

**Report of the Peer Consultation Meeting on
n-Alkanes
(decane, undecane, dodecane)**

**Submission by
American Chemistry Council n-Alkane VCCEP
Consortium
for the
Voluntary Children's Chemical Evaluation Program
(VCCEP)**

**September 14, 2004
Cincinnati, Ohio**

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

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Executive Summary

A panel of scientists with expertise in toxicity, exposure, risk assessment, and children's health met on September 14, 2004, to conduct a peer consultation of a submission on n-Alkanes (decane, undecane, and dodecane). The American Chemistry Council n-Alkane VCCEP Consortium prepared the submission for the Voluntary Children's Chemical Evaluation Program (VCCEP). The purpose of the meeting was to provide a science-based forum to discuss whether the existing data are adequate to characterize the risks of these three n-alkanes to children, and if not, to identify data needs.

The sponsors provided the panel with brief presentations summarizing the submission's assessments of exposure, hazard, risk characterization, and data needs. The exposure assessment focused on products and scenarios identified in the literature as likely to have the highest exposures to children or to prospective parents. Monitoring data from the literature were used to characterize inhalation exposures and modeling was conducted to characterize oral and dermal exposures. Representative scenarios were presented. Inhalation was the major route of exposure. Exposures via the oral and dermal routes were relatively low.

Panelists agreed it was appropriate to consider decane, undecane, and dodecane as a single category, as the sponsors had done. Some members thought including additional occupational exposures would have been helpful, while others recommended more information on non-occupational sources. A few panelists disagreed with the submission's definition of *upper bound exposure* and did not think it clearly conveyed the highest levels of exposure that should have been considered. Several members had difficulty understanding the assessment and were not sure it was sufficiently conservative. Others expressed favorable opinions. Most members of the panel concluded the exposure assessment was sufficient for a VCCEP Tier 1 submission.

To summarize the hazard assessment, the sponsors reviewed studies conducted on the chemicals alone and in mixtures. They said the alkanes data demonstrated no single target organ system for systemic toxicity, and the existing reproductive/developmental studies did not indicate a hazard. The sponsors used benchmarks of 5000 mg/m³ for acute toxicity, 1000 mg/m³ for subchronic toxicity, and 2000-5000 mg/m³ for reproductive/developmental toxicity. They concluded that the high margins of exposure for the alkanes combined with the lack of concern regarding toxicity indicated no need for additional hazard studies.

The panel discussed the available hazard data and assessment. The panel agreed that toxicity data from alkanes (alone or in mixtures), rather than toxicity data from studies of more complex chemical mixtures (e.g., jet fuel), were most appropriate to assess the potential hazards of these VCCEP chemicals. Many members also agreed that the repeat-dose studies did not identify any particular target organs or target life-stages for toxicity. They thought the greatest hazard presented by the alkanes was pulmonary aspiration associated with accidental ingestion. Some members identified areas of concern. One member described the lack of data on young animals, noting that no toxicity data are available for young animals beyond Postnatal Day Four. Another said the hazard database contained a number of gaps, and he disagreed with the sponsors' conclusion that neurotoxicity and carcinogenicity had been addressed adequately. A third member expressed interest in exploring the mechanism of adrenal tumors and its possible link to

alpha-2u-microglobulin. Most panel members concluded that the hazard assessment was sufficient for a VCCEP Tier 1 submission.

The sponsors characterized the alkanes risk by comparing exposure estimates from the selected scenarios with health benchmark values. They defined the characterization criteria used in the assessment and presented tables showing representative (average) and upper bound (95th percentile) margin of exposure (MOE) and margin of safety (MOS) values for infants, children, and occupationally exposed workers (as prospective parents).

Some panelists commended the sponsors for effectively discussing the risk characterization information, while others noted difficulties in understanding the basis for the values presented in many of the tables. A few panelists said the risk characterization should have used more occupational scenarios with higher exposure potentials. The majority of the panel liked the approach of using both MOE and MOS values to characterize the risk presented by the alkanes, but many members had difficulty understanding how and why certain MOE and MOS values were selected. Most, but not all, panel members concluded that the risk characterization was adequate for a VCCEP Tier 1 submission.

The sponsors summarized their data needs assessment, stating that the hazard data give no suggestion that children are more sensitive to alkanes toxicity than are adults. They noted that existing programs are examining health hazards of the complex hydrocarbon mixtures that are the major exposure sources for these alkanes. They concluded that no additional hazard studies are warranted. The sponsors also concluded that no further exposure studies are warranted because the main exposure route for alkanes is via inhalation, and sufficient air-measurements of these chemicals already exist. They suggested that exposure levels might be over-estimated because some measurements may have included other chemicals. While acknowledging the level of alkanes in breast milk is uncertain, the sponsors do not believe this potential source is likely to be significant.

In discussing data needs, individual panel members identified areas of the submission they believed would benefit from additional data, additional analyses, or clearer presentation. Several panelists identified *data gaps*¹. The data gaps mentioned most frequently were related to levels in breast milk, toxicity in young animals, and levels in more consumer products. One member considered more information on alkanes in consumer products to be a *data need*². Another said more information on developmental and neurotoxicity would be a *data need* if further work shows exposures to alkanes are greater than currently estimated. A third panelist wanted analyses conducted on the assumptions and uncertainties of situations with low MOS values.

In summary, most panel members concluded the overall submission was acceptable for a VCCEP Tier 1 screening assessment. Many panelists said they experienced difficulties understanding how the exposure information was selected and used in the risk characterization. When polled individually, most panel members identified at least one data gap, while two panelists identified data needs, and one panelist identified a data analysis need.

¹ *Data gaps* are areas that could benefit from additional data, additional analyses, or clearer presentation.

² *Data needs* are data gaps requiring additional work before the potential risk to children can be adequately characterized.

1. Participants

Sponsor

American Chemistry Council n-Alkane VCCEP Consortium

Presenters

Ralph Gingell, Ph.D. Biochemistry, DABT
Senior Toxicology Advisor
Shell Chemical LP

Andrew Jaques, M.P.H. Environmental and Occupational Health
CHEMSTAR Director
American Chemistry Council

Ross Macdonald, Ph.D. Chemistry
Consultant to n-Alkane Consortium

David Penney, Ph.D. Toxicology
Senior Toxicologist
Sasol North America, Inc.

