered appropriate to estimate the aquatic toxicity for this class of chemicals. In addition, Peta identified several studies that may contain relevant fish data (Peta April 12, 2008). We recommend ExxonMobil investigate these potential data sources. Finally does Exxon Mobile feel that the QSAR data on the individual components adequately address the toxicity of the mixture? ▪ As noted above, reproductive and developmental toxicity data are not available for n-heptane; however acute oral and inhalation toxicity and repeated dose toxicity are low. We note that use profile and potential exposure information is lacking from the test plan. This information would be useful is assessing the data needs for n-heptane.
C3-5 Butene-Isobutylene-Rich	▪ ExxonMobil Chemical Company proposes to use data from the three

	constituent methoxypentanes (MTBE, TAME, MSBE) to fill all SIDS endpoints. ▪ Measured acute aquatic toxicity data were not available for MSBE. The calculated data compare favorably with the measured and calculated data for MTBE and TAME. ECOSAR applies an equation for neutral organics to estimate aquatic toxicity and is therefore considered appropriate to estimate aquatic toxicity for this class of chemicals. MSBE is also volatile and once in the atmosphere, it will be largely degraded through physical processes at a relatively rapid rate. ▪ Genetic, repeated dose, reproductive and developmental toxicity data are not available for MSBE (comprising only 4% of the stream). These data are available for MTBE (65% of stream) and TAME (28% of stream). The weight of evidence suggests that neither is genotoxic. Repeated exposure to these constituents demonstrates a low order of toxicity and is not expected to cause harm to reproduction or the developing fetus. Therefore, based on the SIDS data for the 2 major components of the C3-5 stream, no further *in vivo* testing is needed (for MSBE). ▪ There is little to no information of use profile or exposure in the test plan, and this would be useful is assessing potential data needs.
1,3-Propanediol	▪ The manufacturers of this chemical have made a genuine effort to fulfill the SIDS data points with a weight-of-evidence strategy; the use of reproductive organ effects in a repeated-dose study and developmental data completely appropriate. ▪ Additionally, all the studies for mammalian and fish toxicity offered in the robust summaries are rated a reliability score of 2 or higher; most are done according to OECD guidelines.
Quaternary TEA esters, C16 & C18 unsaturated methosulfate	▪ The test plan for this chemical could be improved by providing the structure of the test chemical, but otherwise it is complete and well-organized. ▪ The use of another quaternary ester to fulfill the reproductive toxicity endpoint appears reasonable; however it is difficult to evaluate the appropriateness of this particular analog because the identity and structure is not provided, nor is the "Human Health & Environmental Risk Assessment" referred to in the test plan provided. ▪ It is not immediately apparent how the developmental endpoint is to be addressed.
Coco, 2-sulfoethyl esters, sodium salts (Sodium Cocoyl Isethionate)	▪ The Sodium Ethyl Sulfonates Coalition (SESC) has performed a qualitative analysis and concluded that there is sufficient data, given the totality of what is known about SCI, including human experience, that certain endpoints need not be tested, specifically the repro/dev endpoint, for which there are no data specifically. The reproductive endpoint is partially addressed using reproductive organ histopathology data from 28-day repeated-dose studies. This approach is a weight-of-

	evidence strategy, although 90-day studies are better for this purpose. ▪ The SESC also argues convincingly that the developmental toxicity endpoint need not be tested, based on a long history of safe use, particularly consumer products. ▪ In addition to a long history of safe use, many studies have been conducted in which SCI-containing products were applied to the skin of volunteers. Results demonstrate that SCI is only minimally irritating to the skin. ▪ The potential for worker exposure during manufacturing and distribution is limited by operational controls including the use of closed reactors and local exhaust ventilation and PPE. Engineering controls are also in place to minimize releases to the environment. Consumer exposure is via dermal route thru soaps and related personal care products. ▪ On page 2 and 14 of the test plan it is stated that there is "low or low to medium dermal absorption." If this is true, this should be thoroughly investigated prior to any new in vivo testing, where the dermal route of exposure is of concern. Any data (Howes, 1975; Howes and Cordell, 1974; page 14 of test plan; we could not locate these studies in the RSS) that demonstrates little or no dermal penetration would obviate the need for any dermal tests to assess potential systemic toxicity, specifically an OECD 422. This approach has been used in past HPV submissions to reduce animal testing while meeting the intent of the HPV program. ▪ Regarding above comment, are there data on other relevant anionic surfactants regarding percutaneous absorption (or modeling of same) or repeat dose/repro-dev toxicity? ▪ If it's decided that an OECD 422 is needed to meet the requirements of the HPCV program, it is strongly encouraged that only one study be done (perhaps on SI below) to meet the needs for both data sets.
Sodium Isethionate	▪ The Sodium Ethyl Sulfonates Coalition (SESC) has performed a qualitative analysis and concluded that there are sufficient data, given the totality of what is known about SI, including human experience, that certain endpoints need not be tested, specifically repeat dose/repro-dev. ▪ In addition to a long history of safe use, many studies have been conducted in which SCI-containing products were applied to the skin of volunteers. Since some SI is also present in final products that use SCI as the primary ingredient, several of these studies were conducted on products that contain up to 15% SI. Results demonstrate that SI is only minimally irritating to the skin. ▪ SESC notes that these SCI and SI are closely related. SCI is produced from SI, and ADME studies indicate that SCI is metabolized to SI by hydrolysis. The SESC therefore appropriately suggests that read across from the SCI data set could address some endpoints for SI, in particular repeated dose and reproductive toxicity and chromosomal aberration. ▪ The potential for worker exposure during manufacturing and distribution is limited by operational controls including the use of closed reactors and local exhaust ventilation and PPE. Engineering

