Report of the Peer Consultation Meeting on Acetone

Submission by:
American Chemistry Council Acetone Panel
for the
Voluntary Children's Chemical Evaluation Program (VCCEP)

Peer Consultation Organized by:
Toxicology Excellence for Risk Assessment
November 18, 2003
Cincinnati, Ohio

March 5, 2004

Table of Contents

List of Appendices

Executive Summary

A panel of scientists with expertise in toxicity testing, risk assessment, exposure assessment, and children's health met on November 18, 2003, to conduct a peer consultation of a submission on acetone. The American Chemistry Council Acetone Panel 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 acetone to children, and, if not, to identify data needs.

The sponsors provided the panel with brief presentations summarizing the submission's assessments of hazard, exposure, risk, and data needs. They noted the available toxicity studies conducted directly on acetone fulfilled most requirements for VCCEP Tiers 1 and 2, and demonstrated acetone's low toxicity. They explained that physiologically based pharmacokinetic (PBPK) models for acetone and isopropyl alcohol (IPA) supported use of IPA toxicity studies to fulfill some of the Tier 2 and 3 data requirements for acetone. The acetone exposure assessment included estimated exposures from both endogenous acetone production and from exogenous sources. The primary source of acetone exposure in all age groups was endogenous production, which ranged from 390 mg/kg-day in infants to 72 mg/kg-day in adults. Nursing infants of mothers with maximum occupational exposure to acetone were estimated to receive up to 7.9 mg/kg-day acetone via breast milk. For non-nursing children and adults the greatest exogenous source of acetone was from food ingestion (up to 0.16 mg/kg-day). The sponsor emphasized that aggregate exposures to upper bound exogenous doses of acetone were substantially below the endogenous production levels in all age groups. They said the hazard assessment did not suggest any increased susceptibility of children to acetone, and the risk assessment indicated that children's exposure to exogenous acetone was unlikely to present adverse health risks. The sponsor concluded that no further studies on acetone were warranted.

Several panelists commented favorably on the hazard assessment data set compiled for the acetone submission. After discussing the PBPK models, most panel members accepted the use of IPA toxicity studies to fill the VCCEP Tier 2 and 3 acetone data gaps. The panel discussed the two available Reference Doses (RfDs) for acetone, and the majority of panelists concluded that using either RfD for risk assessment was questionable because neither RfD accounted for endogenous acetone. One panel member raised concerns regarding the clinical implications of exogenous acetone exposure, noting possible interference with endogenous acetone's role in homeostasis. The majority of the panel was satisfied with the adequacy of the toxicity data on acetone and IPA, and with the hazard assessment.

In discussing exposure scenarios from consumer product use, several panelists did not think that many of the assumptions used in the exposure assessment were truly worst case. Other panel members agreed all the assumptions were not worse case, but noted that acetone exposures from consumer products would be below endogenous production even if more conservative assumptions were used; therefore, they were not concerned. One member suggested that actual product-use data be used to check the accuracy of the exposure models. A few panelists were not convinced that the available exposure information was adequate to conclude that exposure to all target populations had been adequately characterized. They suggested the existing exposure data might be used with the PBPK model to estimate exposures in those situations where

exposure data do not exist (e.g., *in utero*). The majority of panel members concluded that the exposure assessment was sufficient for screening purposes.

Most panelists thought the risk assessment appropriately integrated hazard and exposure information and adequately characterized the risk. Some members said the large differences between exposure levels and toxicity thresholds indicated that exogenous acetone exposures would not present a cause for concern, even if more conservative assumptions had been used in some exposure scenarios. Several panelists mentioned areas where the risk assessment might be improved. They said a number of issues were identified and discussed, but were not presented in a manner relating directly to childhood risk. Some members thought parts of the submission would benefit by increased explanation and clarity. One panelist said product-use data are preferable to exposure models and more could have been done to use exposure scenarios that were truly worst case. Overall, the majority of the panel did not find any major deficiencies in the acetone submission. No panel members identified any data needs for acetone.

Participants

Sponsor

American Chemistry Council Acetone Panel

Presenters

John M. Waechter, Jr., Ph.D. Toxicology, DABT
Toxicologist
The Dow Chemical Company

Paul S. Price, M.S. Civil Engineering
Principal Scientist
AMEC Earth and Environment

Peer Consultation Panel Members

Nicole Cardello, M.H.S. Environmental Health Sciences
Physicians Committee for Responsible Medicine

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)

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

Sam Kacew, Ph.D. Pharmacology
University of Ottawa

Michael L. Gargas, Ph.D. Toxicology
The Sapphire Group

Richard Reiss, Sc.D. Environmental Science and Engineering
Sciences International, Inc.

Jennifer Seed, Ph.D. Developmental and Cellular Biology
U.S. EPA, Risk Assessment Division

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

Karla D. Thrall, Ph.D. Toxicology
Battelle, Pacific Northwest Division

Rebecca L. Tominack, M.D.
St. Louis University School of Medicine and
Missouri Regional Poison Center

Observers and Other Attendees

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

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 Acetone assessment was submitted by the American Chemistry Council Acetone Panel (ACCAP). ACCAP consists of the following companies: Celanese, the Dow Chemical Company, the Goodyear Tire & Rubber Company, Rohm and Haas Company, Shell Chemical LP, and Sunoco, Inc.; the consultant to ACCAP on exposure issues was AMEC Earth and Environment.

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 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 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. ACCAP volunteered to sponsor a Tier 1 assessment for Acetone, utilizing the available information and data (links to the submission document and appendices are available to the public on the Internet at http://www.tera.org/peer/VCCEP/ACETONE/ACETONEwelcome.html). If data needs are

identified through this process, ACCAP will choose whether or not to volunteer for any additional data generation or testing and whether to provide a Tier 2 assessment.

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 where the public is 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 Acetone 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 Acetone 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. It summarizes the sponsor's presentations, the panel discussions, the sponsor 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 sponsor was also 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/ACETONE/ACETONEwelcome.html.

This report is organized into sections corresponding to the submission's hazard assessment, exposure assessment, and risk characterization/data needs sections Issues and concerns raised during the panel discussions do 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.

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 all attendees received copies of the two public comments received. These were from Dr. John Balbus, a VCCEP core panel member who could not attend this meeting due to a scheduling conflict, and from Dr. Hugh Barton of EPA. The comments are found in Appendix C. She also 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. Dr. Dourson noted that *TERA* previously conducted risk assessment evaluations on acetone for the National Institutes of Occupational Safety & Health (NIOSH), but he himself was not involved in that work. No other panel members had any additions or changes in their disclosure statements.

Dr. Dourson, the panel chair, then 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 a consensus position on the charge question. 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 report on the Acetone peer consultation meeting is organized into three sections: hazard assessment, exposure assessment, and risk characterization and data needs.

Hazard Assessment

Sponsor Presentation

Dr. John Waechter, Jr., a toxicologist with the Dow Chemical Company and the Chair of the Acetone Panel Toxicology Research Task Group, briefly summarized the hazard assessment data presented in the sponsor's submitted assessment (see Appendix D for the presentation slides). He noted that direct studies on acetone are available to fulfill almost all of the requirements for VCCEP Tiers 1 and 2. Results demonstrate that acetone possesses low acute toxic potential and does not produce genotoxic or immunotoxic effects. Rat and mouse subchronic oral studies (NTP 1991; Dietz et al., 1991) and inhalation developmental toxicity studies (Mast et al., 1988) were described in detail.

The metabolism of acetone and its immediate precursor, isopropanol (IPA), were described. Physiologically based pharmacokinetic (PBPK) models for both acetone and IPA are available (Gentry et al., 2003; Clewell et al., 2001). These models support using toxicity studies on IPA to fulfill some of the Tier 2 and 3 hazard data requirements for acetone. Specifically, a two-generation reproductive toxicity drinking water study (Bevan et al., 1995) and a chronic

toxicity/carcinogenicity inhalation study (Burleigh-Flayer et al., 1997) conducted on IPA were used in the acetone hazard assessment.

Dr. Waechter discussed two reference doses (RfDs) and one reference concentration (RfC) that have been derived for acetone. The sponsors believe the RfD value of 8.7 mg/kg-day[1] and the RfC of 29 ppm are the most appropriate values to use for human risk assessment, and therefore these are the values used in the acetone submission documents. Dr. Waechter concluded that the existing studies on acetone and IPA are sufficient to fulfill all three tiers of the VCCEP requirements for an acetone hazard assessment.

Clarifying Questions from Panel

In reply to questions about toxicity differences between acetone and IPA and whether IPA could be an acetone metabolite, the sponsors and other panel members responded that the toxicity profiles of the two chemicals were similar and that IPA was an acetone metabolite, but it could also be an acetone precursor if the overall redox state of the liver was reductive.

One panelist asked whether the term "slight change," which was used several times in describing the results of toxicity studies, indicated the findings were outside the normal range. The sponsor acknowledged the term was unclear and agreed it would be preferable to provide percentage changes that occurred and indicate statistical significance. Dr. Waechter noted that percentage changes were provided in several of his slides.

Noting that two RfDs[2] are available for acetone, a panelist wanted to know the status of the EPA's RfD. Another panelist responded that the EPA RfD listed on the IRIS (Integrated Risk Information System) website has been peer reviewed and is considered to be final by EPA.

A panelist asked if the NOAEL (No Observed Adverse Effect Level) values listed in the toxicity studies represented doses of exogenous acetone only. He said the real NOAEL values for the studies should be the exogenous acetone doses plus the endogenous levels of acetone existing in the animals, and he wondered what the endogenous acetone levels were in the test animals. The sponsor confirmed that the NOAEL values for the toxicity studies presented in the submission were for exogenous acetone only. He added that it might be possible to determine endogenous acetone levels in the test animals, and then to add those amounts to the exogenous acetone doses to obtain higher NOAELs, but he said this is not commonly done. He confirmed that the sponsors did not do this in the acetone hazard assessment.

Responding to a question of whether compound-specific uncertainty factors were used in deriving the RfD from the PBPK model, the sponsor noted that default uncertainty values were used, and an uncertainty factor of 30 was applied to the animal dose before converting it to a

[1] The RfD value of 8.7 mg/kg-day is from the PBPK model described in the paper of Gentry et al., 2003 (the prepublication manuscript of this paper is in Appendix D of the sponsor's submission document). The PBPK model uses results of the developmental inhalation study of Mast et al., 1988.

[2] The second RfD value of 0.9 mg/kg-day is from the EPA's Integrated Risk Information System (IRIS) (http://www.epa.gov/iris/subst/0128.htm) and uses results of the subchronic drinking water study of Dietz et al., 1991.

human dose. Panel members discussed the appropriate stage to apply uncertainty factors. Several members said the approach used by Gentry et al. was appropriate. In the case of IPA, they thought it might not make any difference when the uncertainty factors were applied. Other members thought further discussion would be needed before any conclusions could be drawn.

Referring to the second paragraph on page 9 of Appendix D of the submission, a panel member noted the AUC (Area Under the Curve) was calculated for a 10-day exposure. She asked if the NOAEL values (on page 8 of Appendix D) would change if an adverse response were produced by a single, short-term (less than one-day) exposure, rather than from daily exposure over the 10-day time course. Another panelist responded that the values would not change because they are expressed as mg/kg-day. A third panelist agreed, adding that although the NOAEL was the average mg/kg-day exposure over the 10-day gestation period, using this value was appropriate unless a specific, shorter window of vulnerability was known to exist.

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 it is appropriate to use data on IPA to assess risk from exposure to acetone.

- Discuss whether the PBPK model was appropriately developed and validated; the limitations to the model; whether there are any relevant conditions where it should not be applied; and whether the correct dose metric was chosen.

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

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

Oral Reference Dose (RfD)

The panel discussed the two RfD values for acetone: the value derived by Gentry et al., 2003 (8.7 mg/kg-day) and the EPA value listed on IRIS (0.9 mg/kg-day). Several panel members thought the IRIS RfD was not a realistic value, and one member suggested it be re-evaluated. Another member said the sponsors' selection of the Gentry RfD was appropriate and justified. He thought the Gentry RfD was sufficiently conservative to use as a tool for human risk assessment when one considered the large amount of other data available on acetone. These other data included human endogenous levels of acetone, the conservative application of uncertainty factors

(he thought applying uncertainty factors for database insufficiency and for extrapolating from subchronic to chronic was not really necessary), and the lack of data gaps in the toxicity profile. He said these additional data could support an RfD that was higher than the 8.7 mg/kg-day value (i.e., the Gentry RfD) used by the sponsors. Another panelist thought that extensive panel discussion comparing the relative merits of the two RfD values was not necessary because it was clear that they both were very conservative. A majority of the panel members agreed, saying that the hazard data presented in the submission were comprehensive and robust.