Peer Consultation Panel Members

John Balbus, M.D., M.P.H.
Environmental Defense

Thomas Brennan, M.S. Botany
U.S. EPA, Office of Pesticide Programs

George P. Daston, Ph.D. Developmental Biology and Teratology
The Procter & Gamble Company

Michael L. Dourson, Ph.D. Toxicology, DABT
Toxicology Excellence for Risk Assessment (*TERA*)
(Panel Chair)

Jeffrey Fisher, Ph.D. Zoology/Toxicology
University of Georgia

Pertti (Bert) Hakkinen, Ph.D. Comparative Pharmacology and Toxicology
European Commission Joint Research Centre

Elaine A. Cohen Hubal, Ph.D. Chemical Engineering
U.S. EPA, National Exposure Research Laboratory

Sam Kacew, Ph.D. Pharmacology
University of Ottawa

Chad Sandusky, Ph.D. Pharmacology
Physicians Committee for Responsible Medicine

Kimberly M. Thompson, Sc.D. Environmental Health
Harvard University

Pamela Williams, Sc.D. Environmental Health and Health Policy and Management
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Observers and Other Attendees

A list of observers and other attendees is found in Appendix A.

2. Background

This peer consultation meeting has been organized by Toxicology Excellence for Risk Assessment (*TERA*). *TERA* is an independent non-profit organization with a mission to protect public health through the best use of toxicity and exposure information in the development of human health risk assessments. *TERA* has organized and conducted peer review and peer consultation meetings for private and public sponsors since 1996. Under this program, *TERA* is organizing peer consultation meetings for assessments developed as a part of the Voluntary Children's Chemical Evaluation Program (VCCEP). The n-Alkanes assessment was submitted by the American Chemistry Council n-Alkane VCCEP Consortium, which consists of the following companies: Chevron Phillips Chemical Company LP, Sasol North America Inc., and Shell Chemical LP.

The VCCEP program is a voluntary pilot program and part of the U.S. Environmental Protection Agency's (EPA) Chemical Right-to-Know Initiative (<http://www.epa.gov/chemrtk/vccep/childhlt.htm>). The goal of the VCCEP is to enable the public to better understand the potential health risk to children associated with certain chemical exposures. The key question of the program is whether the potential hazards, exposures, and risks to children have been adequately characterized, and, if not, what additional data are necessary. The EPA has asked companies that manufacture and/or import 23 chemicals (that have been found in human tissues and the environment in various monitoring programs) to volunteer to sponsor chemical evaluations in a pilot program. Sponsorship requires the companies to collect or develop health effects and exposure information on their chemicals and then to integrate that information in a risk characterization assessment and a data needs assessment.

The VCCEP pilot program was designed to use a tiered testing approach. For toxicity data, specific types of studies have been assigned to one of three tiers. For exposure data, the depth of exposure information increases with each tier. Tier 1 assessments should use all available data, and therefore some of the Tier 1 chemical assessments will include more than what is indicated for Tier 1. The n-Alkane VCCEP Consortium volunteered to sponsor a Tier 1 assessment for decane, undecane, and dodecane. Data links to the submission document and appendices are available to the public on the Internet at <http://www.tera.org/peer/VCCEP/n-alkanes/n-alkanesWelcome.html>. If data needs are identified through this process, the n-Alkane VCCEP Consortium will decide whether to volunteer for any additional data generation or testing, and whether to provide a Tier 2 assessment for VCCEP peer consultation.

To provide wide-ranging scientific review of the sponsor's assessment, each submission undergoes review and discussion by a peer consultation panel in an open meeting with the public invited to observe. The purpose of the meeting is to provide a science-based peer consultation on the data needs for the chemical, utilizing the assessment submitted by the sponsor as well as the expertise and knowledge of the panel.

The VCCEP Peer Consultation Panel for the n-Alkanes consisted of 11 members independently selected by *TERA*. Each panel member disclosed information regarding potential conflicts of interest and biases for the VCCEP program in general and for decane, undecane, and dodecane in particular. *TERA* evaluated these disclosures in selecting the panel members. The disclosures were publicly presented at the beginning of the meeting (see Appendix B for the panelist disclosure statements). The panel members have experience in various disciplines, including toxicity testing, exposure evaluation, risk assessment, and children's health. The panel received a copy of the submission and key references approximately one month before the meeting, so that they had adequate time to review the documents and prepare for the discussions. Panel members bring a range of views and perspectives to the peer consultations, reflecting the interest in VCCEP by a wide range of stakeholders. The panel does not attempt to reach consensus, rather the individual opinions of the members are noted.

Members of the public were invited to attend the peer consultation meeting to observe the panel discussions. They were also given the opportunity to provide brief oral and written technical comments on the assessment document for the panel's consideration.

TERA prepared this meeting report. The report summarizes the sponsors' presentations, the panel discussions, the sponsors' comments, and any comments from the public. The meeting report is a summary, not a transcript. Individual opinions of the panel members are noted (although not identified by name), along with areas of agreement and disagreement. Panel members have reviewed and commented on the draft report. The sponsors also were given the opportunity to review the draft report to confirm the accuracy of the sponsor presentations and comments. Changes suggested by the panel members or sponsors were shared with the full panel before the report was finalized. *TERA* staff resolved any differences of opinion by reviewing materials from the meeting. This report is made available to the public on the Internet at <http://www.tera.org/peer/VCCEP/n-alkanes/n-alkanesWelcome.html>.

This report is organized into sections corresponding to the submission's exposure assessment, hazard assessment, and risk characterization/data needs sections. Issues and concerns raised during the panel discussions did not always lead to recommendations for additional studies or data compilations. The recommendations of the panel members regarding the need, or lack of need, for additional data apply only to the VCCEP program.

3. Introductions, Conflict of Interest, and Meeting Process

The meeting opened with a welcome by Ms. Jacqueline Patterson of *TERA*. She described the background and purpose of the VCCEP and the agenda for the meeting. Ms. Patterson noted that copies of panel members' biosketches and conflict of interest (COI) and bias disclosure statements were provided to all attendees (see Appendix B). All the panel members then introduced themselves and noted whether they had additions or changes in their disclosure statements. One panel member had an addition: Dr. Fisher noted that he has a contract with the U.S. Air Force to conduct modeling on jet fuels. These fuels contain decane, undecane, and dodecane, as well as hundreds of other alkane and non-alkane chemicals. Dr. Fisher said he did not consider this a conflict of interest, but he was disclosing it as a potential source of bias.