	controls are also in place to minimize releases to the environment. ▪ The reference to personal communication with Unilever on page 13 stating that "dermal penetration is low" should be further elaborated in the test plan. See last 3 comments above for SCI on OECD 422.
p-Toluenesulfonic Acid	▪ Data from p-TSA and a seemingly appropriate analog are provided for aquatic toxicity endpoints as well as several mammalian toxicity endpoints. The only SIDS endpoints not fulfilled are reproductive and developmental toxicity. ▪ This test plan proposes no further testing due to the acidic, corrosive nature of the chemical which caused burns in skin irritation studies and gastrointestinal injury in acute oral studies. We agree that additional testing should not be conducted on the basis of animal welfare considerations and the fact that interpretation of the data would be confounded by the corrosive effects of this chemical. ▪ Some information on potential for human and environmental exposure would be helpful. ▪ Phys/chem., environmental fate and aquatic toxicity endpoints have been addressed. ▪ Past reviews of benzenesulfonic acid in HPV program also waived mammalian testing due to corrosive nature of strong acids.

Pre-meeting Comments on December 2008 HPV Pilot Submissions

Environmental Protection Agency

Chemical	Comments
1,4-Cyclohexanedicarboxylic Acid	In this particular case, the sponsored chemical (known as CHDA) was used as a surrogate for another HPV chemical (DMCD), which is being used as a surrogate for CHDA here. Physical-chemical properties – With the exception of boiling points, all p/c properties are adequate for the purposes of the Challenge Program. We didn't quite understand the partition coefficient robust summary – although it says estimated, it appears that an experiment was conducted. Was it because the isomers were separated on the HPLC column that there is a range of values given? The vapor pressure was estimated and not measured. EPA comments on the DMCD submission suggested that the VP be measured if estimated value is greater than 10^{-5} Pascals (equivalent to 7.5 x 10^{-8} mm Hg). The estimated value for CHDA is 8.7 x 10^{-6} mm Hg. Instead of the calculated boiling point value provided, EPA preferss measured values. Environmental fate – Appears reasonable….no comments. (L) Aquatic toxicity – Adequate acute toxicity data are available for these endpoints for the purpose of the Challenge Program. Mammalian toxicity – All the endpoints appear to be addressed properly. The issue about the relevance of DMCD as a surrogate for CHDA for the reproductive and developmental toxicity endpoints boils down to two issues: (1) the assumption that DMCD is metabolized to CHDA and (2) if (1) occurs, what about the other metabolite (likely methanol)?. Both issues were mentioned in comments to the DMCD submission (submitted by the same sponsor back in 2003). For the presumed demethylation issue, EPA considered it reasonable, but requested references for the statements. The sponsor did provide two citations and they are provided in both the revised DMCD submission and the CHDA submission (Heck and Tyl, 1985 and Barber et al., 1994). I could not get the full Heck and Tyl article, but the abstract did not inform the metabolism issue. In terms of the Barber article, it appears that the alcohol formation from DEHT and DEHP hydrolysis was quite different (DEHT being hydrolyzed at both ester linkages whereas DEHP only on one side). Understandably, these are larger alkyl chains (C8 vs methyl group for DMCD), but does the sponsor have any idea why there was differential hydrolysis and which path DMCD would follow? Other –
Trifluoromethane	Physical-chemical properties – Adequate data are available for the Challenge Program. Environmental fate – Adequate data are available for the Challenge Program. (G) Mammalian toxicity – The use of difluoromethane (HFC-32) is a reasonable surrogate for the repeated-dose and reproductive endpoints for HFC-23. All mammalian toxicity HPV Challenge endpoints appear to