One panelist asked if the PBPK model (described in Appendix D of the submission) accounted for endogenous production of acetone. To answer this question, a panel member contacted the author of the PBPK model manuscript, Dr. P. Robinan Gentry. Dr. Gentry stated that endogenous acetone production was not incorporated in the PBPK model. Upon learning this, some panel members reasoned that, since neither of the two RfD values included endogenous acetone levels, the value of using either RfD for human risk assessment was questionable. One member added that the two RfD values not only did not include the endogenous acetone levels, but they were below normal endogenous levels. He had difficulty accepting any RfD values below endogenous levels. This member also thought compound-specific adjustment factors might have been used for the uncertainty factors in the RfD derivations, rather than using the default values as was done in the submission. The sponsors agreed that RfD values lower than human endogenous levels raised questions, but they believed using the value from the PBPK model helped assure the resulting risk characterization would be conservative (i.e., health protective). Another panelist suggested that the most important issue was whether the human endogenous levels were comparable to the endogenous levels in the animal species used in the toxicity studies. Several panelists suggested the authors of the PBPK manuscript be encouraged to address endogenous issues in their model.

Impact of Exogenous Acetone on Endogenous Acetone Control Mechanisms

One panelist had questions about the range of endogenous human acetone production. She thought the submission should have provided more information about the extent of the range, what it means, and if it is important in determining human risk. Another panel member was concerned that the use of average endogenous acetone production might not adequately capture the variability occurring in these levels. She noted that the human body varies its production of acetone to control metabolism and other homeostatic mechanisms, and the addition of exogenous acetone might interfere with these control mechanisms. As an example, she said exogenous acetone might influence endogenous acetone's control of CYP 2E1 activity in the liver and lymphocytes. She noted that factors such as changes in CYP 2E1 activity, obesity, or racial differences could affect human risk positively or negatively. This panelist noted that ketogenic diets are used to increase endogenous acetone levels to provide benefits in epilepsy. In some conditions, however, increasing acetone levels might have adverse effects on health, rather than beneficial ones.

One member said he was not concerned about the variations in endogenous acetone levels because he believed the AUC, rather than peak levels, is the correct parameter to use for the exposure component of human risk assessment. Another member noted that concerns regarding variations in endogenous acetone levels over time might have merit, but they did not suggest the

need for more animal studies. Other panelists agreed these uncertainties did not indicate additional toxicity studies were needed.

IPA as an Acetone Surrogate and use of PBPK models

Panelists discussed the acceptability of using IPA as an acetone surrogate to fill data gaps in the VCCEP tiered list of toxicity studies. One panelist said she understood the rationale for using IPA to fill the acetone data gaps, but she wanted to see data generated on acetone itself. She said IPA is more toxic than acetone, both acutely and sub acutely (e.g., IPA produces hemorrhagic gastritis); therefore, she reasoned that using IPA as an acetone surrogate may produce toxicities that could mask the more subtle adverse effects of acetone, such as acetone-induced CYP 2E1 hepatic activity. Several other panelists, however, were comfortable using IPA as a surrogate for acetone. One member noted that IPA was more toxic than acetone only at the points of contact. He said IPA may be somewhat more potent than acetone, but the potency difference is not biologically significant given the exaggerated doses of either chemical needed to produce toxicity. He added that the pharmacokinetic data on IPA and acetone blood levels demonstrate the two chemicals can be interchanged in PBPK models. Some panel members thought using IPA as an acetone surrogate would add conservatism to the risk assessment if IPA was indeed more toxic than acetone. The majority of the panel concluded that substituting IPA data for acetone was justified; however, the first panelist was not convinced. She explained that her continuing concern resulted from the fact that the PBPK models for IPA and acetone were based on steady-state pharmacokinetics. Such a pharmacokinetics model does not accurately reflect humans in the real world because people are almost never at a steady state, and they frequently have minimal levels of endogenous acetone present in their blood. She thought using PBPK models based on imposed steady-state conditions in animals was insufficient to accurately represent realistic situations in people.

After discussing the above topics related to the sponsors' hazard assessment, most panel members were satisfied with the existing toxicity data on acetone and on IPA.

Exposure Assessment

Sponsor Presentation

Mr. Paul Price, an AMEC employee and exposure consultant to the sponsors, presented the highlights from the sponsor's submitted exposure assessment (see Appendix D for the presentation slides). He noted that the assessment focused on endogenous and exogenous sources of acetone using a child-centered approach. He explained that endogenous exposure results from human metabolism. The magnitude of this exposure is very much age-related and exhibits appreciable intra- and inter-individual variability over time. Exogenous exposure results from chain-of-commerce activities consisting of industrial uses (chemical intermediates, solvents, etc.), industrial emissions, commercial uses (adhesives, surface coatings, cleaning fluids, etc.), and uses of consumer products (nail products, solvents, etc.) by the general population. Exogenous exposure also occurs from non-chain-of-commerce sources such as vegetative release during photo-oxidation, biomass burning, and vehicle exhausts.

Mr. Price provided estimates of acute and longer-term exposures from the sources mentioned above. He noted that endogenously produced acetone is the predominant source of exposure for children and females of child-bearing age. Maximum acetone production ranges from 390 mg/kg-day in infants to 72 mg/kg-day in adults. Acute and chronic exposure scenarios from a variety of consumer products were presented. Consumer product usage, even under reasonable worst-case conditions, results in one-day doses substantially lower than endogenous doses (e.g., spray painting in a small room with one open window could provide a dose of 5 mg/kg-day). For chronic exposure, dietary consumption (primarily from cows' milk) is the highest exogenous source for most children and adults, with 95th percentile average daily doses ranging up to 0.16 mg/kg-day. Air, water, and consumer products are minor sources of chronic exposure.

Acetone has been detected in human milk, but not quantified. Assuming the acetone concentration in milk equals that in plasma, nursing mothers in the general population are estimated to provide their infants with an average daily acetone dose of 1.5 mg/kg-day. This dose is estimated to increase to 7.9 mg/kg-day from nursing mothers with maximum occupational exposures to acetone.

Clarifying Questions from Panel

In response to panelist questions about availability of acetone exposure data during pregnancy, to the fetus, and to infants breathing their mothers' exhaled air, the sponsor replied that no data were available.

Asked about the impact of cigarette smoking on air concentrations, the sponsor noted that the 8 ppb value presented for ambient indoor air represented combined samples from both smoker and non-smoker homes. He added that smoking one pack of cigarettes per day is estimated to add about 2 ppb acetone to a home's air concentration. The impact of smoking on outdoor air acetone concentration is assumed negligible.

Considering the exposure scenarios from consumer product use, two panel members questioned the assumptions made on room size and ventilation. They suggested that product use might occur in a small room with no ventilation, and they asked whether the assumptions were truly worst-case. The sponsor replied that the room size was assumed to be 20 m^3 (approximately 10x10x7.5 feet) and to have one open window for ventilation. He explained that an open window was assumed because trying to identify the absolute worst-case exposure situations would lead to a "slippery slope" going beyond realistic high-end use to excessive misuse situations. He noted, however, that if the room were assumed to have no open windows and no ventilation, the exposure for each consumer product would be about three times higher than the one-day dose values listed in the submission and shown in the presentation slides (e.g., spray painting would result in a dose of 15 mg/kg-day, rather than 5 mg/kg-day). The sponsor noted that even if no ventilation were assumed, exposure from consumer product use would still be much lower than the human endogenous production of acetone.

Referring to the sponsor presentation slides (Slides 6 and 7: *Endogenous Production of Acetone – Relating Blood Levels to Dose* and *Age Specific One-Day Doses*), panelists asked how the

plasma concentrations were derived and why the graph showing the relationship between plasma concentration and turnover rate did not go through the origin. Dr. Kathy Musa-Veloso, an expert on endogenous production and metabolism of acetone and use of ketogenic diets to treat epileptic children who attended the meeting at the request of the sponsors, replied that the derivation was based on equations used by Reichard et al. (1979) and that the graph shown in the presentation slide was taken from that publication. First order kinetics was assumed for acetone production and elimination. Details of the derivation are provided in Appendix H of the submission. The graph does not go through the origin because if the regression line is extrapolated to make the plasma concentration zero, the corresponding acetone turnover rate is approximately 23 micromol/m^2/min. This situation can theoretically occur if acetone production and utilization are equal. She emphasized that a high degree of uncertainty exists in this area of the graph because it falls outside the range of generated data used to fit the relationship of acetone turnover rate and plasma concentration. Dr. Musa-Veloso further explained that the Reichard et al. (1979) data were originally derived from adults. The slope of the line describing the relationship was later used to estimate the acetone turnover rate in children, using the plasma acetone values determined by Peden (1964). This methodology is considered highly conservative for two reasons. First, because it assumes the relationship between plasma acetone and acetone turnover in children is similar to the relationship in adults, while, in reality, children have a higher capacity than adults to produce and utilize ketone bodies. Second, because the adults studied by Reichard et al. (1979) were obese, and obese adults do not become ketotic as easily as their non-obese counterparts.

Panel Discussion of the Exposure Assessment

The panel discussion on 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.

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

Sufficiency of Data to Characterize Exposures

Several panel members commended the sponsors on the large amount of data compiled for the exposure assessment. They noted that presenting data on consumer products is difficult, but thought the assessment did a good job identifying the wide variety of acetone-containing product

types and uses, and determining the acetone content of the product formulations. Discussing the extent to which worst-case scenarios were presented, some panelists thought that product usage should be assumed to occur in rooms without any ventilation, especially since the sponsor had calculated that a complete lack of room ventilation could increase exposures three-fold (i.e., the spray-paint example discussed above). Some panelists thought the exposure assessment should assume young children were present in the room where the products were being used, rather than being elsewhere in the house.

Some panelists suggested studies on product-use exposures be conducted to obtain actual data, rather than relying on models to predict these exposures. They said actual measurements of acetone exposure during use would be an improvement over model exposures created through multiple assumptions, each potentially open to question. Other panelists responded that conducting such studies might not be necessary because many consumer product companies already have usage data on their products. They noted that the submission (in Section 8.2.2, pages 70-75) included acetone sources, routes, target populations, and high-end uses. They believed the information provided was sufficient for a screening exposure assessment.

A panelist provided the panel with an excerpt taken from the *American Journal of Emergency Medicine* (Watson et al., 2003) showing numbers of acetone poisonings categorized by product types, ages of subjects, and medical outcomes. She said thousands of exposures occur each year from accidents or misuse of products containing acetone and thought these events should be acknowledged in the exposure assessment. Other panel members did not think worst-case scenarios for VCCEP exposure assessments needed to include accidents or intentional misuse situations. They also did not think scenarios of same-day, maximum exposures to multiple products needed to be included, even though some members identified situations in which such events might occur (e.g., beautician exposure to multiple finger nail products).

Time Periods Relevant to Childhood Exposures

Some panel members, citing the lack of exposure data *in utero* or during pregnancy, did not think the available data were adequate to conclude that exposure to all target populations had been characterized. They did not propose conducting additional studies, but rather suggested the huge amount of exposure data already compiled might be used together with the PBPK model and the toxicity data to estimate exposures in those situations where data are lacking. For example, attempts could be made to relate product use by parents to effects on fetal body weights and to determine if target organs for toxicity in adults are relevant for infants. Two members, noting that single doses of teratogens might produce adverse effects, said they would favor using maximum acute or one-day doses from the exposure assessment to estimate the potential exposure values for prenatal toxicity endpoints.