Three sets of written public comments regarding the n-alkanes were received (Appendix C). (The author of one set of comments also made an oral presentation during the course of the meeting, as noted in the meeting Agenda in Appendix B.)

Dr. Dourson, the panel chair, described how the meeting would be run. He explained that discussions would be based on the items found in the Charge to the Panel (located in Appendix B). He noted that all panelists would have the opportunity to state their own positions on the charge items and to ask one another clarifying questions and further discuss the issues. No attempt would be made to reach consensus positions on the charge items. The chair reminded the panel that the purpose of the peer consultation is not to critique the submission document *per se*, but to answer questions on data adequacy for characterizing risk to children.

This meeting report is organized into three sections: exposure assessment, hazard assessment, and risk characterization/data needs.

NOTE: in the following presentations and discussions, unless otherwise noted, the term "alkanes" means the three chemicals that are the subject of this VCCEP peer consultation: n-decane, n-undecane, and n-dodecane.

4. Sponsor Introduction

Mr. Andrew Jaques of the American Chemistry Council outlined the sponsors' presentations and provided background for the inclusion of n-decane, n-undecane, and n-dodecane in the VCCEP pilot program (see Appendix D for the presentation slides). He noted that these three chemicals are being treated as a single category because they are similar in occurrence, chemistry, and

toxicity. Human exposure results primarily from their inclusion in jet and diesel fuels, kerosene, solvents, paints, adhesives, and various consumer products.

5. Exposure Assessment

5.1 Sponsor Presentation

Dr. Ross Macdonald, consultant to the n-Alkane VCCEP Consortium, summarized the exposure data presented in the sponsor's submitted assessment (see Appendix D for the presentation slides). He noted the exposure assessment focused on products and scenarios identified in the exposure literature as likely to have the highest potential exposure to children or to prospective parents. Monitoring data from the exposure literature was used to characterize the inhalation exposure route and supplemental modeling was conducted to characterize oral and dermal routes of exposure. Inhalation was identified as the major route of exposure. The high-exposure scenarios presented were (1) chronic exposure to indoor air, (2) short-term exposure to air in a newly painted home, and (3) occupational exposure to air while working with fuels and paints. Very little data were available for exposures via the oral route (including breast milk) or the dermal route, but the data available and the modeling indicated exposures from these routes were relatively low. The numbers used in the presentation slides for the representative (average) concentrations and the upper bound concentrations are total values for the three alkanes added together. These numbers were obtained from the average and upper bound values of several different air monitoring surveys.

5.1.1 Clarifying Questions from the Panel

Dr. Macdonald responded to inquiries on terminology by clarifying that when the sponsors used the term "upper bound exposure level" in the assessment document or presentation slides, they meant the upper 95th percentile of measurements from a log normal distribution. A 5 percent probability exists for exposures to exceed this "upper bound exposure level" value. The panelists understood the way in which the sponsors were defining this term, but some members said that, in most cases, the term is defined differently: i.e., an "upper bound" value is greater than any of the measured numbers in a dataset. One panelist suggested that, to avoid confusion, the term "95th percentile" should be used instead of "upper bound."

In reply to questions about the percentage of alkanes in products, Mr. Jaques and Dr. Macdonald responded that jet fuel is about 25% n-alkanes. However, jet fuel includes a range of n-alkanes, typically from C9-C16, so the three alkanes in the VCCEP make up only a fraction of the 25% n-alkanes present in jet fuel. Decane, undecane, and dodecane each occur at approximately 2-3% in jet fuel. For the aliphatic hydrocarbon solvents (e.g., mineral spirits) used in paints, the situation is similar: total n-alkanes are around 25% and the three alkanes in the VCCEP are estimated to be about 2-5% each in the hydrocarbon solvent. Hydrocarbon solvents in alkyd-based (oil-based) paints typically comprise about 25-50% of the finished paint. The three alkanes are not likely to be present in latex paints because aliphatic hydrocarbon solvents are used very little in latex paint.

Some panel members wanted more information about the Aerias (2003) database discussed on page 29 of the submission. They wondered why the sponsors did not use the higher alkane air concentration values reported in that database. In response, the sponsor provided background information on Aerias and on Air Quality Sciences, a commercial analytical laboratory funding Aerias. The sponsors explained that the higher concentration values from Aerias were not used because they are maximum values existing only in environments requiring remedial action. In addition, the monitoring techniques used in determining these values are not peer reviewed, and ranges of concentrations are not provided – only the average and maximum values are reported. For these reasons, the sponsors have no confidence in the higher concentration values and did not use them. The average values were used, however, because they are consistent with the average values the sponsors obtained from other sources.

Two panel members asked why more exposure data were not presented from other types of consumer products, such as cosmetics, perfumes, and other personal care items. The sponsors replied that they had attempted to locate relevant data on these products by accessing the Cosmetic Ingredient Review and other sources, but they could not identify data specific to the three alkanes of interest. A panelist suggested that they might obtain such data by making phone calls to staff personnel at trade associations such as the Soap & Detergent Association (SDA) or the Cosmetic, Toiletry, and Fragrance Association (CTFA).

5.2 Public Comments on the Exposure Assessment

Mr. Scott Prothero of the EPA, one of three people who had submitted written public comments, presented his comments orally (see his written comments in Appendix C). He stated that more data regarding occupational exposure should have been included in the submission, and the highest exposed populations had not been adequately discussed.

Responding to panelists questions of whether he or the EPA were aware of any specific exposure data excluded from the submission or whether they had searched for data from Europe or contacted NIOSH (National Institute for Occupational Safety and Health), Mr. Prothero said they had not. He added that jet fuel workers were identified as having the highest exposures, but no information was provided about other types of occupational exposures that might be higher.

5.3 Panel Discussion of the Exposure Assessment

The panel discussion of the exposure assessment addressed four charge items:

- Discuss whether the fate of this chemical is adequately understood.
- Based on the information at hand, discuss whether the available data are adequate to characterize exposure to children and prospective parents, taking into consideration the conditions of exposure (sources, routes, frequency, duration, intensity, etc.).
- Discuss whether all time periods relevant to childhood exposure [(a) parental exposure prior to conception, (b) prenatal development, (c) and postnatal development to the age of sexual maturation] have been adequately considered.