	have been met. (L)Aquatic toxicity – Analog test data provided is considered adequate to asses the acute fish and invertebrate hazard of the sponsored chemical the Challenge Program. To support the submitted SAR algal endpoint data on the sponsored chemical an analog with test data needs to accompany the predicted results. Other –
Residual Oils (Petroleum Oxidates and Derivatives)	This chemical is being added to an existing HPV category ("Petroleum Oxidates and Derivatives Thereof"). This category has eight members and is divided into two subcategories; Subcategory I with only one substance and Subcategory II with the remaining substance. The EHPV chemical (CASRN 64742-99-0) is proposed as an addition to Subcategory II and this appears reasonable. Physical-chemical properties – The sponsor is to be commended for measuring all of the physical-chemical properties (except vapor pressure) for this complex mixture. Environmental fate – I agree with the proposal to perform a biodegradation test on 64742-99-0; all other endpoints are acceptable. This reviewer also appreciates the attempt and documentation to perform the hydrolysis study. (L) Aquatic toxicity – EPA agrees with the TP to conduct acute fish, invertebrates, algal, and daphnia chronic reproduction toxicity testing, but does not agree with using loading concentrations. EPA suggests testing chemicals of this type at or below the water solubility limit. All tests should be conducted analytically using flow through method, mean-measured concentrations, and with a recognized solvent carrier (surfactants should not be used) of < 100 mg/L. Mammalian toxicity – I agree with the proposal to perform an OECD 422 on 64742-99-0. Other – This reviewer also agrees with the sponsor's idea to wait until 2010 to perform the intended testing to await the outcome of REACH/data sharing.
C4-6 Isopentene Rich-Ether Fraction Stream	The sponsor proposes to use surrogate data for this stream by using data from three of the 13 constituents listed on p. 6 of the Test Plan. Although it is true that these three constituents make up to 91% of the stream, that is based on each of the three making up 100% of their "chemical group" (this does not apply to cyclohexene, which is in its own group, but does to the others as representatives of methoxypentanes or heptanes). In fact, the three chosen constituents can make up to only 56% of the stream. Physical-chemical properties – For mixtures such as this stream, it is not practical to pick constituents to represent the mixture for physical-chemical properties. As EPA is starting to do in its ChAMP/RPB assessments, perhaps the best way to approach this is with a statement such as: "These complex mixtures will not have a well-defined molecular weight, melting point, boiling point or vapor pressure, log Kow, or water solubility." Environmental fate – As with physical-chemical properties, perhaps a

	similar statement would apply to photodegradation and fugacity (both usually estimated values – so difficult to do with a mixture because you are forced to pick a representative chemical). (L)Aquatic toxicity – The acute aquatic measured data for each endpoint on each major chemical component of the stream has not been performed to satisfy data adequacy for the purposes of the Challenge program. For the heptane and cyclohexene components only a single daphnia and fish tests, respectively, have been performed. EPA believes that in this case QSAR predictive values alone does not provide enough confidence that the streams will behave toxicology as a mixture in the absence of more measured acute and chronic data for these two components. EPA suggests testing the mixture to help determine the overall acute toxicity to daphnia and algae. Specifically acute toxicity for fish and a chronic daphnia 21-d reproduction tests are recommended. To prevent loss of any test material, zero head space, flow-through methods and measured concentration should be employed. Mammalian toxicity – I have no problem with the data provided for the three consitutents on their own. The issue mixtures: do you test the mixture, or do you pick an appropriate representative chemical(s). In terms of which to pick, it comes down to two things – either the one(s) thought to be the most toxic or the one(s) present in the highest concentration. I guess I question both of these for mammalian toxicity for the C4-6 stream. As mentioned above, TAME and *n*-heptane may not fit either of these criteria. In terms of toxicity, what about considering methyl hexane vs. heptane? Some thoughts on how to proceed: • SAR on all constituents to see which might be most toxic for the various endpoints and then do SIDS on that one chemical. • Perform 28-day study on stream and compare to available data from constituents • Are there any data on other constituents that could inform this issue? Other – NOTE: The robust summaries were difficult to read/understand from pp. 32-157 and pp. 233 – 282 (were these duplicate outputs from a IUCLID report?). However, the summaries for cyclohexene and TAME were very thorough. In terms of heptane, the same applies, but I was surprised there were no repro or developmental toxicity data.
C3-5 Butene-Isobutylene-Rich	The approach to address the HPV Challenge endpoints for this stream is similar to that used for Case #12 (C4-6 IRF Stream). However, in this case, there are only four constituents identified (see Table 1 on p. 6 of the test plan) with another row in the table devoted to a fifth one called "other VOCs"; this last of which comprises only 2.8% of the stream. Thus, unlike the C4-6 IRF stream, a constituent approach based on concentration may be more appropriate here (because of a lower number of constituents and a higher concentration of each one). Physical-chemical properties – As mentioned for the C4-6 IRF stream, it is not practical to pick constituents to represent the mixture for physical-chemical properties. As EPA is starting to do in its ChAMP/RPB assessments, perhaps the best way to approach this is with a statement such