One panel member had done calculations to compare the acetone dose from a high exposure, product-use scenario to the acetone dose required to reach the most sensitive toxicity threshold in an animal reproduction study. For additional conservatism, he had assumed the dose was administered to the animals during the time of maximum fetal vulnerability. The exposure scenario used was a pregnant woman spray painting in a small room with no ventilation (assumed exposure of 15 mg/kg-day). The toxicity threshold he used was 400 mg/kg-day, based

on the lower benchmark dose ($BMDL_{05}$) for the F_1 and F_2 generations from the two-generation developmental toxicity study of Shipp et al. (1996). The panel member said this comparison, which was intended to estimate a worst-case situation, did not indicate cause for concern. Other panelists responded that if the exposure value of 15 mg/kg-day were compared to the acetone RfD value of 8.7 mg/kg-day used by the sponsor, instead of to the bench mark dose, it would *not* support the lack of safety concern; however, they went on to emphasize that this RfD was of questionable relevance for human risk assessment because it was lower than human endogenous acetone levels. They suggested it would be more meaningful to compare the 15 mg/kg-day exposures to the average endogenous production value in human adults, which is 41 mg/kg-day. They thought this comparison would support the conclusion that exposures to exogenous acetone were unlikely to be of concern, even in reasonably foreseeable worst-case conditions.

Two panelists remained unconvinced that acetone exposures to children had been adequately characterized, saying the sponsors should have used more conservative exposure assumptions. In their opinion, the consumer product-use exposure assessments sometimes avoided realistic worst-case exposure scenarios by assuming (1) single users, often with only limited surface areas exposed, (2) children being out of the room during product use, (3) vaporization occurring only during the usage period, instead of continuing from disposed cotton balls, acetone dumped into open waste baskets, etc. In spite of these reservations, neither panel member concluded that the lack of complete characterization necessarily indicated the existence of data needs. They thought construction of adequate, realistic exposure scenarios could be accomplished largely with existing information.

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.

Risk Characterization and Data Needs

Sponsor Presentation

Dr. John Waechter, Jr. and Mr. Paul Price summarized the risk characterization and data needs (see Appendix D for the presentation slides). They reviewed the short-term, one-day, and chronic exposure concentration data and made the following comparisons: the short-term exposures were compared to the one-hour and eight-hour draft Acute Exposure Guideline Levels (AEGL-1); the one-day exposures were compared to estimates of age-specific endogenous acetone production; and the chronic exposures were compared to the RfD and RfC that were based on the Gentry et al.(2003) PBPK model and the Mast et al. (1988) study. The sponsors concluded that the RfD and RfC represent safe doses for population lifetime exposures, including the prenatal (in utero) and postnatal subgroups.

In characterizing the risk, the sponsors presented the Hazard Indices (HI; defined by the sponsor as Average Daily Dose divided by RfD) for infants and for other age groups under a variety of exposure conditions. If breast milk ingestion was not considered, the aggregate exposures to upper bound exogenous doses for all age groups were one to two orders of magnitude below endogenous production levels. Infants had higher potential exposure to acetone than other age groups because of breast milk ingestion. If nursing mothers were occupationally exposed to

acetone for 40 hr/wk at the Threshold Limit Value (ACGIH, 2001), the HI approached a value of 1 using the RfD of 8.7 mg/kg-day; the HI exceeded 1 using the EPA RfD of 0.9 mg/kg-day. The sponsors emphasized that using either of these RfDs to determine an HI value introduced a high degree of conservatism into the risk assessment.

The sponsors concluded that neither the hazard nor the exposure assessments suggest any increased or unique susceptibility of children to acetone, and quantitative risk characterization indicates children's exposure to acetone from ambient background and consumer product sources is unlikely to present health risks. While acknowledging that uncertainties exist in both the hazard and exposure assessments, the sponsors do not believe these uncertainties affect their risk characterization conclusions.

Regarding data needs, the sponsors concluded no further studies are warranted for the VCCEP hazard or exposure assessments.

Clarifying Questions and Comments from the Panel

One panel member asked for additional information on the AEGL-1 guidelines, wondering if they were qualitative values. The sponsor responded that the data used for these guidelines were qualitative and were based on questionnaires. The AEGL-1 guidelines are intended for emergency response, and they provide useful information on potential adverse effects during acute exposures, such as whether children's eyes are likely to become irritated. Other panelists did not think the information from the AEGL-1 Guidelines was especially important for the purposes of the VCCEP risk characterization, but they did not object to the sponsors using these guidelines for comparisons.

Panel Discussion of the Risk Characterization

The panel discussion on the risk characterization addressed 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 thought some of the animal study results indicated children might be more sensitive than adults to acetone-induced adverse effects. He noted that acetone's critical effect was on fetal body weight (Mast et al. 1988) and that the two-generation study with IPA (Shipp et al. 1996) showed decreased postnatal survival. He said the risk assessment did not adequately acknowledge the implications of these findings for the relative sensitivity of children. Another member disagreed, saying these studies supported acetone's safety for children because reproduction toxicity did not occur until very high doses were administered. The sponsor noted that the Mast et al. (1988) publication included studies in both rats and mice. The rat study showed reductions in maternal body weight gain, as well as reduced fetal weight; therefore, it did not indicate that fetuses were more sensitive than adults. In the mouse study, adverse effects were seen in dams at dose levels below those showing effects in fetuses. Regarding the decreased postnatal survival noted in the Shipp two-generation IPA study, the sponsor explained that the postnatal lethality resulted from inability of the fetuses and neonates to metabolize IPA

to acetone associated with their low alcohol dehydrogenase activity levels. Therefore, the neonatal toxicity noted in that study is specific to IPA and not relevant for acetone. Another panelist did not think the IPA study provided enough data for anyone to conclude whether children were more at risk than adults.

A panelist wondered whether there might be a reason to compare the short-term exposure levels to endogenous acetone production, rather than to the AEGL-1 values, as the sponsor had done. The sponsor replied that, if the body is viewed as a single compartment, acetone is constantly being metabolized and replaced via endogenous production. If short-term exposure levels were compared to endogenous levels over comparably short time frames, as the panelist suggested, the results would not be much different than making the comparison over a longer time frame, as was done in the sponsors' risk assessment.

Panel Discussion of Data Needs

The panel discussion of Data Needs addressed two 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.

Many panelists were complimentary of the submission, noting the large amounts of data compiled for the hazard and exposure assessments and the helpfulness of the PBPK model. Some members mentioned that the large differences between exposure levels and toxicity thresholds gave them assurance that no meaningful concerns existed, even though they thought more conservative assumptions might have been used in some consumer product usage scenarios.

Other members thought the submission could be improved in some areas. They said some of the issues identified were not resolved, and the steps leading to their resolution were not readily apparent. These included (1) the degree of conservatism needed when modeling worst-case exposure scenarios from consumer product use; (2) the necessity of obtaining actual product-use data to confirm the exposure levels predicted from modeling; (3) the proper use of results from a PBPK model that does not include endogenous production; and (4) the relevance of RfD and RfC values that are below normal endogenous production levels.

One member said that, despite the large amount of data presented in the submission, she would have difficulty definitively stating the risks that acetone may present to children. She thought her difficulty arose because the submission did not present the data in a manner that related directly to childhood risk. Another panelist added that she saw gaps in understanding, especially in the exposure assessment. As a result, she did not feel completely comfortable concluding that all the risks to children had been adequately characterized. A third member expressed concern that endogenous production of acetone was not understood in many commonly occurring health and disease-state situations. She said acetone may be beneficial in controlling some forms of

recalcitrant epilepsy, but the chemical also may participate in the long-term toxicity of other conditions, such as diabetes. She emphasized that the impact of adding an exogenous acetone bolus to existing endogenous levels is not sufficiently understood. Relatively small exogenous doses may adversely affect important body control mechanisms, such as enzyme induction and blood buffering. She further suggested that the submission could be clarified by providing an initial discussion of acetone's role as an active endogenous substance. She said acetone's role in this capacity is well known in the metabolic physiology community, as was described earlier in the VCCEP meeting by Dr. Musa-Veloso. Acetone's endogenous role sets it apart from most other chemical xenobiotic exposures, and the existing exposure and toxicity studies with acetone must be evaluated against this background. Several panelists noted, however, that resolving these issues (e.g., relating the PBPK model to endogenous production) was not necessarily the responsibility of the sponsors. Many panel members thought that some parts of the submission would benefit by increased explanation or additional data compilation.

The Panel Chair asked each of the 11 panel members, in turn, to state individually whether they had identified any data needs for the hazard or exposure assessments. (For the purposes of VCCEP, *data needs* are defined as data gaps for which additional information is required before the potential risk to children can be adequately characterized.) Despite the concerns some panelists had expressed about aspects of the submission, none of the panel members identified any data needs for the acetone assessment.

In summary, many panel members stated that the dataset compiled and presented on acetone was comprehensive, and the major areas were sufficiently addressed. Some panelists voiced concerns about a lack of clarity in the way data and analyses were presented in some sections of the submission. They thought the manner of data presentation made it difficult to use the information to characterize children's risk. Others did not think the assumptions used in certain exposure assessments were truly worst-case. Overall, however, the majority of the panel did not find any major deficiencies in the acetone submission. No data needs were identified.

References

American Conference of Governmental Industrial Hygienists (ACGIH). 2001. Documentation of the TLV for Acetone. ACGIH. Cincinnati, Ohio.

Bevin, C., T.R. Tyler, T.H. Gardiner, R.W. Kapp, Jr., L. Andrews and B.K. Beyer. 1995. Two-generation reproductive toxicity study with isopropanol in rats. J. Appl. Toxicol. 15(2):117-123.

Burleigh-Flayer, H, R. Garman, D. Neptun, C. Vevan, T. Gardiner, K. Kapp, T. Tyler and G. Wright. 1997. Isopropanol vapor inhalation oncogenicity study in Fischer 344 rats and CD-1 mice. Fund. Appl. Toxicol. 36(2):95-111.

Clewell, H.J. III, P.R. Gentry, J.M. Gearhart, T.R. Covington, M.L. Banton and M.E. Andersen. 2001. Development of a physiologically based pharmacokinetic model of isopropanol and its metabolite acetone. Toxicol. Sci. 63:160-172.

Dietz, D.D., J.R. Leininger, E.J. Rauckman, M.B. Thompson, R.E. Chapin, R.L. Morrissey and S. Levine. 1991. Toxicity studies of acetone administered in the drinking water of rodents. Fund. Appl. Toxicol. 17:347-360.

Gentry, P.R., T.R. Covington, M.E. Andersen and H.J. Clewell III. 2002. Application of a physiologically-based pharmacokinetic model for isopropanol in the derivation of an RfD/RfC. Regul. Toxicol. Pharmacol. 36(1):51-68.

Gentry, P.R., T.R. Covington, M.E. Andersen and H.J. Clewell III. 2003. Application of a physiologically-based pharmacokinetic model for reference dose and reference concentration estimation for acetone. J Toxicol. Environ. Health. 66(23):2209-2225.

Mast, T .J., J.J. Evanhoff, R.L. Rommeim, K.H. Stoney, R.J. Weigel and R.B. Westerberg. 1988. Inhalation developmental toxicology studies: Teratology study of acetone in mice and rats. Final Report. Prepared for the National Institute of Environmental Health Sciences, National Toxicology Program. Pacific Northwest Laboratory, Battelle Memorial Institute. Contract DE-AC-06-76RLO 1030.

Morgott, DA. 2001. Acetone. In: Patty's Toxicology. 5th ed., vol. 6. E. Bingham, B. Cohrssen, and C. H. Powell, Ed. John Wiley and Sons. New York, New York.

National Toxicology Program (NTP). 1991. Toxicity Studies of Acetone (CAS No. 67-64-1) in F344/N Rats and B6C3F1 Mice (Drinking Water Studies). NIH Publication No. 91-3122, NTP TOX3. Research Triangle Park, NC.

Peden, VH. 1964. Determination of individual serum "ketone bodies" with normal values in infants and children. J. Lab. Clin. Med. 63:332-343.

Reichard, G.A., Jr., A.C. Hoff, C.L. Skutches, P. Paul, C.P. Holroyde and O.E. Owen. 1979. Plasma Acetone Metabolism in the Fasting Human. J. Clin. Invest. 63:619-626.

Reichard, G.A., Jr., A.C. Hoff, C.L. Skutches, P. Paul, C.P. Holroyde and O.E. Owen. 1979. Plasma Acetone Metabolism in the Fasting Human. J. Clin. Invest. 63:619-626.

Shipp, A.M., B.C. Allen, C. Van Landingham, P.R. Gentry and K.S. Crump. 1997. Quantitative dose-response analysis - Application of the benchmark method to the multigeneration rat reproduction study for isopropanol. Report prepared for the Chemical Manufacturers Association Isopropanol Panel.

U.S. Environmental Protection Agency (U.S. EPA). 2003. Integrated Risk Information System (IRIS). Acetone Summary File. National Center for Environmental Assessment, Washington, DC. Available online: http://www.epa.gov/iris/subst/0128.htm.