- Discuss whether the estimates of exposure have been calculated appropriately and correctly.

Before addressing the charge items, the Chair asked the panel whether they believe it is appropriate to consider decane, undecane, and dodecane as a single group. Some members said it is appropriate because the three chemicals usually occur together as mixtures and have similar uses. One member pointed out that occurring together in mixture is not nearly as important as whether the chemicals have similar physical, chemical, and toxicological properties. Others responded that all these properties are similar, and the chemicals have similar kinetic properties as well. Based upon all of these considerations, the panel concluded that considering decane, undecane, and dodecane as a single group is appropriate.

The panel then addressed the four charge items by means of the following discussions.

5.3.1 Fugacity and Fate

A panel member raised the issue of fugacity modeling. (Fugacity also was the subject of one set of written public comments found in Appendix C). She asked the sponsors to explain their decision to use a Level 1 fugacity model, which considers only equilibrium partitioning, when it seems that a Level 3 model would provide more information by including degradation, advection, etc. The sponsors responded that it was not possible to use Level 3 fugacity modeling for the alkanes because the rates of dispersion of these chemicals are not known. Several panel members acknowledged the difficulty in using fugacity modeling for the alkanes. One member described analytical difficulties he had encountered while doing mass-balance work with decane because of the chemical's tendency to adhere to glass surfaces. Some panelists thought the exposure assessment should have provided more discussion of the fugacity issues. Given that only the Level 1 fugacity model was used, one panelist noted that water might contain more alkanes than the exposure assessment indicates, but she emphasized that water still appears to be a minor pathway. The sponsors added that the drinking water exposure modeling assumes that the n-alkane concentration is at its limit of solubility, and thus its maximum level attainable, in water.

Recalling the information presented in previous VCCEP submissions, a member expressed concern that the exposure assessment of the alkanes contained minimal discussion of the metabolism and fate of these chemicals. He wondered whether any of the metabolites might provide more exposure to humans or be more toxic than the parent alkanes themselves. The sponsors replied that the metabolism and fate of the alkanes is generally the same as that of all other volatile organic hydrocarbon chemicals. Metabolism occurs via oxidation. There is no reason to suspect that the human exposure or the toxicity of the metabolites would be any greater than that of the parent alkanes.

5.3.2 Sources and Routes of Exposure

Several panelists complemented the sponsors on the large volume of data compiled in the exposure assessment. One member acknowledged the difficulties in estimating exposures that

ranged from the national level to individual living rooms. He said that in many situations the monitoring data on the alkanes was good enough to preclude the need for modeling, and that monitoring data are always preferable to modeling estimates. However, he wished more information had been provided for the given scenarios, such as the amount of paint that was used and the content of alkanes in the paint. He was unsure whether the exposures of professional painters had been assessed adequately.

Asked whether any other sources of occupational exposure might have been cited, the sponsors noted that searches of numerous databases including CONCAWE (1995, 1996, 1999) (the oil companies' European organization for environmental, health, and safety issues) provided data on other potentially high-exposure activities. These included alkanes transportation in the trucking industry, working in the petroleum refining, electrical insulation, or shoe manufacturing industries, working as gasoline service station attendants or taxi drivers, etc. All these activities were found to provide much less exposure to the alkanes than the scenarios presented in the submission.

One panelist thought the overall scope of the exposure assessment was too limited. He said the assessment implied that consumer products do not contain meaningful amounts of alkanes; however, many of them do. The sponsor replied that looking at all possible sources of alkanes from consumer products would be beyond the scope of a screening assessment. In response, the panelist suggested the document might have stated more clearly the exposure sources that were *not* included.

Other panel members also expressed concern that the exposure assessment did not include all possible sources and routes of exposure. They noted that the occupational scenarios presented focused on only two activities: jet refueling and painting. One member noted that Air Force personnel standing behind jets prior to take-off would be exposed to large amounts of jet fuel via inhalation and dermal routes. Some members suggested more discussion could have been given to occupational exposures from manufacturing and processing activities, especially when these activities are in the petroleum refining industry where most of the alkanes usage occurs. They also thought more discussion of non-occupational exposure sources such as cigarette smoke and consumer products would have been useful. Finally, they said more information was needed to justify discounting the dermal and oral routes as pathways of meaningful exposures.

5.3.3 Time Periods of Exposure and Target Populations

Referring to the *Integrated 24 Hour Exposure and the Occupational Exposure* section on pages 36-39 of the submission, a panelist noted that many of the values listed in the text were higher than the values used in the highest exposure scenarios. She asked why the sponsors did not present scenarios based upon the higher concentrations from several of these microenvironments and occupations. The sponsors replied that when the exposure duration in these microenvironments was considered, the total exposure values were lower than those presented in the selected scenarios. Another member disagreed with the sponsors' statement that using a weight-of-evidence approach was appropriate to identify scenarios intended to be worst-case situations. She thought it was more appropriate to present microenvironment scenarios experienced by vulnerable populations when these populations were exposed to unusually high

concentrations. The sponsor replied that one of the most vulnerable, highly exposed populations is that of children breathing indoor air at home, and this scenario was presented. The panelist responded that another scenario that should have been presented was school children riding several hours daily on diesel-powered buses.

Two panelists questioned the exposure assessment's conclusion that children are unlikely to be primary users of consumer products containing alkanes (page 28). They thought that more work was needed to identify those alkanes-containing products that might be used or contacted by children.

While commending the sponsors for addressing oral and dermal exposure possibilities, a panelist asked why data on accidental ingestions of alkanes-containing products (e.g., kerosene) was not included. The sponsors said that while accidental and product-misuse ingestions were known to occur, the Consumer Product Safety Commission (CPSC, 2001), which tracks such events, does not record these ingestion data in a form that enables quantification. In addition, no data related specifically to alkanes ingestion are available. They added that the incidence of accidental ingestions of alkanes is likely to be low because of child-resistant packaging requirements for products that contain alkanes.

One panelist said the very low estimated values for infant exposure to alkanes from breast milk (Appendix F in the submission) were not credible because they came from studies done in the early 1980s. He explained the analytical techniques used in those studies have been superseded by improved methodology. He suggested that more current information is needed, and he wondered if breast milk from occupationally-exposed, nursing women might be a significant exposure route that is being overlooked. Another member said he would expect to find alkanes in breast milk because the chemicals are lipophilic, and breast milk is high in fat. In the absence of analytical data, he thought modeling could be done to estimate concentrations. Other panelists agreed this information would be useful.