	as: "These complex mixtures will not have a well-defined molecular weight, melting point, boiling point or vapor pressure, log Kow, or water solubility." Environmental fate – As with physical-chemical properties, perhaps a similar statement would apply to photodegradation and fugacity (both usually estimated values – so difficult to do with a mixture because you are forced to pick a representative chemical). Mammalian toxicity – For mammalian toxicity, I do not see the value of adding MSBE – there is only one data point and it is for acute inhalation toxicity. The available information in the robust summaries appear thorough and reasonable for all endpoints for both TAME and MTBE. Of course, MTBE has been a well-characterized chemical and there is a current IRIS assessment that is ongoing. (L)Aquatic toxicity – Adequate data are available for the Challenge Program. Other – The CASRN for methyl sec-butyl ether is wrong in the opening paragraph of the test plan (p. 5); it should be 6795-87-5 instead of 994-05-8 – it is correct in Table 1. Also, as in the C4-6 IFR submission, the robust summaries were difficult to read/understand from pp. 48-335 and pp. 429-457 (were these duplicate outputs from a IUCLID report?).
1,3-Propanediol	Physical-chemical properties – robust summaries are a bit skimpy and don't indicate whether some values are measured or estimated Environmental fate – looks good….no comments (L)Aquatic toxicity – Adequate measured data are provided for acute fish, invertebrates, and algal toxicity and compare well to QSAR predicted values. Mammalian toxicity – A couple of observations regarding reproductive and developmental endpoints. For reproductive toxicity, the evaluation of various sperm endpoints seems more detailed than normal – why was this done? On the other hand, in that same robust summary (p. 38 in robust summary file) there is no mention of the evaluation of female reproductive organs. The fact that no effects on ovary organ weights were seen (from p. 29 in robust summary file) should also be mentioned in the fertility section. For developmental toxicity, although only two dose groups were used (plus control), the information appears minimally acceptable for HPV Challenge purposes. Other –
Quaternary TEA esters, C16 & C18 unsaturated methosulfate	(G)Physical-chemical properties – looks like all properties were measured….it is interesting that the log Kow is > 6.5 but the water solubility is > 2000 mg/L (I guess it is a property of quats/surface active agents??). (L)Physical-chemical properties – Reported measured data are adequate for screening level purposes of the Challenge Program. Water solubility reported at such high levels is likely to be results of the chemical being dispersible rather than soluble in water. Sponsor should review results and verify that the chemical is actually water soluble or dispersible given such a high log Kow value. (L)Environmental fate – Hydrolysis (ester) in water was reported at >120 hrs, but during algal testing it was reported that ester hydrolysis (37%

	degradation) occurred within 72 as a result of microbial attack under test conditions. It would be helpful if a table of algal growth above and below the curve, and composition of algal growth medium are provided to help interpret test results. (see below under aquatic toxicity) (L)Aquatic toxicity – Adequate data are available for all aquatic endpoints with the exception of the algal test. Data adequacy for algae is pending the submission of a more enhance robust summary i.e., table of algal growth above and below the curve, and any information on test medium to verify the possibility and amount of microbial degradation occurring during testing. In addition, it was reported at 72 hours only 8% of nominal concentration was present. If this is the case the 72-h EC50 may be less than that reported for this study. Based on SAR results this chemical is expected to be toxic to algae between < 1 to 5 mg/L. Any explanation to these questions and statements would help in interpreting test result. Mammalian toxicity – The acute toxicity, repeated-dose toxicity and genetic toxicity endpoints look good and have good summaries. I cannot comment on the repro/dev endpoints because the submission is not complete – it points to a future report that will describe results in another substance that will be used to fulfill these endpoints. I have a few questions: • What analogs or surrogates will be used for the developmental/reproductive endpoints? • What is the venue or forum for the report (i.e., is it OECD HPV, US HPV, REACH)? • What is the status of this report? Other – Why are there two different CAS numbers to describe the same UVCB? What is the mixture identified in the inventory? Also, ChemID Plus (http://chem.sis.nlm.nih.gov/chemidplus/) did not recognize the CAS No. 919995-81-2 – is this possibly the EINECS number?
Coco, 2-sulfoethyl esters, sodium salts (Sodium Cocoyl Isethionate)	Physical-chemical properties – All properties are estimated. (L)Aquatic toxicity – It is not known whether all tests were corrected for 100 percent active ingredient in the case of DEFI Base 66%. In addition, these tests should have been conducted in high enough concentration to determine if there are no acute effects at 100 mg/L. The testing as reported does not give a definitive value for invertebrates in this regard and should be retested. To reduce observed physical toxicity due to precipitation, a recognized carrier (surfactants should not be used) should be used at concentration of no greater than 100 mg/L. All concentration should be analytically monitored. Mammalian toxicity – The acute toxicity studies appear fine, however, it is assumed because of the different test substances used that the doses presented reflect the dose of the test substance and not SCI. For example, in the first study (p. 20 of robust summary) 5000 mg/kg of a 47.5% SCI test substance reflects the dose of the test material and not calculated as SCI. Similarly, all other acute toxicity studies were performed with test materials that contained as low as 15% SCI or 20% SCI ("DEFI"). Since it is not believed to be acutely toxic, I am not concerned about toxicity and do not think more acute toxicity studies need to be performed, but am just