Watson, W.A., T.L. Litovitz, G.C. Rogers, W. Kleinschwartz, J. Youniss, S.R. Rose, D. Borys and M.E May. 2003. 2002 Annual report of the American association of poison control centers toxic exposure surveillance system. Am. J. Emerg. Med. 21(5):394, 397.

APPENDIX A

LIST OF ATTENDEES

Voluntary Children's Chemical Evaluation Program (VCCEP)
Peer Consultation on Acetone

November 18-19, 2003

List of Attendees

Dr. Rudolph Breglia
Sunoco, Inc.
PO Box 1135
R&D Riverside D337
Linwood, PA 19061-7135
610-859-1174
rjbreglia@sunocoinc.com

Dr. Dan Briggs
Toxicology Excellence for Risk Assessment
1757 Chase Ave.
Cincinnati, OH 45223
513-542-7475
briggs@tera.org

Mr. Fred Burns
Shell Chemicals
910 Louisiana
Houston, TX 77478
713-241-5717
fred.burns@shell.com

Ms. Patsy Clegg
Shell Chemical Company
PO Box 4320
Houston, TX 77210
713-241-2521
pmclegg@shell.com

Dr. Richard Costlow
Rohm and Haas Company
727 Norristown Road
PO Box 0904
Springhouse, PA 19477-0904
216-641-7331
rcostlow@rohmhaas.com

Dr. Ralph Gingell
Shell Chemical LP
PO Box 4320
Houston, TX 77210
713-241-0244
ralph.gingell@shell.com

Mr. Bill Gulledge
American Chemistry Council
1300 Wilson Blvd.
Arlington, VA 22209
703-741-5613
william_gulledge@americanchemistry.com

Mr. David Krieg
Dow Chemical Company
2301 N. Brazosport Blvd
Bldg. B1603
Freeport, TX 77566
979-238-9424
dkrieg@dow.com

Ms. Sarah McLallen
American Chemistry Council
1300 Wilson Blvd
Arlington, VA 22209
703-741-5607
sarah_mclallen@americanchemistry.com

Dr. Kathy Musa-Veloso
CanTox Health Sciences International
2233 Argentia Rd., Suite 308
Toronto, Ontario L5N2X7
905-542-2900
kmusa-veloso@cantox.com

Ms. Patricia Nance
Toxicology Excellence for Risk Assessment
1757 Chase Ave.
Cincinnati, OH 45223
513-542-7475
nance@tera.org

Ms. Julie Panko
AMEC Earth and Environmental
707 Grant Street
Suite 3000
Pittsburgh, PA 15219
412-258-3612
julie.panko@amec.com

Voluntary Children's Chemical Evaluation Program (VCCEP)
Peer Consultation on Acetone

November 18-19, 2003

List of Attendees

Ms. Ann Parker
Toxicology Excellence for Risk Assessment
1757 Chase Ave.
Cincinnati, OH 45223
513-542-7475
parker@tera.org

Ms. Jacqueline Patterson
Toxicology Excellence for Risk Assessment
1757 Chase Ave.
Cincinnati, OH 45223
513-521-7426
patterson@tera.org

Dr. Kenneth Pavkov
ExxonMobil Biomedical Sciences
1545 Route 22 East
PO Box 971, Room LC 370
Annandale, NJ 08801-971
908-730-1067
kenneth.l.pavkov@exxonmobil.com

Mr. Paul Price
AMEC Earth and Environmental
129 Oakhurst Rd.
Cape Elizabeth, ME 04107
207-799-3406
psprice@pipeline.com

Ms. Bebe Raupe
Bureau of National Affairs, Inc.
PO Box 498769
Cincinnati, OH 45249
513-677-2870
braupe@bna.com

Mr. William Rawson
Latham & Watkins
555 Eleventh Street, NW
Suite 1200
Washington, DC 20004
202-637-2230
william.rawson@lw.com

Ms. Lee Salamone
American Chemistry Council
1300 Wilson Blvd.
Arlington, VA 22209
703-741-5212
lee_salamone@americanchemistry.com

Dr. Chad Sandusky
Physicians Committee for Responsible Med.
5100 Wisconsin Ave, NW
Suite 400
Washington, DC 20016
202-686-2210
csandusky@pcrm.org

Dr. Bill Thomas
Celanese Acetate
PO Box 32414
Charlotte, NC 28232-2414
704-554-2670
bill.thomas@celaneseacetate.com

Mr. Kenneth Unice
AMEC Earth and Environmental
707 Grant Street
Suite 3000
Pittsburgh, PA 15219
412-258-3614
kenny.unice@amec.com

Dr. John Waechter, Jr.
Dow Chemical Company
Bldg. 1803
Midland, MI 48674
989-636-1859
jwaechter@dow.com

Ms. Rosemary Zaleski
ExxonMobil Biomedical Sciences, Inc.
1545 Route 22 East
PO Box 971
Annandale, NJ 08801
908-730-1009
rosemary.t.zaleski@exxonmobil.com

APPENDIX B

Peer Consultations on Acetone

Meeting Materials

November 18-19, 2003

Kingsgate Conference Center, Salon A
University of Cincinnati
Cincinnati, Ohio

Table of Contents

Overview of the Peer Consultation Process

Introduction

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 consultation meetings for private and public sponsors since 1996 (see http://www.tera.org/peer for information about the program and reports from meetings). As a part of this program, *TERA* is organizing peer consultation panel meetings for assessments developed under the Voluntary Children's Chemical Evaluation Program (VCCEP). This panel meeting will review assessment on Acetone, which was submitted by the American Chemistry Council (ACC) Acetone Panel.

The VCCEP program is a voluntary pilot program and part of the Environmental Protection Agency's (EPA) Chemical Right-to-Know Initiative. The goal of EPA's VCCEP program is to enable the public to better understand the potential health risk to children associated with certain chemical exposures. EPA has asked companies which manufacture and/or import 23 chemicals (that have been found in human tissues and the environment in various monitoring programs) to volunteer to sponsor their evaluation in Tier 1 of a pilot of the VCCEP. Sponsorship requires the companies to collect or develop health effects and exposure information on their chemical(s) and then to integrate that information in a risk assessment and a "data needs" assessment. More information about the VCCEP is available in the December 26, 2000 Federal Register (65 FR 81700) (http://www.epa.gov/oppt/chemrtk/ts00274d.htm) and on EPA's VCCEP web site (http://www.epa.gov/chemrtk/vccep/index.htm).

The purpose of this meeting is to provide a science-based peer consultation on the data needs for acetone. The assessment developed by the sponsor is being considered by a panel of scientific experts using a peer consultation process developed by *TERA*. These experts have experience in toxicity testing, exposure evaluation, risk assessment, and children's health. *TERA* has selected Peer Consultation Panel members after careful consideration of nominations from the public, and is responsible for convening and chairing panel meetings to discuss the sponsors' submissions. *TERA* will prepare a report for the meeting and make this available to the public at http://www.tera.org/peer/VCCEP/ACETONE/ACETONEwelcome.html. The peer consultation meeting is open to the public.

Background on the Voluntary Children's Chemical Evaluation Program (VCCEP)

The ACC Acetone Panel has volunteered to sponsor a Tier 1 assessment for acetone, including hazard, exposure, risk characterization, and data needs assessments, utilizing available data. The key question of the program and the peer consultation is whether the potential hazards, exposures, and risks to children have been adequately characterized and if not, what additional data are necessary.

The program was set up to use a tiered testing approach, which is explained in the December 26, 2000 Federal Register notice. For toxicity data, specific types of studies have been put into three tiers. For exposure data, the depth of exposure information increases with each tier, with Tier 1 a screening level assessment and Tiers 2 and 3 more advanced assessments using exposure studies, monitoring data, and modeling. The Federal Register notes that the Tier 1 assessment should use all available data, and therefore some of the chemical assessment documents will include more than what is in the Tier 1 level.

The peer consultation is designed to be a forum for scientists and experts to exchange scientific views on the need for additional toxicity and exposure data and analysis. In selecting the panel, *TERA* has sought to involve stakeholders by considering their nominations for panel members, and has sought to have a range of perspectives on the panel. This is not a consensus based approach; rather the individual panel members will discuss their own views. In the meeting report, opinions of the individual panel members will be noted, along with areas of agreement and disagreement.

The VCCEP program is a voluntary program. The sponsor has volunteered to prepare the Tier 1 assessment. If data needs are identified through this process, the sponsor will choose whether or not to volunteer for Tier 2.

Acetone Peer Consultation Panel

The VCCEP Peer Consultation Panel for acetone consists of eleven members: seven of the nine VCCEP Core Panel Members for Year 1 and four additional *ad hoc* members specifically selected for this meeting. The Panel includes scientific experts in toxicity testing, risk assessment, exposure assessment, medicine, PBPK modeling, and children's health. Collectively, this panel has many publications and presentations on topics related to children's health risk.

A core group of panel members participates in all panel meetings to ensure consistency among the reviews. *TERA* received 50 nominations for core panel members in early 2002 from VCCEP stakeholders and other interested parties. After a thorough review of these nominees, as well as others independently identified, *TERA* selected a group of nine scientists in June 2002.

Additional *ad hoc* experts are invited by *TERA* to participate in panel meetings on a case-by-case basis to provide additional expertise relevant to a specific chemical or issue. Nominations were solicited from interested parties for *ad hoc* panelists for the acetone panel, with the nomination period closing in September 2003. *TERA* independently selected four additional *ad hoc* scientists for the panel. *Ad hoc* panelists have the same status and responsibilities as the core group panelists.

Each panel member has disclosed information regarding potential conflicts of interest and biases related to the VCCEP program, the sponsor, and acetone. *TERA* evaluated these disclosures when selecting panel members. Short biographical sketches and disclosure statements for panel members are provided below.

Conduct of the Peer Consultation

TERA developed a "charge" document that identifies the scientific issues to be discussed by the panel. The panel received a copy of the submission, the charge, and key references approximately a month prior to the meeting, to ensure adequate time to carefully review the document and be prepared for the discussions.

The meeting will be organized to make the best use of the time available to hear the opinions of the experts on the charge questions and the data needs. The meeting will begin with panel introductions and discussion of conflict of interest and bias issues. The discussion will then address the four assessment sections of the sponsor's submission (hazard, exposure, risk characterization, and data needs). To start each discussion section, the authors of the assessment document will make a short presentation. These presentations will highlight the salient points and issues, and give the panel the opportunity to ask clarifying questions of the authors.

Public Observation and Comments

Members of the public are invited to attend the VCCEP peer consultation meetings and observe the Panel discussions. To ensure that adequate space is available, we ask people to register in advance for the meeting. The public was also given the opportunity to prepare brief technical comments on the assessment document and submit these in writing prior to the meeting. *TERA* shared the comments with the panel and sponsors prior to the meeting and copies are available for all attendees at the meeting. Observers will be permitted to make brief technical comments at the meeting as time permits. Panel members and sponsors may ask clarifying questions of those making comments.

Meeting Report

TERA will prepare a meeting report summarizing the sponsor presentations, the opinions and recommendations expressed by the panel, and any oral comments from the public. Written public comments will also be included. The meeting report will not be a transcript. The report will be reviewed by the panel for accuracy. Sponsors and observers presenting oral comments will be offered the opportunity to review the summaries of their presentations. The finalized report will then be made available to the public at http://www.tera.org/peer/VCCEP/ACETONE/ACETONEwelcome.html.

Agenda for the VCCEP Peer Consultation for Acetone
University of Cincinnati, Kingsgate Conference Center, Salon A

Tuesday, November 18, 2003

8:00 **Registration and Check In**

8:30 **Meeting Convenes**[3]
Welcome: Ms. Jacqueline Patterson, *TERA*
Introductions and Disclosures, Panel
Meeting Process: Dr. Michael Dourson, Chair

9:00 **Sponsor Introduction and Presentation on Hazard Assessment**
Presenter: Dr. John Waechter, Jr., Dow Chemical Company

Public Comments on Hazard Assessment

Panel Discussion

12:30 **Lunch**

1:30 **Sponsor Presentation on Exposure Assessment**
Presenter: Mr. Paul Price, AMEC Earth and Environmental

Public Comments on Exposure Assessment

Panel Discussion on Exposure Assessment

5:00 **Adjourn**

Wednesday, November 19, 2003

8:00 **Registration**

8:30 **Meeting Re-convenes**
Sponsor Presentation on Risk Characterization and Data Needs
Presenter: Dr. John Waechter, Jr., Dow Chemical Company, and
Mr. Paul Price, AMEC Earth and Environmental

Public Comments on Risk Characterization and Data Needs

Panel Discussion on Risk Characterization and Data Needs

12:00 **Closing Remarks and Evaluation of Meeting**

12:15 **Adjourn**

[3] The Chair will call a 15-minute break each morning and afternoon.