5.3.4 Exposure Estimations

Two panelists commented that it was difficult to understand how the different types and degrees of exposures compared to each other. One member said she was not able to determine how or why the sponsors selected the scenarios they did, or why these scenarios represented the highest exposures. She saw no evidence that other possible scenarios had been adequately considered and found no explanation for their rejection. She said a systematic documentation of the rationale for identifying the highest exposure scenarios would have improved the presentation. As an example, she suggested that it would have been helpful to show how indoor air, outdoor air, personal breath monitors, etc. compared with one another.

Panel members discussed the calculation of exposure estimates. One member described the difficulty she experienced in trying to find the data presented in Table 6.1 (*Exposure Concentrations for Selected Scenarios*, page 27) from the sources of these data listed in Appendix A. She thought the manner of data transfer from the appendix to the table was confusing. She noted it was important that readers be able to understand how and why the numbers in the table were selected from the lists in the appendix and to confirm that the

selections were made appropriately. Several other members also said the presentation style of the exposure assessment was difficult for them to follow. This made them uncertain that the assessment was sufficiently conservative.

One member stated that terminology was of key importance in Tier 1 assessments such as this one. He objected to using the term “bounding” for an estimate based on the 95th percentile, when 5% of actual values would be expected to exceed the estimate if the entire population were to be sampled. He believed Tier 1 assessments should define the extreme ranges of exposure and provide those values, rather than the 95th percentile values. He also thought the number of observations and the confidence levels should be listed in the assessment. The sponsor explained that their use of the term “bounding” was a contraction of the original term. The complete term used originally was “upper 95th percentile bounding value.” The panel member responded that there might be better ways to describe exposure data and their related uncertainties than using the terms “95th percentile” and “upper bound.” Another suggested that the “central tendency of exposure” and the “regression to the mean” are other approaches that might be considered.

Some panelists expressed favorable opinions of the exposure assessment. One member said that adding together the 95th percentile exposures of all three chemicals, as was done in the assessment, was quite conservative. Another member complemented the sponsors, saying they had done a remarkable job on the exposure assessment, especially since no specific guidance for a Tier 1 exposure assessment had been given. However, he noted that the Margin of Safety (MOS) shown in Table 8.6 (page 80) is “1.1.” Because this is a relatively low value, he said it was important to fully describe the uncertainty and confidence associated with the value. He also thought it was important to look at how frequently the exposures resulting in a MOS of 1.1 might occur.

Addressing the charge item of whether the estimates of exposure had been calculated appropriately and correctly, a panelist noted he was unable to use the information provided to obtain the sponsors’ value for the infant dose from breast milk (page 35, Table 6.3: *Calculation of Infant Dose from Human Milk based on the Erickson et al (1980) Study*). The sponsors replied that the Unit Conversion Factor in the table contained a typographical error; it should be “1 Kg/1000 g.” Responding to another question from the same panel member on the source of the neat undecane concentration (page 41, Table 6.4: *Dermal Exposure Modeling Results*), the sponsors explained that the listed value of 0.75 g/cm³ had been calculated from undecane’s density. They also clarified that the subchronic inhalation NOAEL of 2.5 E5 ug/m³ was used as the health benchmark for the calculations in Table 8.5 (*Margin of Exposure for Short Term Domestic Exposure during Renovation*) and in Table 8.6 (*Margin of Safety Based on RfC for Short Term Domestic Exposure during Renovation*). The sponsors noted that other ambiguities and errors had been identified in the document after the submission occurred. These items and their corrections are listed in an Errata document. (The Errata document was placed on TERA’s VCCEP n-Alkanes website (<http://www.tera.org/peer/VCCEP/n-alkanes/n-alkanesWelcome.html>) a few days before the meeting, and paper copies were distributed to the meeting attendees. The Errata document also is appended to this meeting report as Appendix E).

Referring to Appendix D of the submission (Calculation of Inhalation Concentration Equivalent of an Oral Dose), a panelist suggested that a 50% ratio of inhalation to oral absorption was more

appropriate than separate estimates of 50% inhalation absorption and 100% oral absorption. He said this was especially true since information presented earlier in the submission indicates the oral absorption is less than 100%.

In summary, after discussing the above topics related to the sponsors' exposure assessment, most panel members concluded that the assessment was sufficient for screening purposes in the VCCEP program. Many panelists provided recommendations for improving the completeness and clarity of the exposure assessment.

6. Hazard Assessment

6.1 Sponsor Presentation

Dr. Ralph Gingell, a Senior Toxicology Advisor for Shell Chemicals LP, presented a summary of the hazard information contained in the sponsor's submitted assessment (see Appendix D for the presentation slides). He noted that all three chemicals have similar toxic properties. The numerous studies conducted on these chemicals, alone and in complex mixtures, are listed in the submission and described in the Robust Summaries. For some toxicity endpoints, data on shorter and longer chain alkanes are included for comparative purposes. He noted that few higher tier safety studies on the individual chemicals were conducted because these chemicals are not major articles of commerce. Data on hydrocarbon fuels were not included in this submission because these fuels contain non-alkane compounds with toxicities not representative of the alkane category that is the subject of this VCCEP peer consultation. Dr. Gingell summarized the animal toxicity endpoints for acute and subchronic toxicity, reproductive and developmental effects, genotoxicity, neurotoxicity, carcinogenicity, and metabolism. He emphasized that the alkanes showed no single target organ system for systemic toxicity, and reproductive/developmental toxicity was less than systemic toxicity. He said that, based upon the available toxicity data, the sponsors used an Acute Toxicity Health Benchmark of 5000 mg/m³, a Subchronic Health Benchmark of 1000 mg/m³, and a Reproductive/Developmental Toxicity Health Benchmark of 2000-5000 mg/m³. Dr. Gingell concluded that although no data are available to directly address potential immunotoxicity or developmental neurotoxicity, the high margins of exposure for the alkanes and the lack of any indication of these effects from the existing studies indicate no need for additional hazard studies.