	interested in accuracy in reporting. For repeated-dose toxicity studies, the two 28-day studies are acceptable (one with a 72.4% SCI test material and the other with 90% Jordapon test material). The genetic toxicity endpoints of gene mutation and chromosomal aberrations have been met through in vitro tests….although one of the two Ames assays used a 66% SCI formulation. According to the existing HPV Challenge guidance, the developmental and reproductive toxicity endpoints have not been met….use of a 28-day study to evaluate reproductive organs is not a long enough exposure period. Other – There are issues with the purity of the test substances (range from 15-90%) in the mammalian toxicity tests.
Sodium Isethionate	Physical-chemical properties – Most of the properties are estimated, with some (apparently) measured values being reported from secondary sources. Environmental fate – Looks good …no comments Mammalian toxicity – Two of the endpoints are acceptable – acute toxicity and gene mutations. This reviewer believes the chromosomal aberration, repeated-dose toxicity, reproduction and developmental toxicity endpoints have not been met for the purposes of the HPV Challenge Program. The arguments for no more testing are (from pdf page 14, labeled page 13 of the test plan): (1) no acute toxicity; including no irritation; (2) SAR analyses confirming no gene mutation affects and suggesting that the compound does not penetrate skin; (3) some information exists with SCI (see Case #8); and (4) not much knowledge would be gained by performing longer-term animal testing. Taking these arguments individually: 1. I agree that there is no acute toxicity, but this does not necessarily mean there would be no toxicity observed in longer-term studies; 2. More information on this statement is needed: several SAR models are identified (DEREK and TIMES) and personal communication with a Unilever representative. My questions: What were the DEREK estimates for all the other "icities"? I am not familiar with TIMES – what is it? 3. I understand the apparent relationships between SCI and SI (SI being both an intermediate to make SCI and a metabolite of SCI) and think it is reasonable to have tests in one apply to the other. However, as stated by this reviewer on the SCI case (#8), there are HPV data gaps for reproductive and developmental toxicity. Also, this reviewer could not find the citation (Howes 1975) mentioned in the test plan (again, pdf page 14, labeled page 13). 4. I understand this statement and so propose the following: perhaps a path forward for SCI and SI would be to perform an OECD 422 with SI and have it apply to both SCI and SI? Also, perhaps the chromosomal aberration endpoint can be met by using the SCI data (L)Aquatic toxicity – Adequate data are available for the Challenge Program.
p-Toluenesulfonic Acid	Benzenesulfonic acid is proposed as a surrogate for p-TSA for many of the

	HPV Challenge endpoints. Although it is not being used for mammalian toxicity, this reviewer does wonder whether the known and documented difference in the toxicity of benzene vs. toluene (based on distribution in the body and very different target organs – blood for benzene and brain for toluene) is applicable to some of the other endpoints. However, the fact that it has such a low (estimated) pKa of -2.58 suggests that it is a very strong acid and dissociation at environmentally relevant (and even physiologically relevant) pHs would likely not occur….. Physical-chemical properties – The robust summaries for these endpoints (for p-TSA) have virtually no information except for the value for each endpoint. They should be amplified (i.e., method used, measured or estimated, etc.). Environmental fate –None of the biodegradation tests individually meet the HPV Challenge endpoint for biodegradation. The sponsor's assessment for biodegradation is reasonable. Mammalian toxicity – Available data exist for acute toxicity and genetic toxicity (gene mutation and chromosomal effects). This reviewer does not agree that the 28-day study is acceptable; however, I do agree that no further testing is necessary given the corrosive nature of the compound. (L) Aquatic toxicity – Adequate data are available for the Challenge Program. (L) Other – EPA agrees with supporting data for benzene sulfonic acid to satisfy aquatic endpoints for sponsored chemicals were data gaps exist.

Pre-meeting Comments on December 2008 HPV Pilot Submissions

Dr. Hazel (Skip) Matthews

Chemical	Comments
1,4-Cyclohexanedicarboxylic Acid	1,4-Cyclohexanedicarboxylic acid (CHDA), manufactured by one company, Eastman Chemical Co., at one site, is produced and used in a largely closed system, though there is some potential for workplace exposure and minimal environmental release. Though CHDA is apparently of low toxicity and is a data poor chemical, review of this Test Plan indicates data addressing each of the SIDS elements for CHD are available and/or estimated, or derived from a surrogate chemical by approved methods. Data previously developed for a similar compound, dimethyl-1,4-cyclohexanedicardboxylate, is proposed to address most of the SIDS endpoints for the physicochemical, environmental fate, ecotoxicity, and human health effects needed for 1,4-cyclohexanedicarboxylic acid (CHDA). The use of surrogate data is justified by stating that the surrogate chemical will be readily metabolized to CHDA by esterase enzymes. This has been confirmed for the surrogate chemical, but not for DHDA. CHDA has limited potential for release into the environment and, with exception of algae, appears to be of low toxicity to all organisms tested. Given these facts and the fact that CHDA is used exclusively as an industrial intermediate and does not appear in any consumer products, it might be assumed that this chemical poses little threat to the environment or human health. The only obvious problem with this submission is the fact that most of the data in the Robust Summaries exist as some sort of computer gibberish that can not be read. It is assumed that this problem will be easily remedied.
Trifluoromethane	Review of the Test Plan and Robust Summaries submitted for trifluoromethane (HFC-23) indicate this small, volatile chemical is virtually chemically and biologically inert. Environmental problems associated with its production and uses are due almost exclusively to its chemical stability, persistence in the atmosphere, and resulting effect on global warming. Data addressing the required SIDS end points for HFC-23 are described in some detail in an IUCLID Data Set which serves as a Robust Summary. Whereas studies of HFC-23 are not available to address all the required end points, data developed for structurally related fluoroethanes, difluroethane and tetrafluoroethane, are appropriately bridged to address these end points as necessary. All studies indicate that HFC-23 toxicity is largely limited to sedation when animals or humans are exposed to high concentrations. It is assumed that HFC-23 is transported from its site of production to numerous sites of use. It is also noted in the Test Plan that more HFC-23 is produced than is used and that the excess is transported for incineration. Frostbite on direct exposure to the vapor is mentioned as a possible human health risk. It is assumed that a second human health risk, suffocation, might be associated with this chemical on exposure to high concentrations in a confined space such as could occur in an accidental release in the course of its transport and/or use. This fact