VCCEP Peer Consultation Acetone Panel Charge

Introduction

The primary objective of the Peer Consultation Panel is to discuss whether the potential hazards, exposures, and risks for children have been adequately characterized for each of the VCCEP chemicals, based on the information contained in assessment documents submitted by the chemical's sponsor and other pertinent information brought to the meeting by panel members, sponsors, and observers. If risk cannot be adequately characterized, then data needs should be identified. The panel's job is not to critique the assessment document *per se;* rather, the panelists use the document and its references as a source of information (along with personal knowledge, expertise, and observer comments) to answer the questions regarding data needs. The panel is not required to reach a consensus position on any issue or conclusion. Panelists who believe a chemical has not been adequately characterized will be asked to identify what additional information is needed and why it is necessary. All the panelists will be encouraged to discuss and debate each other's suggestions and comments, providing scientific rationales for their points of view. *TERA* will compile the panel discussions in a meeting report that will be sent to the sponsor and made available to the public.

To help the panel discuss the sponsor's submission and address whether a chemical has been adequately characterized, *TERA* has prepared this charge, which identifies a number of discussion topics. The topics are consistent with the directions for VCCEP submissions given in the December 26, 2000, Federal Register: http://www.epa.gov/oppt/chemrtk/ts00274d.htm. These topics will form the basis for the panel discussions.

Panelists should keep in mind the following directives from the Federal Register regarding any recommendations for additional testing: (1) If specific toxicity studies are indicated, they should be chosen from the next tier of studies within the overall framework and should allow flexibility, if possible, to pursue either additional toxicity testing and/or exposure evaluation, allowing sponsors to select the option which will most quickly, directly, and cost-effectively reduce uncertainty and allow the creation of a risk assessment; (2) EPA is committed to avoiding duplicative testing, and to reducing, refining, and replacing animal testing when valid alternatives exist; (3) if relevant alternative test methods become validated, EPA will consider their immediate implementation in the program; (4) EPA encourages sponsors to combine tests where possible to conserve resources and reduce the number of animals required for testing; and (5) the Tier 2 and Tier 3 testing will be limited to chemicals for which there is a clear need.

Please note that we anticipate revising these discussion topics based upon experience gained at the VCCEP peer consultation meetings.

Questions Regarding the Hazard Assessment

1. 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.

2. Discuss whether it is appropriate to use data on isopropanol to assess risk from exposure to acetone.

3. Discuss whether the PBPK model was appropriately developed and validated; the limitations to the model; whether there are any relevant conditions for which it should not be applied; and whether the correct dose metric was chosen.

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

Questions Regarding the Exposure Assessment

5. Discuss whether the fate of this chemical is adequately understood.

6. 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.).

7. 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.

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

Questions Regarding the Risk Characterization

9. 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.

Questions Regarding the Data Needs Assessment

10. 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.

11. Identify any additional exposure data and analyses that are needed and discuss why this information is necessary.

Panel Biographical Sketches and Conflict of Interest and Bias Information

An essential part of Peer Consultation Panel selection is the identification and disclosure of conflicts of interest and biases. Prior to selecting the core and *ad hoc* panelists, each panel member is asked to complete a questionnaire to determine whether their activities, financial holdings, or affiliations could pose a real or perceived conflict of interest or bias. (See http://www.tera.org/peer/VCCEP/VCCEPCOI.html for *TERA's* policy and questionnaire for the Peer Consultation Program related to VCCEP). Questionnaires are reviewed by *TERA* staff and discussed further with panel candidates as needed.

For the Peer Consultation Program related to VCCEP, a conflict of interest (COI) for a candidate would include:

- Working for an organization sponsoring the chemical to be reviewed at the panel meeting,
- Having direct personal financial investments in the sponsoring organization or in the chemical itself, or
- Authoring the sponsoring organization's assessment documents submitted to the VCCEP panel.

Bias for a peer consultation panel candidate would be predisposition towards the subject matter to be discussed at the panel meeting that could influence the candidate's viewpoint. Examples of potential bias would be situations in which a candidate:

- Has previously taken a public position on subjects to be discussed by the panel, or
- Is affiliated with an industry, governmental, public interest, or other group with a partiality regarding subjects to be discussed by the panel.

Most scientists with technical expertise in areas relevant to these peer consultation panels will have existing opinions about the subject matter. Therefore they may be considered to have some degree of bias.

The purpose of these peer consultation panels is to gather expert scientific opinion from a range of experts, including those who may be affiliated with organizations or companies with an interest in the outcome. All panelists were selected by *TERA* based upon their expertise and qualifications. They are employed by many types of organizations. *TERA* strives to create a balance of expertise and affiliations for each peer consultation meeting; however, individual panel members represent their own expertise and views, not those of their employer, of any group who may have nominated them, or any group with whom they may be associated. This peer consultation panel is a distinguished group with many years experience in a wide range of disciplines.

Toxicology Excellence for Risk Assessment (*TERA*) is conducting this VCCEP peer consultation under its Peer Consultation Program. This program is principally funded by a Cooperative Agreement with the U.S. EPA, the purpose of which is to design, develop, and manage a Peer Consultation process that will serve as a public scientific forum. *TERA's* role in managing the peer consultation is undertaken primarily at the request of and for the benefit of non-federal stakeholders, particularly the sponsors of VCCEP chemicals.

TERA has performed work for organizations associated with VCCEP, both in the past and at the present time. These include the U.S. EPA, the American Chemistry Council, and some companies that are sponsors of VCCEP chemicals. In the past, *TERA* has conducted assessments and analysis for a number of chemicals included in the VCCEP pilot program (i.e., acetone, decabromodiphenyl ether, methyl ethyl ketone, and toluene) and is currently doing work on trichloroethylene. This work has been done for a variety of public and private sponsors, but none of it is directly related to the VCCEP assessments.

A brief biographical sketch of each panel member is provided below, together with a disclosure statement describing any potential conflict of interest or bias issues. The disclosure statements do not address funding provided by organizations unrelated to VCCEP or these chemicals and sponsor. For the core panelists, the disclosure statements cover the chemicals and sponsors in the entire VCCEP pilot program. For the *ad hoc* panelists, the disclosures are specific to acetone and the acetone sponsor.

Ms. Nicole Cardello

Ms. Nicole Cardello until recently was a staff scientist with the Physicians Committee for Responsible Medicine (PCRM), a non-profit organization that promotes nonanimal experimental methods in medical and scientific research. As a scientist with PCRM, she reviewed every test plan submitted under EPA's High Production Volume (HPV) chemical-testing program. She has submitted technical reports describing the toxicity data and available exposure information for HPV chemicals. She also wrote articles for the quarterly journal, *Good Medicine*.

Ms. Cardello previously worked as an environmental scientist for the U.S. EPA's National Exposure Research Laboratory, where she evaluated the design, performance, and collection efficiency of a personal electrostatic precipitator for aerosol exposure studies, and as a research scientist at the Johns Hopkins School of Hygiene and Public Health, where she evaluated the collection efficiency of a bioaerosol sampler, developed a dermal exposure database for pesticides of public health concern, and investigated the physical properties of the skin that facilitate absorption.

Ms. Cardello received her M.H.S. in Environmental Health Science from Johns Hopkins School of Hygiene and Public Health where her work focused on environmental and occupational monitoring and the role of exposure information in risk assessments and epidemiological studies. She received her B.S. in Environmental Science and Engineering from the University of North Carolina at Chapel Hill , where she researched the human health effects of waterborne pathogens and constructed dose-response models of *Cryptosporidium parvum* and GI effects.

Ms. Cardello has served as part of an expert panel for the U.S. EPA's Workshop on Characterizing and Presenting Chemical Exposure Assessment Results, and participated in the EPA/ACC Technical Workshop for Exposure Assessment under the Voluntary Children's Chemical Evaluation Program (VCCEP). She is a member of the International Society of Exposure Analysis.

DISCLOSURE:

Ms. Cardello is a VCCEP Core Panel member. She is currently pursuing post-graduate studies at Johns Hopkins University. Previously, she worked at the U.S. EPA National Exposure Research Laboratory and, more recently, as a staff scientist at the Physicians Committee for Responsible Medicine. She currently is working (part-time) on a pesticide risk assessment project under a contract EPA has with Johns Hopkins. Both EPA and the PCRM have taken public positions on the VCCEP pilot chemicals, the tiered test methods, and on the VCCEP program itself.

Dr. George Daston

Dr. George Daston is a Research Fellow for the Procter & Gamble Company (P&G) where he has worked since 1985. He has worked the past 21 years in the field of developmental toxicology and risk assessment, particularly in the area of children's risk assessment. Dr. Daston is also an adjunct professor in the Department of Pediatrics and Developmental Biology Program at the University of Cincinnati and Children's Hospital Research Foundation, and lectures in courses on teratology, developmental biology, toxicology, and risk assessment.

Dr. Daston received his Ph.D. in Developmental Biology and Teratology and a B.S. in Biology from the University of Miami. Prior to joining the Procter & Gamble Company, Dr. Daston worked for the U.S. EPA's Health Effects Research Laboratory as a National Research Council Research Associate and as an assistant professor for the Department of Biological Sciences at the University of Wisconsin.

His research interests include teratogenic mechanisms, *in vitro* methodologies, and risk assessment. His most recent research includes toxicant-nutrient (especially zinc) and maternal-embryonal interactions in developmental toxicity, the role of pattern formation genes in abnormal development, genomic approaches to endocrine disrupter screening, and improvements in risk assessment methodology for non-cancer endpoints.

Dr. Daston's activities in professional societies include serving as Chair of the Reproductive and Developmental Effects Subcommittee of the American Industrial Health Council, Chair of the Developmental and Reproductive Toxicology Technical Committee of ILSI-Health Effects Sciences Institute; President of the Society of Toxicology's Reproductive and Developmental Toxicology Specialty Section, President of the Teratology Society, member of the National Academy of Sciences Board on Environmental Studies and Toxicology, and member of EPA's Endocrine Disrupter Screening and Testing Advisory Committee (EDSTAC).

Dr. Daston has recently served on the organizing committees for an ILSI/EPA/AIHC workshops on benchmark dose methodology and human variability in toxic response; an EPA workshop on endocrine-mediated toxicity; and as co-chair of an AIHC/EPA workshop on Leydig cell tumors, an ILSI/EPA workshop on interpreting reproductive toxicity endpoints, and a NIEHS workshop on the state of validation of the FETAX assay for teratogen screening.

Dr. Daston is an Associate Editor of *Toxicological Sciences*, Editor-in-Chief of *Birth Defects Research Part B: Developmental and Reproductive Toxicology*, on the Editorial Board of *Human and Ecological Risk Assessment* and *Reproductive Toxicology,* and an ad hoc reviewer for *Teratology*, *Journal of Nutrition* and other journals. He has published over 90 peer-reviewed articles, reviews and book chapters, and has edited three books.

DISCLOSURE:

Dr. Daston is a VCCEP Core Panel member. He is employed by the Procter & Gamble Company (P&G). P&G uses thousands of chemicals, which it purchases individually, or in mixtures. It is possible that some VCCEP pilot chemicals are included in these purchases. P&G purchases chemicals from numerous suppliers, including companies that are sponsors of the VCCEP pilot chemicals. Dr. Daston served as an External Peer Reviewer for the May 2003 Toxicological Review of Acetone used by EPA for the Agency's current IRIS hazard and dose-response assessment.