6.1.1 Clarifying Questions from the Panel

Addressing a presentation slide that showed dosing with Stoddard Solvent IIC³ resulted in benign adrenal tumors in male rats and the sponsor's comment that this effect might be related to nephropathy, a panelist asked if the investigators in this study had concluded that the adrenal tumors were secondary to nephropathy. The sponsor confirmed that the study investigators had raised this possible mechanism. The same member asked what dose of jet fuel was needed to cause the observed immunotoxicity. Another panelist responded that the jet fuel immunotoxicity study was done *in vitro*. He added that, based upon data obtained from medical records of Air

³ Stoddard Solvent IIC is a liquid mixture of petroleum distillates containing n-alkanes, isoalkanes (branched), and cycloalkanes (naphthenes), generally in the C₁₀-C₁₃ range, with less than 2% aromatics.

Force personnel from three Air Force bases in the United States, immunotoxicity has not been shown from *in vivo* studies, and no worker cases of immunological responses to jet fuels have been reported.

When asked to clarify the possible association between alkanes and “painter’s syndrome,” the sponsors referred the question to Dr. Richard McKee (an ExxonMobil toxicologist). Dr. McKee explained that in the 1960s some investigators had associated the hydrocarbon solvents used in paints with various neuropathies. At the time, the occurrence and cause of painter’s syndrome was controversial; today the syndrome no longer appears to exist. Reasons for this are not known, but they may be related to changes in paint compositions or to better ventilation within painting environments. From what we know today, it cannot be determined whether the alkanes caused the neurological effects known as painter’s syndrome. In response to other questions, the sponsors replied that the nephrotoxicity in male rats observed in three of the subchronic studies could be explained by the mechanism associated with the male rat-specific protein alpha-2u-microglobulin. (A panel member who had examined the complete study reports confirmed this.) The sponsors noted that the U.S. EPA has determined that changes in male rat kidneys resulting from an alpha-2u-microglobulin-related process are not relevant for assessing human risk.

A panel member asked why 1000 mg/m³ was chosen as the Subchronic Health Benchmark in view of the fact that Nau et al. (1966) reported that C₁₁-C₁₂ mixtures demonstrated adverse effects at lower values. The sponsors replied that all studies showing adverse effects at doses lower than 1000 mg/m³ used mixtures containing chemicals more toxic than the alkanes. The effects in the Nau et al. study (1966) were attributed to alkylaromatic chemicals, including alkylbenzenes, which were present in the C₁₁-C₁₂ mixtures. The panelist responded that this fact was unclear from the way the study data were presented in the hazard assessment. He then asked what animal studies had been conducted using immature animals. The sponsors said the only toxicity studies that used immature animals were the two listed in the assessment and described in the Robust Summaries (Maraschin et al., 1995; Yoshimura et al., 1996). The panelist recommended that an uncertainty factor for lack of sufficient data be considered in the margin-of-exposure calculation. Referring to page 69 of the submission, he asked why the saturated air concentration for decane (8 gm/m³) was not used as the acute health benchmark, given that no deaths occurred at this concentration. The sponsors explained they selected 5 gm/m³ as a conservative acute benchmark because only limit-dose studies were available on decane, undecane, and dodecane, and 5 gm/m³ was a median dose from the studies that did not show any toxicity.

6.2 Panel Discussion of the Hazard Assessment

The panel discussion on Hazard Assessment addressed the following items from the charge to the panel:

- Discuss whether the information available on mode of action, toxicity studies, and ADME (absorption, distribution, metabolism, and elimination) is adequate to identify and assess potential hazards a) to prospective parents, b) *in utero*, and c) to the infant and child.

- Discuss whether the quantitative hazard and dose-response information (e.g., RfD, RfC) is appropriately chosen or developed.

The panel addressed these charge items through discussions of the topic presented below.

6.2.1 Adequacy of Toxicology Studies for Hazard Assessment

Several panelists commented that the data presented were adequate for a Tier 1 screening-level assessment of the alkanes. They noted the repeat-dose studies, including the developmental and reproductive studies conducted on individual chemicals or on mixtures, did not identify any particular target organs or target life-stages for alkanes toxicity. Although there are no developmental neurotoxicity studies in animals, the existing data do not indicate any trigger for central nervous system (CNS) effects. They also pointed out that the limit doses used in many of the studies were high and showed no potential toxicity hazard. Another member added that unpublished studies evaluating the learning ability of children of Air Force personnel showed no meaningful effects. The panelists agreed with the sponsors that toxicity data from studies of the n-alkanes (alone or in mixtures), rather than toxicity data from studies of more complex chemical mixtures (e.g., jet fuel) should be used to assess the hazard. They thought the greatest hazard is pulmonary aspiration associated with accidental oral ingestion of these chemicals, and this adverse effect is sufficiently characterized by the existing studies. They thought the sedation observed in some studies was a reversible neurological effect that did not indicate the need for a developmental neurotoxicity study. Another member stated that Air Force personnel exposed to high concentrations of jet fuel experienced temporary headaches and confusion, but no apparent memory loss.

A panelist explained that he had reviewed some of the unpublished EMBSI (ExxonMobil Biomedical Sciences, 1991) study reports and compared them with the data presented in the submission. He also compared the data in the reports to the results listed in Table 7.3 of the submission (*Summary of the Repeat Dose Toxicity of n-Alkanes and Related Materials*). For the inhalation studies, he was comfortable using 3.14 g/m³ (from Nau et al. 1966) as the most appropriate NOAEL (No Observed Adverse Effect Level). For one of the oral toxicity studies (summarized as RPDT-9 on page B-31; 90-Day Subchronic Oral Toxicity Study in Rats, EMBSI Study No. 158270), the panelist believed the most appropriate NOAEL is 500 mg/kg-day, rather than 5000 mg/kg-day, because of gastrointestinal and anal staining effects noted at the 2500 mg/kg-day dose level. (The study investigators had interpreted the effects occurring at the 2500 mg/kg-day dose level as an adaptive response to the irritant properties of the test substance.) The panelist said this difference in opinion regarding the NOAEL for this study did not change his acceptance of the Subchronic Health Benchmarks listed in the text of the hazard assessment. The same panelist also noted that two reproduction/developmental studies had been conducted on the alkanes (Maraschin 1995; Yoshimura et al. 1996). Both these studies stopped dosing rat pups at Lactation Day 3 or 4; as a result, no alkanes toxicity data are available for young animals that are beyond that age. In spite of this concern, the panelist concluded the summation of existing data from all the toxicity studies are sufficient to allow a risk assessment to be conducted.