	may be mentioned in the MSDS for this chemical, but might also be mentioned here.
Residual Oils (Petroleum Oxidates and Derivatives)	This material which acts as a lubricant and rust inhibitor, consists of a complex combination of high molecular weight carboxylic acids. As such, it is somewhat undefined, and has not been the subject of a number of studies to determine its environmental fate and toxicity. However Petroleum Oxidates and Derivatives (POD) share a number of properties with similar petroleum derivatives that have been subject to at least minimal testing and may serve as a source of "read across" data to address required SIDS elements. Additional testing is proposed to determine each of the ecotoxicity endpoints, as well as repeated dose toxicity and reproductive/developmental effects. In summary, this submission consists of a well organized Test Plan and Robust Summary that clearly describe the limited data available and propose appropriate testing using OECD protocols to address data gaps. However, it stated that decisions for additional testing are said to await the input of other producers which is anticipated prior to 2010. Thus, it would seem appropriate to reserve approval of this submission until plans for the necessary testing are confirmed.
C4-6 Isopentene Rich-Ether Fraction Stream	Environmental and human risks associated with exposure to this complex mixture of chemicals has been evaluated by review of data previously developed for its three major components: tert-amyl methyl ether (TAME); n-heptane, and cyclohexene. This seems a very reasonable approach as these three chemicals and/or very closely related chemicals account for 67 to 91% of the stream, and other components of the stream are structurally similar. No component of the stream, accounting for greater than 1% appears to have any unique toxicity or potential for accumulation in the environment. Each of the major components of this mixture of chemicals on which this submission is based has been the subject of significant toxicological characterization. Review of the extensive information provided indicates that virtually all of the required SIDS endpoints have been addressed for each of these major components. This work is described primarily in unpublished lab reports, but most of these studies were conducted under GLP and appear very sound. Robust Summaries of the resulting data are presented in the form of an IUCLID Data Set for each chemical. On reviewing these summaries it is somewhat bothersome that they contain many pages of numbers and notes that add significantly to the bulk of the report without adding significant information. If permitted, I would recommend eliminating any pages that do not contain relevant information. Otherwise, this submission satisfactorily addresses the requirements of the HPV Challenge and no further work is recommended. Note: It might be pointed out that TAME is an organic ether. Organic ethers are generally of low toxicity but, like TAME, may be very persistent in water. They are also detected by human taste and smell at very low concentrations. Thus, environmental contamination with such compounds may be a particular problem not addressed by the SIDS end points used by the HPV Challenge. To my knowledge, we do not have a way to point out potential problems such as "nuisance contamination." When this or another similar problem is well known, should they be pointed out or should these reviews be restricted to the standard SIDS end points?

C3-5 Butene-Isobutylene-Rich	This submission addresses a hydrocarbon stream, C3-5 butene-isobutylene-rich, which consists primarily, >95%, of three compounds methyl-tert-butyl ether (MTBE), tert-amyl-methyl ether (TAME), and methyl-sec-butyl ether (MSBE), the latter of which accounts for a relatively minor portion, ~ 3.6% of the total. Thus it is appropriate , as proposed, that the Test Plan and Robust Summaries focus on these three chemicals with emphasis on MTBE and TAME. The Test Plan describing available data for these major constituents of the stream is well organized and referenced to address each of the requested SIDS endpoints. Each of the subject chemicals is of relatively low toxicity, but has significant potential for persistence in the environment. The Robust Summaries are presented in the form of IUCLID Data Sets and, as such, are carefully organized and presented. (The considerable number of pages containing only numbers and/or brief notes is, however, somewhat distracting and add considerably to the bulk of the Robust Summaries. Would it be permissible if they were eliminated for purposes of the HPV Challenge?) In summary, the C3-5 butene-isobutylene rich stream is adequately addressed by available data describing the fate and toxicity of its major constituents; thus, no further testing is recommended. Note: Organic ethers such as those described here are generally of low toxicity but, as seen with these compounds, they may be very persistent in water. They are also detected by human taste and smell at very low concentrations. Thus, environmental contamination with organic ethers, as has been observed with MTBE, is a particular problem not addressed by the SIDS end points required by the HPV Challenge. To my knowledge, we do not have a way to point out this and similar problems of which we are aware, but are not addressed by the SIDS endpoints. Should such problems be pointed out, or should these reviews be limited to the required SIDS endpoints?
1,3-Propanediol	This Test Plan provides a concise summary of the relatively extensive Robust Summary for 1,3-propanediol. It appears that this chemical has little or no toxicity in all systems tested and that all the necessary SIDS have been addressed. Relatively minor comments or suggestions we might make are the following. 1. In section 2.2.1, Sources of Environmental Exposure, it is stated that environmental exposure occurs primarily through accidental spills. This statement seems somewhat in conflict with that in Use Patterns, section 2.1 where it is stated that 1,3-propanediol may also be used in deicing fluids, engine coolants and personal care products, uses that may also be significant sources of Environmental Exposure. 2. Whereas numerous references are given for other data, no reference is given for the lack of occupational exposure limits or consumer exposure. 3. Though it is not required and we do not think the data would raise concerns regarding the use of 1,3-propanediol, it would be of interest to have some data on the toxicokinetics, metabolism, and distribution of this chemical in mammals. Since this chemical is formed naturally, and is relatively polar, we can probably assume that it distributes with total body water and is rapidly metabolized by 1,3-propanediol dehydrogenase and excreted as the parent compound and metabolites.
Quaternary TEA esters, C16 & C18 unsaturated	The Test Plan for quaternary TEA esters, C16 & C18 unsaturated methosulfate, provides a concise, well organized description of data to address most of the SIDS