Dr. Michael L. Dourson

Dr. Michael Dourson directs Toxicology Excellence for Risk Assessment (*TERA*), a nonprofit corporation dedicated to the best use of toxicity data for estimating risk assessment values. *TERA*'s projects include the development of complex risk assessments, such as soluble nickel salts; research into improvements of risk methods, such as differential sensitivity of children and adults to chemical toxicity, organizing peer review and consultation meetings for risk assessment topics and documents; and education and outreach on risk assessment values through lectures and data bases, including the International Toxicity Estimates for Risk (*ITER*).
Before founding *TERA* in 1996, Dr. Dourson held leadership roles in the U.S. Environmental Protection Agency for fifteen years; as chair of EPA's Reference Dose (RfD) Work Group, charter member of the EPA's Risk Assessment Forum and chief of the group that helped create the Integrated Risk Information System (IRIS) in 1986. Dr. Dourson received his Ph.D. in Toxicology from the University of Cincinnati and a B.A. in biology from Wittenberg University. Dr. Dourson's research interests include investigating methods to extrapolate toxicity data garnered on experimental animals or healthy adults to the appropriate sensitive human population. Topic such as adversity of effect, and characterization of risk are also of interest.

Dr. Dourson has served on numerous expert panels, such as EPA's peer review panels for IRIS assessments and its Risk Assessment Forum, *TERA*'s International Toxicity Estimates for Risk (*ITER*) independent peer reviews and consultations, FDA's Science Board Subcommittee on Toxicology, the NSF's Health Advisory Board, and SOT's harmonization of cancer and non-cancer risk assessment. Dr. Dourson has also organized over 16 symposia for 9 different organizations on a variety of topics, including: effective risk communication; chromium; information resources for toxicology and environmental health; risk assessment of essential trace elements; risk characterization; EPA's IRIS; role of toxicology in tomorrow's risk assessment practice; techniques for quantifying uncertainty in risk assessment; statistical and dose response models in risk assessment; workshop on benchmark dose methodology; basics of risk assessment; improvements in quantitative noncancer risk assessment; and neurotoxicity risk assessment.

Dr. Dourson is a Diplomate of the American Board of Toxicology and served on its Board as President, Vice President, and Treasurer. He is currently Secretary for the Society for Risk Analysis. He has also served as president of the Dose-Response Specialty Group of the Society for Risk Analysis, of the Society of Toxicology's Specialty Section on Risk Assessment and of the Ohio Chapter of the Society for Risk Analysis. He is currently on the editorial board of three journals. Dr Dourson has published more than 70 papers on risk assessment methods, has co-authored over 100 government risk assessment documents, and has made over 90 invited presentations.

DISCLOSURE:

Dr. Dourson is a VCCEP Core Panel member. He is Director of the non-profit organization Toxicology Excellence for Risk Assessment (*TERA*). Previously, he was employed by the U.S. EPA. *TERA* has performed work for organizations associated with VCCEP. These include the U.S. EPA, the American Chemistry Council, and some companies that are sponsors of VCCEP chemicals. In the past, *TERA* has conducted assessments and analysis for a number of chemicals included in the VCCEP pilot program (i.e., acetone, decabromodiphenyl ether, methyl ethyl ketone, and toluene) and is currently doing work on trichloroethylene. This work has been done for a variety of public and private sponsors, but none of it is directly related to the VCCEP assessments

Dr. Michael L. Gargas

Dr. Michael L. Gargas, Ph.D., Managing Principal of *The Sapphire Group*™, is a toxicologist with over 26 years of related environmental experience. Dr. Gargas oversees and prepares human health risk assessments, conducts toxic tort support investigations, serves as an expert witness, interacts with regulatory agencies, and addresses critical toxicological issues through applied and basic research on behalf of clients. His clients include private industry, trade associations, law firms, regulatory agencies, and private citizens. Dr. Gargas' area of expertise is in human health risk assessment and biochemical toxicology research with emphasis in the areas of inhalation toxicology, chemical metabolism, physiologically based pharmacokinetic (PBPK) modeling, and chemical dosimetry, with specific application of these approaches to risk assessments. Prior to joining *The Sapphire Group*™, Dr. Gargas served as a Principal Health Scientist with ChemRisk (a risk assessment and toxicology consulting firm), a senior research scientist at the Chemical Industry Institute of Toxicology (CIIT), and as a toxicology research scientist with the U.S. Air Force (as a civilian) and the U.S. Navy (on active duty).

Dr. Gargas completed undergraduate degrees in Medical Laboratory Technology and Biology from George Washington University and Wright State University, respectively and his doctorate in Biomedical Sciences (Toxicology Specialty) is from Wright State University. Dr. Gargas has been honored by the Society of Toxicology with the Frank R. Blood Award, the Department of the Air Force Invention/Patent Award (Co-Inventor) for an *In Vivo* Dermal Absorption System for Rats, Invention No. 15, 859 (U.S. Patent Number: 4,582,055) and the Outstanding Technical Civilian of the Year Award, from the Air Force Aerospace Medical Research Laboratory. Dr. Gargas has held or currently holds memberships in the Society of Toxicology and the Society for Risk Analysis and has served on the editorial board of *Toxicology and Applied Pharmacology*. Dr. Gargas has been invited to present numerous guest lectures on toxicology and risk assessment topics and is an Adjunct Assistant Professor of Toxicology at Wright State University, serving as director for a graduate course in biokinetics and toxicology.

Dr. Gargas has conducted toxicology research on numerous volatile organic compounds (VOCs) including benzene, toluene, styrene, xylenes, furan, ethylene, ethylene oxide, glycol ethers, butadiene, acrylonitrile, the halogenated methanes, ethanes, and ethylenes, as well as the non-volatiles 2,3,7,8-tetrachlorodibenzo-p-dioxin, chromium, and lead. He has been involved in a number of international seminars and conferences as a member of the organizing group and has close contacts with regulators in many parts of the world including the USA, Canada, and Europe. He has also published numerous book chapters and publications on a wide range of health and toxicologic topics.

DISCLOSURE:

Dr. Gargas has been selected as an *ad hoc* member for the VCCEP panel on Acetone. He is a Managing Principal of *The Sapphire Group*™. Dr. Gargas through his employer has consulted to a number of ACC panels, although not the Acetone Panel, and to a number of Acetone Panel sponsor companies, but not on acetone.

Dr. Elaine Cohen Hubal

Dr. Elaine Hubal is a chemical engineer for the U.S. EPA's National Exposure Research Laboratory working in that lab's human exposure research program studying children's residential exposures to environmental contaminants. Her research is on reducing uncertainty in risk assessment with a specific focus on children's exposure. She is developing exposure factor data to reduce reliance on default parameters in risk assessment. She previously worked as a chemical engineer for the Research Triangle Institute, and Camp Dresser and McKee. She also served as a Predoctoral Fellow at the Chemical Industry Institute of Toxicology.

Dr. Hubal received her Ph.D. and M.S. in Chemical Engineering from North Carolina State University and a S.B. in Chemical Engineering from Massachusetts Institute of Technology.

Dr. Hubal has served on a variety workgroups, panels, and committees. She currently serves as a member of the Interagency Dosimetry Working Group, EPA's Risk Assessment Forum Children's Exposure Technical Panel, the American Chemistry Council's Human Exposure Assessment Technical Implementation Panel, and the Study Design Working Group for the National Children's Study. She was an invited participant to the NERL Dermal Exposure Workshop, Outdoor Residential Task Force Workshop, ILSI Aggregate Exposure Assessment Model Evaluation and Refinement Workshop, the Chemical Manufacturer's Association's Exposure Workshop, and the EPA/ACC Technical Workshop for the Voluntary Children's Chemical Evaluation Program (VCCEP).

Dr. Hubal's current research interest is designing studies to evaluate dermal exposure assessment approaches and collect exposure factor data in support of the Food Quality Protection Act. She has worked on the development of a modeling platform to predict contaminant fate and transport of environmental pollutants to perform exposure assessments in support of the Hazardous Waste Identification Rule, developed and worked with a variety of computational models to describe the simultaneous mass transport and reaction of inhaled gases in the airway lining, and conducted research in the area of industrial pollution prevention by developing a framework to evaluate the environmental impact of pollution prevention activities which directly relates to the energy requirements to process air, water, and solid waste emissions.

Dr. Hubal has published in the areas of children's exposure and human health risk modeling.

DISCLOSURE:

Dr. Hubal is a VCCEP Core Panel member. She is employed by the U.S. EPA, working at the National Exposure Research Laboratory. EPA has taken public positions on the VCCEP pilot chemicals and on the tests included in the VCCEP Tiers. Dr. Hubal is also a public member of the American Chemistry Council's Human Exposure Assessment Technical Implementation Panel.

Dr. Sam Kacew

Dr. Sam Kacew is a professor in the Department of Cellular and Molecular Medicine, Faculty of Medicine, as well as a scientist of the Institute of Population Health at the University of Ottawa. His responsibilities include teaching medical students and graduate students the techniques required to write and publish peer-review papers. His current research involves the effects of chemical contaminants in breast milk on infants, the role of confounding factors in toxicity testing, as well as the basis for differences in responsiveness to chemicals between infants and adults.

Dr. Kacew received his Ph.D. in Pharmacology from the University of Ottawa. He served as a Postdoctoral Fellow for the Medical Research Council of Canada at the University of Montreal. Dr. Kacew was certified in 1994 as a Fellow of Academy of Toxicological Sciences. He has received numerous awards, including several achievement, recognition, public communications and travel awards from the Society of Toxicology (SOT), the United States-China Foundation, and the National Science Council of the Republic of China.

Dr. Kacew has served on dozens of expert panels and committees, including as a member of the National Advisory Committee on Environmental Contaminants and the Implications for Child Health, and as a member of the National Academy of Sciences of the USA , Committee on Toxicology. He has also served as a chairman for a variety of symposiums, panels, and committees including the SOT Annual Meeting's General Toxicology Session, the Federation of American Societies for Experimental Biology Annual Meeting, an Assessment Panel for the Canadian Council on Animal Care, a SOT Symposium on Use of Moderate Dietary Restriction in Safety Assessment, and a SOT Symposium on the Role of Diet and Obesity in Endocrine Disruption.

He has presented hundreds of invited lectures for a variety of federal and state government agencies, colleges and universities, private companies, and international organizations. He was an invited participant to the American Society for Pharmacology and Experimental Therapeutics Meeting, the Federation of American Societies for Experimental Biology Annual Meeting, the International Life Sciences Institute, the Chalk River Nuclear Labs, Turkey Society of Biochemistry and the Korea Society of Toxicology.

Dr. Kacew is on a number of grant committees and has served as an external referee for grants and fellowships for a wide variety of organizations and government agencies. He is currently the Editor-in-Chief the *Journal of Toxicology and Environmental Health*, an Associate Editor for *Toxicology and Applied Pharmacology*, an assistant editor for TOMES (Micromedex, Inc.), as well as a member of the editorial board of a number of other journals. Dr. Kacew has over 140 publications in peer-reviewed journals and books in the area of toxicology, risk assessment, and children's health. He has also served as an editor for a number of books on toxicology and children.

DISCLOSURE:

Dr. Kacew is a VCCEP Core Panel member. He is a Professor in the Department of Cellular & Molecular Medicine in the Faculty of Medicine at the University of Ottawa in Canada. Several years ago, in 1993 and 1995, he received honoraria from two VCCEP sponsors, Mobil Oil and Dow, for talks he delivered at their facilities. Dr. Kacew served as an External Peer Reviewer for the May 2003 Toxicological Review of Acetone used by EPA for the Agency's current IRIS hazard and dose-response assessment.

Dr. Richard Reiss

Dr. Richard Reiss is a Vice President at Sciences International, Inc. (Sciences), a health and environmental consulting firm in Alexandria , Virginia . He has over 10 years of experience in the health and environmental sciences with expertise in risk assessment, exposure assessment, environmental chemistry and fate, mathematical modeling, and applied statistics.

Dr. Reiss has expertise in both air quality and chemical risk assessment, including human health and ecological risk issues. He has published articles and reports, and given technical presentations on all of these issues. He has conducted research in urban and indoor air quality and provides consulting services to governmental and industrial organizations for urban air quality, industrial hygiene, and air toxics issues. Dr. Reiss also consults with numerous organizations and companies on chemical fate and transport, and exposure. He has conducted risk assessments, data analyses, probabilistic exposure modeling and environmental exposure modeling for environmental agents, such as pesticides, industrial chemicals, consumer product chemicals, and asbestos. He has expertise in the use of mathematical models for conducting advanced exposure assessments. He also performs statistical analyses, including dose-response modeling to evaluate chemical toxicity. He has directed the development of data for new and existing products to better understand potential human health and environmental effects associated with chemicals.