Several other panelists addressed additional concerns. One panelist said the hazard database cannot be characterized as robust because it contains a number of gaps. He noted that the neurotoxicity study (Lammers and de Groot, 1999) dosed animals for only three days. He disagreed with the conclusion stated in the hazard assessment that neurotoxicity and carcinogenicity had been addressed adequately, and he suggested a longer-duration neurotoxicity study might be indicated. When asked by another panelist if he believed a bioassay should be conducted to address carcinogenicity, he replied that these chemicals appear to be tumor promoters with about 1/10 the potency of phorbol esters. He thought that might be a cause for concern. Another panelist was satisfied with the existing data on neurotoxicity, but he expressed interest in exploring the mechanism of male rat adrenal tumors induced by Stoddard Solvent IIC and its possible link to alpha-2u-microglobulin-induced male rat kidney toxicity. The sponsor added that the industry Solvents Panel has retained the services of an academic consultant (Dr. Tischler) to explore mechanisms of carcinogenicity with Stoddard Solvent IIC and other materials and possible association between adrenal tumors and alpha-2u-microglobulin-induced nephropathy in male rats.

A member added that a recent publication (Smith et al., 2004) has shown the alkanes to be enhancers of dermal penetration, and they are used for this purpose with some dermally-applied pharmaceuticals. Although dermal penetration enhancement is not directly related to the alkanes hazard assessment, the panel member thought it important to note because it may indicate a potential to increase the systemic exposure, and therefore the toxicity, of other chemicals.

In summary, after discussing the sponsors' hazard assessment, most panel members concluded it was sufficient for a Tier 1 VCCEP submission.

7. Risk Characterization and Data Needs

7.1 Sponsor Presentations

Dr. Ross Macdonald, consultant to the n-Alkane VCCEP Consortium, and Dr. Dave Penney, Senior Toxicologist for Sasol North America, Inc., presented the sponsors' Risk Characterization and Data Needs assessments (see Appendix D for the presentation slides). In presenting the Risk Characterization, Dr. Macdonald explained that the sponsors characterized the alkanes risk by comparing the exposure scenarios presented previously by Dr. Macdonald with the Health Benchmark values presented previously by Dr. Gingell. After reviewing the scenarios and benchmark values, Dr. Macdonald defined the characterization criteria (Margin of Exposure, MOE; Margin of Safety, MOS) and presented tables showing representative (average) and upper bound (95th percentile) MOE and MOS values for infants, children, and occupationally exposed workers under conditions varying from acute to chronic. The lowest upper bound MOE and MOS values for short-term exposures were 275 and 1.1, respectively. It was emphasized that use of a subchronic health benchmark for a short-term acute exposure was considered conservative. Use of the acute benchmark would result in MOEs in excess of 1,000. For chronic exposures, the representative and upper bound MOEs were 6,000 and 1,900 respectively, with corresponding MOS values of 24 and 8. Aggregation of infant short-term exposures from all possible sources (via inhalation while at home during painting/renovation, via ingestion of water

and breast milk, and via dermal contact) resulted in representative and upper bound MOEs of 1,800 and 266, respectively, when compared with the sub-chronic benchmark. The corresponding MOS values were 8 and 1.

In presenting the Data Needs Assessment, Dr. Penney said the hazard data give no suggestion that children are more sensitive to alkanes toxicity than are adults, and the sponsors concluded that no additional hazard studies are warranted. He added that existing programs currently are examining the health hazards of the complex hydrocarbon mixtures, which are the major exposure sources for these alkanes. Dr. Penney said that the main exposure route for alkanes is via inhalation and sufficient air-measurements of these chemicals already exist, therefore no further exposure studies on these chemicals are warranted. In discussing uncertainties, Dr. Penney noted that the exposure levels to the n-alkanes might be over-estimated because some measurements may have included iso-alkanes and other chemicals. Another uncertainty is the level of alkanes in breast milk from occupationally exposed, nursing women. Although no data exist from this exposure source, the sponsors do not believe it is likely to be significant.

7.2 Panel Discussion of Risk Characterization

The panel's clarifying questions and discussion of risk characterization occurred concurrently and included discussion of the following charge item:

- Discuss whether the Risk Characterization appropriately integrates the exposure and hazard information for this chemical and adequately characterizes the risk a) to prospective parents, b) *in utero*, and c) to the infant and child.

One panelist commended the sponsors for presenting both MOE and MOS values together, stating that this was an effective approach for discussing the risk characterization information. However, he and several other panelists noted difficulties in understanding the basis for the numbers presented in many of the MOE and MOS tables (especially the tables on pages 80 and 82 of the submission). They said it was not clear whether individual tables used acute, short-term, or chronic benchmarks for calculating the MOE and MOS values, and a sufficient rationale for making such choices was not presented. The text accompanying each table should have explained which benchmark was selected for the table and why.

A member thought the MOS values of "1.1" for infants, children, and adults listed on page 80 in Table 8.6 (*Margin of Safety Based on RfC for Short-term Domestic Exposure during Renovation*) on page 80 were unrealistically low because they were based on a chronic benchmark. He said use of a short-term or acute benchmark would have been more appropriate for this table. Another member said MOS was defined differently for workers and non-workers on page 78, and then the term was used on subsequent pages without clarifying which definition applied. He also thought the MOS was not sufficiently protective of vulnerable populations, and this should have been reflected in the document.

Others suggested the discussion should have used more scenarios from work habits and practices. They said data were available on airport personnel engaged in refueling, and thought that worst-case scenarios likely would involve going into fuel tanks to clean them and standing

behind jet planes before take-off. In such situations, total exposures would include dermal exposure from clothing soaked with fuel plus possible inhalation of vapors, even though self-contained breathing equipment would likely be used.

One member questioned the conclusion that the EPA Research House Study was conservative because of the air exchange rates used, which impact the concentrations of chemicals present in the air. He said that many houses today have air exchange rates less than that of the EPA Research House. Another said that, while he generally favors the use of monitoring data, the EPA Research House Study may be one case where using the Wall Paints Exposure Model (WPEM) is more appropriate. Since the WPEM was validated using the n-alkanes, the model may give more realistic values for developing a focused risk assessment than would be obtained from using the monitoring data. The reason for this is that the amount of paint used in the monitored study may have been artificially high. The panelist believed that using the WPEM model would result in a more realistic assessment that in this case would likely mean less exposure.