methosulfate	endpoints required for the HPV Challenge. The respective studies are described in more detail in well-organized and referenced Robust Summaries. Review of the summaries of these studies indicates that most used a recommended protocol, OECD or other, and were conducted under GLP. The only deficiencies noted in this submission were the failure to provide a structural formula, quantity produced, and failure to address the developmental toxicity/teratogenicity endpoint. This latter deficiency is noted in the Test Plan which also says "studies are proposed".
Coco, 2-sulfoethyl esters, sodium salts (Sodium Cocoyl Isethionate)	This Test Plan and Robust Summaries represent a very thorough discussion of information addressing the production, use, and safety evaluation of sodium cocoyl isethionate. The Test Plan is very well written and referenced to describe available data addressing the results of extensive toxicity studies, virtually all of which indicate sodium cocoyl isethionate is a very safe chemical. Most of the references are in the form of company reports and, as such, are not available in the open literature. However, review of summaries of these studies in the Robust Summaries of this submission indicates that most of the toxicity studies were conducted under GLP and that the results were derived from carefully designed studies. Thus, this submission very satisfactorily meets and/or exceeds the requirements of the HPV Challenge.
Sodium Isethionate	Sodium Isethionate (SI) is used primarily as an intermediate in the production of sodium cocoyl isethionate (SCI) and, according to this Test Plan may be present in bath detergent bars containing SCI, up to 15%. However, results of studies described in this Test Plan and Robust Summaries indicate SI poses little threat to the environment or human health. The mix of GLP and non-GLP studies described in company reports addressing the fate and toxicity of SI are concisely described in referenced in the Test Plan and Robust Summaries. It appears that, with exception of repeated dose toxicity and reproductive/developmental toxicity, all required SIDS endpoints have been adequately addressed. Though it is unlikely that significant toxicity would be observed, these three endpoints could, and given the level of human exposure, probably should be determined by a repeat dose/reproductive/developmental study.
p-Toluenesulfonic Acid	p-Toluenesulfonic acid is a strong acid and, as such, its primary mechanism of toxicity, corrosion, is well understood. Nevertheless, most of the SIDS endpoints required for submission under the HPV Challenge have been addressed by one or more studies of this chemical or bridged from a proposed surrogate chemical, benzenesulphonic acid. Benzenesulphonic acid is a very appropriate surrogate for p-toluenesulfonic acid, and bridging of data from one chemical to the other should be encouraged to minimize further testing. A review of data, available or bridged, for this chemical and the respective Robust Summaries indicates that, with exception of reproductive/developmental data, all necessary SIDS endpoints have been addressed. Given the fact that results of these studies indicate observed toxicity is due to corrosion, it is proposed that no further animal toxicity studies be conducted. We strongly support this proposal.

Appendix D – Additional Materials Provided to the Sponsors

PCRM

SYSTEMIC TESTING BY THE DERMAL ROUTE CAN BE PRECLUDED BY IN VITRO OR IN SILICO PERCUTANEOUS ABSORPTION STRATEGIES

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SUMMARY

Recent developments in percutaneous absorption testing now make it possible to determine, using either *in silico* or *in vitro* prediction methods, to what degree a specific chemical will be absorbed through the skin. If there is concern for exposure by the dermal route but chemicals have little or no dermal penetration potential, systemic toxicity tests can be avoided. Within programs such as the US EPA's High Production Volume chemical challenge, this approach can be particularly rewarding. Here we present data generated using the QSAR model EPA DERMWIN for the mixture Commercial Hydroxyethyl Piperazine (CHEP) (1,4-piperazinediethanol, piperazine, hydroxyethylpiperazine, and water), sponsored by Dow Chemical Company. To check the applicability of the model, experimental and modeled absorption data for ten amines were compared; the ratio of experimental to modeled data was of acceptable concordance and the absorption of CHEP was modeled. The components were predicted to minimally absorb through the skin, with estimated average total absorption at 1.99 mg/kg/day. When considered together with other factors, this estimation supported the conclusion not to conduct a stand-alone dermal reproductive and developmental toxicity study as originally proposed. This approach protects public and worker health while avoiding resource- and animal-intensive tests such as dermal developmental or reproductive toxicity.