Dr. Reiss is the Managing Editor of Risk Analysis: An International Journal, the leading scholarly journal for risk analysis. He was the winner of the 2001 Chauncey Starr award from the Society for Risk Analysis. This award recognizes a risk analyst less than 40 years of age that has made major contributions to the field of risk analysis. He also served as the chair of the Exposure Assessment Specialty Group of the Society for Risk Analysis.

Dr. Reiss is a member of the Society for Risk Analysis, the American Association for the Advancement of Science, the Society of Environmental Toxicology and Chemistry, and the International Society of Exposure Analysis.

DISCLOSURE:

Dr. Reiss has been selected as an *ad hoc* member for the VCCEP panel on Acetone. Dr. Reiss is an environmental engineer and health scientist and is a Vice President at Sciences International. Through his employer and previous employer (Jellinek, Schwartz & Connolly), Dr. Reiss has provided consulting services to the ACC, but not the Acetone Panel or on acetone. One project with ACC was the development of a framework for the VCCEP. The framework lays out a generic methodology for approaching VCCEP assessments and was published in the October issue of *Risk Analysis: An International Journal*. Sciences International provided a proposal to conduct the VCCEP assessment for the ACC Acetone Panel, but was not selected and has not done any work for the Panel. To the best of Dr. Reiss' knowledge, his employer has no current work with the ACC Acetone Panel member companies.

Dr. Jennifer Seed

Dr. Jennifer Seed is a Branch Chief with the Office of Pollution Prevention and Toxics, Risk Assessment Division, Existing Chemicals Assessment Branch of the U.S. EPA. She provides supervision and leadership to a staff of scientists with expertise in toxicology, epidemiology, biostatistics, and ecotoxicology. This branch is responsible for developing human health hazard and risk assessments, toxicology and ecotoxicology test guidelines in support of OECD harmonization efforts and alternatives to animal testing through ICCVAM activities. Dr. Seed serves on a number of EPA committees and workgroups in these areas.

Dr. Seed also worked as a biologist for the Health and Environmental Review Division, where she conducted human health hazard and risk assessments of environmental chemicals regulated under the TSCA. She developed and reviewed Agency risk assessment guidelines for reproductive toxicity and testing guidelines for assessing developmental neurotoxicity for OPPT and OPP, as well as developing and teaching courses on developmental neurotoxicity for U.S. EPA and other agencies. She helped develop OPPT's children's health strategy

In addition to her work at EPA, Dr. Seed also served as a senior scientist for ILSI Risk Science Institute where she developed and managed teams of scientists from academia, industry, and government charged with resolving issues in toxicology and risk assessment. From 1996 to 1997 she worked as a private consultant on toxicology and risk assessment projects. Dr. Seed received her Ph.D. in Developmental and Cellular Biology and a B.A. in Anthropology (minor in Biology) from the University of Washington. She served as a Postdoctoral Fellow with the Department of Biochemistry, University of Washington.

Dr. Seed has served on a variety of committees, panels, and workgroups. She currently serves on the U.S. EPA's Risk Assessment Forum, as well as the RfD/RfC technical Panel that is responsible for reviewing the methods used by the agency in developing RfD/RfCs to ensure that children and other susceptible subpopulations are adequately protected and on the FQPA 10x workgroup that is developing the implementation policy of the FQPA 10x factor to ensure adequate protection of children's health. Dr. Seed served as a member of the U.S. EPA's Reference Dose Workgroup and co-chaired the Reproductive and Developmental Toxicity Harmonization Workgroup, as well as served as the Chair of the international OECD team to develop a guidance document for reproductive toxicity and as an OPPT representative for the ORD/OPPTS Toxics/Pesticides Research Coordination Team. She has also served on the ILSI steering committee for behavioral developmental toxicity project, scientific advisor for the ILSI Residue Technical Committee, co-chaired the ILSI working group on skeletal variations and children's health risk assessment, SOT steering committee for a workshop on harmonization of risk assessment for cancer and noncancer endpoints, OECD's working group for developmental neurotoxicity guidelines, and EPA's Technical Panel on Framework for Human Health Risk Assessment. Dr. Seed has published in the area of developmental and reproductive toxicity and human health risk assessment, and has contributed to a number of EPA test guidelines and other documents.

DISCLOSURE:

Dr. Seed is a VCCEP Core Panel member. She is employed by the U.S. EPA, working in the Risk Assessment Division of the Office of Pollution Prevention and Toxics. She is EPA Project Officer for the Cooperative Agreement between EPA and *TERA* for developing peer consultation. EPA has taken public positions on the selection criteria used for the VCCEP pilot chemicals and on the toxicology tests included in the VCCEP Tiers. Dr. Seed routinely reviews documents supporting EPA IRIS values; these include documents for acetone and isopropanol.

Dr. Kimberly M. Thompson

Dr. Kimberly M. Thompson is Assistant Professor of Risk Analysis and Decision Science in the Department of Health Policy and Management at the Harvard School of Public Health. She is the Director of the Kid Risk Project that seeks to improve the lives of children by using analytical methods to characterize children's risks and strategies to reduce those risks. Dr. Thompson directs a professional education course on Probabilistic Risk Analysis: Assessment, Management, and Communication, and she seeks to effectively integrate technological, social, political, legal, and economic issues into risk analyses that inform public policy and improve decision making. Her research interests focus on the issues related to developing and applying quantitative methods for risk assessment and risk management, and consideration of the public policy implications associated with including uncertainty and variability in risk characterization.

Over the last decade, for both private and public clients Dr. Thompson has consulted on computer applications, projects concerning environmental quality, fate and transport of toxic chemicals in the environment, analysis of remedial alternatives at landfills and abandoned sites, efforts to characterize uncertainty and variability in risks, and development of white papers for the EPA on topics related to children's risks. Dr. Thompson's most recent consulting includes work with the MIT Lincoln Laboratory as part of an integration team studying the development of a national health surveillance and biodefense system, and her recent book Overkill focuses on microbiological risks in what she calls this "Age of Risk Management."

Dr. Thompson received a Sc.D. in Environmental Health from Harvard University 's School of Public Health. She received a M.S. and B.S. in Chemical Engineering from the Massachusetts Institute of Technology. Dr. Thompson has served on several National Academy of Sciences committees and subcommittees and a number of other expert review panels. She has been an invited presenter at a variety of workshops, conferences, and annual meetings, such as the Boston Mayor's Symposium on Youth Development, the Congressional Research Services' Children's Environmental Risks: Federal Activities in Perspective Symposium on Risk Assessment and Risk Communication, and a NIH/NIEHS Workshop on the Role of Human Exposure Assessment in the Prevention of Environmental Disease. She also served as the chair of the Exposure Assessment Specialty Group of the Society for Risk Analysis.

Dr. Thompson has written over 30 peer-reviewed journal publications in the areas of human health modeling, probabilistic risk assessment, children's health and risk communication. She has also reviewed manuscripts for over a dozen journals, including the Journal of Toxicology and Environmental Health, Risk Analysis, Health Policy, and the Journal of the American Medical Association.

Disclosure:

Dr. Thompson is a VCCEP Core Panel member. She is Associate Professor of Risk Analysis and Decision Science and Director of the Kids Risk Project at Harvard University in the School of Public Health. She received funding from EPA in 2000 to chair a workshop and prepare a publication discussing changes in children's exposure as a function of age. Dr. Thompson's research program benefits from unrestricted grants made to Harvard University by the American Chemistry Council and Synthetic Organic Chemicals Manufacturers Association. Both of these organizations are sponsors of VCCEP chemicals.

Dr. Karla D. Thrall

Dr. Karla Thrall is currently the Technical Lead and Staff Scientist in the Biological Sciences Division at Battelle, Pacific Northwest Division where she has worked since 1992.

Dr. Thrall received a Ph.D. in Toxicology from Washington State University and a B.S. in chemistry from Humboldt State University in California. She is a Diplomate of the American Board of Toxicology.

Dr. Thrall's research interests are primarily in the development and experimental validation of physiologically based pharmacokinetic (PBPK) models to describe the absorption, distribution, metabolism, and elimination of chemicals in the human body.

She is associated with the Pacific Northwest Association of Toxicologists, the Society of Toxicology, and the American Industrial Hygiene Association, and is an Adjunct Professor in the Environmental Science program at Washington State University , Tri-Cities Branch Campus.

Disclosure:

Dr. Thrall has been selected as an *ad hoc* member for the VCCEP panel on Acetone. She is the Technical Leader of the Biological Monitoring & Modeling Group of Battelle's Pacific Northwest Laboratories. Dr. Thrall, through her employer, has worked on two projects for ACC in the past, but not for the Acetone Panel or on acetone. Battelle is a large organization and may have other contracts with ACC or with the Acetone Panel or its sponsors; however, Dr. Thrall is not personally aware of any contracts. Dr. Thrall is an author on a manuscript (*A real-time method to evaluate the nasal deposition and clearance of acetone in the human volunteer. Inhalation Toxicology 15:523-538, 2003).* The work that formed the basis of this manuscript was supported by the U.S EPA.

Dr. Rebecca L. Tominack

Dr. Rebecca Tominack is one of the medical directors of the Missouri Regional Poison Center in Saint Louis . She is also director of the physician residency training program in Occupational and Environmental Medicine at Saint Louis University School of Medicine. There she holds academic joint appointments as adjunct Associate Professor in Occupational and Environmental Medicine and in the Division of Toxicology within the Department of Pediatrics. She is also an adjuvant associate professor in Community Health in the Saint Louis University School of Public Health where she teaches the masters level courses in Human Toxicology and Environmental Toxicology.

Prior to joining academia, Dr Tominack held various positions relating to product and environmental stewardship in the corporate headquarters of Monsanto Company in St. Louis .

Dr. Tominack earned a degree in pharmacy from the University of Maryland in Baltimore in 1977, graduating as valedictorian. She then graduated summa cum laude from the University of Maryland School of Medicine in 1981. She completed postgraduate residency training in Internal Medicine at Maryland , and then entered a research fellowship in virology at the National Institutes of Health. She trained in an additional fellowship in Clinical Toxicology and Pharmacology at the University of Virginia School of Medicine, during which time she trained 6 months at the National Poison Center in Taipei , Taiwan .

Dr. Tominack is board certified in Internal Medicine and in Medical Toxicology. She is a Fellow of the American Academy of Clinical Toxicology and a Fellow of the American College of Medical Toxicology. She serves on the editorial Board of the Journal of Toxicology Clinical Toxicology as a Senior Editor, and was previously the Deputy Editor.

Dr. Tominack has consulted to agencies of the state and federal governments as well as the International Program of Chemical Safety of the World Health Organization. She lectures frequently on toxicology subjects.

Disclosure:

Dr. Tominack has been selected as an *ad hoc* member for the VCCEP panel on Acetone. She is a medical director of the Missouri Regional Poison Center in Saint Louis and director of the physician residency training program in Occupational and Environmental Medicine at Saint Louis University School of Medicine.

Sponsor Presenter Biographical Sketches

Mr. Paul S. Price
Principal Scientist
AMEC Earth and Environment

Mr. Price is a modeler and researcher on exposures to chemicals at AMEC Earth and Environment. He is also involved in developing software for the assessment of exposure to pesticides and other substances. Mr. Price has more than 20 years of experience in assessing exposure to chemicals for industry, government, and trade associations. He has authored over 20 articles on exposure and risk assessment. Areas of interest include Monte Carlo modeling, dose reconstruction, aggregate and cumulative risk, children's exposures, and consumer products and pesticide exposures. Mr. Price has served on advisory boards for the EPA, the Department of Defense, the State of California, and the Army Corp of Engineers. Mr. Price has a Masters degree in Civil Engineering (University of Maryland, 1979) and a Bachelors degree in Chemistry (University of Maryland, 1974).

Dr. John M. Waechter, Jr.

Ph.D., D.A.B.T.
The Dow Chemical Company

Dr. Waechter is the principal Toxicology Consultant to the Epoxy Products and Intermediates Business of The Dow Chemical Company as well as serving the Dow's basic acrylate business in the same capacity. His responsibilities include providing representing the company as a toxicology expert on various intra-company, industry-wide and government panels as well as designing and managing the conduct of any needed toxicology research. He is the current chairman of Toxicology Research Task Group of the American Chemistry Council's Acetone Panel.