A panelist wondered whether the upper bound exposure concentration would cover all populations. He said this question must be answered in order to know whether the risk characterization is adequate. Since the MOE values are applied equally to all populations without considering possible differences in sensitivity, he thought that chronic, rather than acute, MOE values should be used. He said the chronic values would provide more assurance of protecting potentially sensitive populations, such as embryos.

Speaking more generally, a panelist reminded the panel and sponsors that a main purpose of risk characterization is to help identify areas of uncertainty. She did not think the risk characterization succeeded in doing that because of the confusing way the data were presented. For short-term domestic exposure situations, she thought more analysis was needed, and she recommended each assumption be reviewed to determine its impact on the risk. She suggested determining whether each assumption was sufficiently conservative, whether it really mattered, and how it affected the risk (i.e., a sensitivity analysis of the assumptions).

In summary, the panel liked the approach of using both MOE and MOS values to characterize the risk presented by the alkanes. However, many members said they experienced difficulty understanding how and why the MOE and MOS values were selected for the scenarios presented in the tables. Several panelists recommended ways to clarify the data presentation and to show more clearly the degree of uncertainty associated with the MOE and MOS values. Others suggested additional scenarios should have been considered and additional analyses conducted. Most panel members concluded that the risk characterization was adequate for a VCCEP Tier 1 submission, while a few others disagreed and concluded it was not.

7.3 Panel Discussion of Data Gaps and Needs

The panel's clarifying questions and their discussion of data needs occurred concurrently and included discussion of the following charge items:

- Identify any additional hazard information that is needed and discuss why it is necessary. The focus should be on those studies listed in the next VCCEP tier.
- Identify any additional exposure data and analyses that are needed and discuss why this information is necessary.

The Panel Chair reviewed the definitions of *data gaps* and *data needs*. He explained that, in the context of the VCCEP, *data gaps* are any areas in which information is lacking, and *data needs* are those data gaps for which additional information is required before the potential risk to children can be adequately characterized. He then asked each panel member to identify and discuss any data gaps or data needs they found in the hazard, exposure, or risk assessments.

While not terming it a data gap or need, several panelists thought that the rationale for benchmark selections in the Risk Characterization should be clarified, and the degree of uncertainty associated with the MOE and MOS values should be presented in a more understandable manner. These members thought that adding further explanations would greatly improve the presentation and help enable the panelists to determine whether sufficient information exists to adequately characterize the risk to children. Another panelist expressed concern that a number of the important animal studies on the alkanes were unpublished, and therefore not available to the public. He acknowledged, however, that Robust Summaries of the unpublished studies were appended to the submission (Appendix B of the submission), and that all panel members had been given the opportunity to review the complete studies before the meeting.

7.3.1. *Data Gaps*

Most panel members identified one or more *data gaps*, which they defined as areas that could benefit from additional data, additional analyses, or clearer presentation. The data gaps listed by the panel members are grouped together as follows:

- Six panelists mentioned measuring or estimating the alkanes content of breast milk, especially the milk from occupationally exposed women.
- Five panelists thought more toxicity information on young animals might be obtained. Two of these members mentioned developmental neurotoxicity and two-generation reproduction studies. One also identified an immunotoxicity study. He suggested more information be presented on differences in the physiology and biochemistry of children compared to adults and that the consequences of these differences be considered.
- Four panelists thought more information should be presented on alkanes content from a wider range of consumer products that might be used or contacted by children. One of these members recommended contacting industry trade associations to request this information.
- Two panelists recommended additional modeling work to increase confidence in exposure values, especially those values based upon short-term exposures.

- Two panelists listed neurotoxicity, with one saying the hazard assessment should be revised to explain more clearly why neurotoxicity is not a concern requiring further testing.
- Two panelists wanted additional exposure scenarios presented, especially situations involving occupational exposures (e.g., to jet fuels).
- One panelist wanted additional information on the alkanes content of air from buildings suspected of causing occupant health problems.

7.3.2. *Data Needs*

While most of the panel members identified *data gaps*, they did not consider these to be *data needs*, i.e., requiring additional work before the potential risk to children can be adequately characterized. However, two panel members identified and discussed items they considered *data needs*, and a third panel member identified what she termed an *analysis need*.

- Obtaining information on the presence of alkanes from a wider range of consumer products was identified as a data need by one member.

The panel discussed this potential data need. The originating panelist thought this was necessary because the product data presented in the assessment appeared to be incomplete. He said additional data might demonstrate that the alkanes exposure of vulnerable populations is greater than currently estimated. If so, this could result in MOS values less than “1”. More information might be available from existing data such as the percent content of alkanes in products and the market share of these products. If such information was not available, the panelist believed a product survey should be conducted.

Other panelists questioned whether obtaining additional consumer product data on alkanes would be meaningful; with one saying the major consumer exposures to alkane-containing products had already been identified. He doubted that additional data would displace the worst-case scenarios described in the sponsors’ exposure assessment. Another member disagreed, and thought more data might be useful, especially data on products such as floor cleaners that were used on surfaces likely to be contacted by infants.

The sponsor noted that under the SIDS (Screening Information Data Set) program, ACC currently is compiling the type of data for hydrocarbon solvents that the panelist identified as a data need.

- Obtaining more information on developmental and neurotoxicity was identified as a *conditional data need* by one member. He termed the need *conditional* because he would consider it a *data need* only if refined exposure assessments based on a wider range of consumer products shows alkanes exposures to be greater than currently estimated.

Otherwise, he would consider obtaining more information on developmental and neurotoxicity to be a *data gap*, rather than a *data need*.

- In addition to the identification of *data gaps* and *data needs*, one panel member identified what she termed *analysis needs*. She said these needs could be satisfied by reviewing and further analyzing the assumptions and uncertainties in situations where small margins of safety existed. In addition, she believed comparisons of indoor air estimates to personal breath measurements are needed. This information would help determine whether the uncertainties in the risk characterization are significant.

In summary, most panel members concluded the overall submission on the alkanes was acceptable for a Tier 1 screening assessment, but many of them said they experienced difficulties understanding how the exposure information was used in the risk characterization. Several *data gaps* were identified, most of them in the areas of exposure assessment and risk characterization. Two *data needs* were identified, one of which was conditional, and one *analysis need* was identified.

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