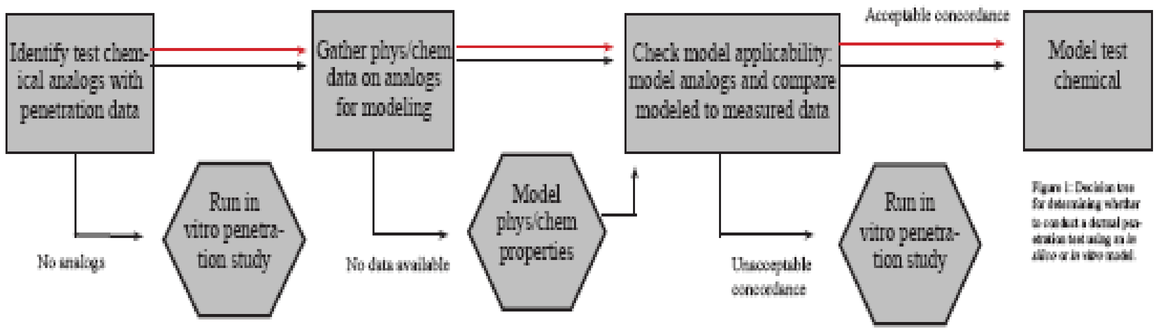
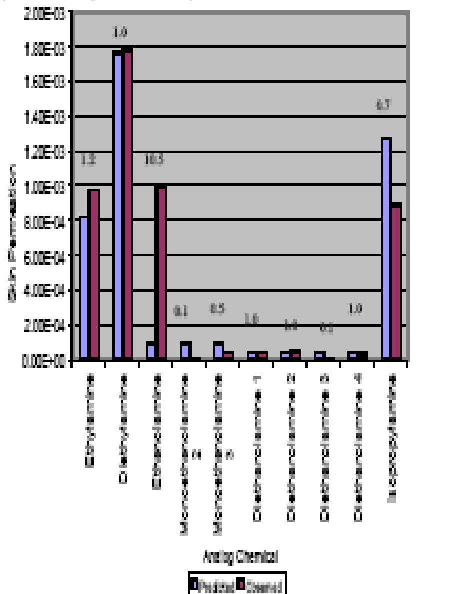


Figure 1: Decision tree for determining whether to conduct a dermal penetration test using an in silico or in vitro model.

Figure 2: Modeled and measured skin permeation values (cm/hr) for 10 analogous chemicals. Observed/predicted ratios are given above each comparison.



METHODS

The experimental process is shown in Figure 1, with our path in red.

A satisfactory concordance (Fig 2) justified modeling the PA of the CHEP components, and this was performed accordingly. The dermal penetration coefficient for each component was then used to calculate the estimated dermal uptake using this equation: dermal uptake (mg) = Kp (cm/hr)*conc (mg/cc)*contact time (hr)*contact area (cm2). Results for each component are shown in Table 1.

*DERMWIN™ was developed by the USEPA and Syracuse Research Corporation, and is available publicly as part of the EPISuite suite of programs (http://www.epa.gov/oppt/).

Table 1: Data input and results for DERMWIN model. Total body exposure is 1.99 mg/kg/day with a 15 minute contact time.

	Piperazine		Hydroxyethylpiperazine		Dihydroxyethylpiperazine		
INPUT PARAMETER	HAND	WHOLE BODY	HAND	WHOLE BODY	HAND	WHOLE BODY	Unit
Contact surface area	420	16900	420	16900	420	16900	cm^2
Skin permeability coefficient	0.000	0.000	0.000	0.000	0.000	0.000	cm/hr
Contact time	0.25	0.25	0.25	0.25	0.25	0.25	hr
Residue conc. in product	220	220	517	517	275	275	mg/cc
Dermal uptake	1.70E+3	7.00E+4	1.30E+3	5.20E+4	2.10E+2	8.30E+3	ug/event
Contact events per day	1	1	1	1	1	1	#/day
Total uptake	1728	69527	1297	52205	206	8296	ug/day
Mean body weight	65.4	65.4	65.4	65.4	65.4	65.4	kg
Average Daily Dose	0.03	1.06	0.02	0.8	0	0.13	mg/kg/day

RESULTS/CONCLUSIONS

• Results of the analagous chemical comparisons are shown in Fig. 2. The EPA DERMWIN model accurately predicted a chemical's penetration coefficient in humans in 7/10 cases, over-predicted 2/10, and under-predicted 1/10. Observed:modeled ratios ranged from 0.10 to 10.5 (mean 1.71).

• Modeled penetration for the three chemical CHEP components (water was not modeled) is shown in Table 1. Total estimated absorption of CHEP, with a 15 min whole body exposure, would be ~2 mg/kg/day.

• A complete Screening Information Data Set exists for piperazine, the component predicted to have the highest absorbed dose (1.06 mg/kg/day). In addition, CHEP is produced and consumed within a closed system and workers use personal protective equipment.

With the acceptance and continued use of *in vitro* and *in silico* approaches to measure percutaneous absorption, investigators and regulators should consider whether prerequisite PA testing can fit into a weight-of-evidence consideration to avoid dermal systemic testing, including for acute, sensitizing, subchronic, and chronic endpoints when evaluating restricted-use chemicals or in screening-level programs, priority-setting, risk assessment, and other situations.