Dr. Waechter has been extensively involved in many trade associations. He has served as Chairman for both Toxicology Research Task Group for the Bisphenol A Global Industry Group the American Plastics Council and the Epoxy Resin Toxicology Committee at the Society of the Plastics Industry, Inc. He also serves on the Technical Committees of the Basic Acrylic Monomer Manufacturers, the Phenol Panel at the American Chemistry Council and the Epichlorohydrin/Trichloropropane Task Force at the Society of the Plastics Industry Inc.

Dr. Waechter also served for five years as a Group/Technical Leader for the Pharmacokinetics and Metabolism Group of the Dow Toxicology Research Laboratory. Although his principal activity is a toxicology consultant to the business, he continues to mentor other doctoral and non-doctoral staff in the conduct of toxicology research and mentor their activities as consultants to the businesses.

Dr. Waechter is a member of the International Society for the Study of Xenobiotics and has published fifteen peer-reviewed journal articles on toxicology and pharmacokinetics. He was also the first author for two chapters on the toxicology of Epoxide Compounds in the last edition of Patty's Toxicology, a frequently cited source by government, industry and academia for toxicology information. He has made numerous presentations to various government agencies, including the Environmental Protection Agency, the US Food and Drug Administration, Health Canada, and UK Health and Safety Executive.

APPENDIX C

Voluntary Children's Chemical Evaluation Program (VCCEP)
Peer Consultation on
Acetone

Observer Policy & Submitted Comments

November 18-19, 2003

Kingsgate Conference Center, Salon A
University of Cincinnati
Cincinnati, Ohio

Table of Contents

VCEEP Peer Consultation Policy and Procedures for Observers

TERA conducts VCCEP peer consultations under the *TERA* Peer Consultation and Review Program. The Voluntary Children's Chemical Evaluation Program (VCCEP) peer consultation meetings are open to the public to observe the proceedings. To ensure adequate space is available, we ask that all Observers register in advance for the meeting. Registration information for specific meetings can be found at http://www.tera.org/peer/vccep.

In the VCCEP pilot program, industry Sponsors are preparing assessments of the available toxicity and exposure information on a list of 20 chemicals, to determine whether the toxicity and exposure data are sufficient to adequately characterize the risk of the chemical to children or prospective parents. A group of scientific experts (Peer Consultation Panel) with experience in toxicity testing, exposure evaluation, and risk assessment will evaluate each assessment. The public is invited to attend the meetings and observe the Panel discussions.

Written Comments

Written technical comments from the public received prior to the meeting will be shared with the Panel and Sponsors. Instructions for submitting comments are found with each meeting's registration information. These comments should be brief (no more than five pages) and should address scientific and technical matters as outlined in the Panel Charge. The purpose of Observer comments is for stakeholders and others to share scientific data and analyses with the Panel and Sponsors. Written comments should be sent to *TERA* two weeks prior to the meeting so that the Panel members and authors have the opportunity to review and consider the comments prior to the meeting. *TERA* will make copies available to other Observers at the meeting.

Oral Comments

In addition to written comments, there will be some time set aside at the peer consultation meeting for observers to make brief technical comments to the panel (2-3 minutes). Those wishing to present technical comments at the meeting should register with *TERA* in advance and provide a written copy of the comments as outlined above. Depending on the time available during the meeting, the Chair may allow additional oral technical comments. Comments should be limited to technical issues and *TERA* reserves the right to limit the time devoted to Observer comments. Since the purpose of the observer comments is to share scientific data and analyses, panel members and Sponsors will be provided the opportunity to ask clarifying questions of those Observers making comments. Note – these peer consultations are not public hearings. The meeting's main purpose is to gain the insights and opinions of the expert panel and as a result, only a limited amount of time can be available for Observers to address the panel. Those wishing to make comments are strongly encouraged to provide clear and concise written comments for the panel to consider.

Meeting Report

TERA will prepare a meeting report, which will summarize the range of opinions and recommendations expressed by the panel. Sponsor presentations and Observer comments will also be summarized. The Sponsors and Observers will be offered the opportunity to review text on their presentations to make sure the text is accurate. A draft of the complete report will be sent to panel members for comments and concurrence prior to finalization.

John M. Balbus, MD, MPH

Comments on Acetone Submission
November 10, 2003
(Dr. Balbus could not attend the meeting due to a scheduling conflict.)

My only comments relate to the creation of exposure scenarios. For a consumer product component like acetone, it is critical to model not only use under "usual circumstances", in this case assuming use of exhaust fans and open windows, but also under less than optimal circumstances. To assume that all children exposed to this product (such as through spot remover or nail polish remover) will only be under adult supervision or will always open a window is not conservative and underprotective.

With a compound that has endogenous production such as acetone, the key questions to be considered for VCCEP should focus on high-level short-term (<1 hour) exposures. It is clear that when averaged out over a day, the total absorption or TWA inhalation concentration of acetone from an external exposure will be minimal compared to endogenous production over the same period. What is less clear, and in my opinion underemphasized in this analysis, is whether peak exposures may reach an irritative/inflammatory level, or whether peak blood concentrations may reach an unusually high level, over a much shorter time period.

I note that the upper 10% distribution of the 1 hour TWA of the spot remover scenario exceeds the AEGL-1 level even when assuming the product is used with windows open. As per my comments above, for the purposes of this program, I think the sponsor should consider peak exposure scenarios in which ventilation is inadequate. The end result may or may not lead to a different conclusion, but the analysis could then be considered adequately conservative.

Hugh Barton, Ph. D.
U. S. Environmental Protection Agency
Office of Research and Development

I regret that I am unable to participate in the TERA review of the acetone VCCEP submission. I have read the document and the Gentry et al. 2003 publication and provide here technical comments on the use of internal dosimetry in this analysis.

I, along with colleagues in US EPA/ORD/NHEERL/ETD/PKB, have carried out a detailed review of the isopropanol/acetone modeling and the supporting data for purposes of evaluating the model for potential use in the isopropanol IRIS assessment. We recommended that the modeling be used for that purpose. This is a rare instance when both animal and human in vivo pharmacokinetic data are available for both parent compound and metabolite. Overall, the model does a good job of simulating the pharmacokinetic data for both compounds, with the notable exception of the dermal exposure route for isopropanol, which is not relevant to the analysis for acetone. Thus, I strongly support the use of this model for analyses of acetone and isopropanol by the oral and inhalation routes in rats and humans.

The acetone analysis described in the Gentry et al. 2003 publication is an example of just how useful pharmacokinetic modeling can be for improving dose-response analysis. The classical approach of using only oral data to derive an RfD and only inhalation data to derive an RfC can require excessive animal toxicity studies or, as done in the recent acetone IRIS assessment, the assumption of significant uncertainty in the dose-response analysis and the lack of derivation of a value for one route. Thus, route extrapolation is one valuable reason to implement internal dosimetry based approaches.

The Gentry et al. 2003 study goes one step further, and implements an approach previously explored theoretically in a publication describing a "family approach" for deriving RfDs or RfCs (Barton et al., 2000). Dosimetry and toxicity data for the parent compound and subsequent metabolites can be used to limit the need for multiple toxicity studies while creating a more "complete" toxicity database for any one of the metabolically related compounds. Isopropanol and acetone are essentially ideal due to the stoichoimetric conversion of isopropanol to acetone; the approach is more difficult to implement with complex or branched metabolic pathways. Both compounds also enter the systemic circulation, so systemic exposure potentially leading to toxicity is clearly occurring and can be quantified (as opposed to a metabolite being further metabolized in situ without entering the systemic circulation). I would note that the Barton et. al., 2000 publication won the award from the Risk Assessment Specialty Section of the Society of Toxicology in 2001 as Outstanding Published Paper Advancing the Science of Risk Assessment. Furthermore, the Office of Pesticide Programs routinely uses information on the presence of metabolites in animal toxicity studies to qualitatively determine the need for additional testing of residues on foods representing metabolites or breakdown products of the parent compound. I believe this indicates support for the approach in the Risk Assessment and Toxicology scientific communities. The Gentry et al. 2003 analysis uses the chronic toxicity and reproductive/development studies for isopropanol along with the acetone oral subchronic and inhalation developmental studies to obtain a complete data base of toxicity studies and uses them quantitatively in dose-response analysis. I strongly support this approach and believe their

results demonstrate the great value of this approach in addressing uncertainties that may appear to exist when standard default approaches are utilized based upon parent chemical dosing with the "appropriate" route.

The issue of how to determine "acceptable" exposure levels for exogenous exposures to a compound produced endogenously is not a trivial one. Acetone is relatively nontoxic so this issue can seem unimportant. But, we naturally produce toxic chemicals, such as some aldehydes and reactive oxygen species. Although our bodies have "detoxicification and repair" mechanisms, the success of those systems likely impacts how healthy and long our lives are and the effectiveness of those systems is likely a substantial contributor to population variability. Thus, the tone in the acetone submission that since we produce it endogenously it is not a problem is not a strong argument in and of itself. The additional argument that treating diseased populations with a ketogenic diet somehow defines acceptable exposures for the remainder of the population is not strong either since the risk-benefit tradeoffs for potential side effects versus therapeutic gain are different; detailed and extensive clinical trials may perhaps provide a clearer understanding of any human risks.

However, the comparisons to endogenous production in the acetone document are quite useful and informative. They provide significant perspective on the exogenous exposures, particularly in light of the notably higher endogenous production in children associated with their higher metabolic rates. The comparison to estimates of amount of endogenous acetone in mother's milk are also valuable. In the case of acetone, the very limited toxicity observed at approximately 2 g/kg/day in the subchronic rat study as well as the limited developmental effects combined with the information on the toxicity observed in chronic and developmental exposures with isopropanol should increase our confidence that appropriately defined exogenous exposures will not be detrimental. However, there is no predetermined or simple answer to "how much more exposure" is acceptable. The Gentry et al. 2003 analysis provides a quantitative approach for estimating acceptable exogenous exposures which, combined with the information on endogenous production, provides a useful approach to a non-trivial question. Further analyses of human data available now or in the future may provide further information.

Overall, the modeling and internal dosimetry based analysis represent a strong and sophisticated approach to addressing the available scientific database in a comprehensive, transparent, and practically useful dose-response analysis addressing issues for children and adults.

Barton, H.A., Deisinger, P.J., English, J.C., Gearhart, J.M., Faber, W.D., Tyler, T.R., Banton, M.I., Teeguarden, J., and Andersen, M.E. (2000) Family approach for estimating reference concentrations/doses for series of related organic chemicals. Toxicol. Sci. 54, 251-261.

Hugh A. Barton, Ph.D.
Pharmacokinetics Branch,
ETD, NHEERL, ORD
US EPA
Telephone: 919-541-1995
Fax: 919-541-4284

Email: barton.hugh@epa.gov

Mail Address
U.S. EPA
B143-01
Research Triangle Park, NC 27711

These comments are the professional opinions of the author and do not describe official Agency policy.

APPENDIX D

SPONSOR PRESENTATION SLIDES

Acetone VCCEP

HAZARD ASSESSMENT

Presented by:
Dr. John Waechter

Peer Consultation Panel for the US EPA
Voluntary Children's Chemical Evaluation
Program

American Chemistry Council Good Chemistry Makes it Possible

Responsible Care

Acetone Hazard Assessment

- All Tier 1, 2 requirements were available with data on acetone with exception of immunotoxicity and a two generation reproduction study.
- A guideline immunotoxicity study on acetone funded by the VCCEP sponsors has now been completed.
- The extensive metabolism of isopropanol (IPA) to acetone allows for the use of IPA hazard data along with acetone data to fulfill requirements of Tier 2 and Tier 3.

Tier 1

- Reliable studies on acetone are available for all VCCEP Tier 1 requirements
- *Acute toxicity*
  - *Multiple studies in several species indicate that the acute toxicity of acetone is very low*
  - oral: LD_{50} : 5200 - 9800 mg/kg; inhalation: 8 hr LC_{50} - 21,150 ppm
- *Genotoxicity*
  - *Multiple studies indicate that acetone is not a genotoxicant*
  - Negative *in vitro* gene mutation assays & studies of chromosomal aberrations in mammalian cells and negative *in vivo* erythrocyte micronucleus test in hamsters (Tier 2)

Tier 1

- *Repeated dose oral toxicity*
  - *90 Day subchronic toxicity studies in rats and mice (NTP, 1990; Dietz et al., 1991) (Tier 2)*
    - *"…the effects of acetone were either subtle in nature or occurred during very high levels of exposure confirming acetones's low level of toxicity."*
    - Effects in rats observed at lower doses than in mice
      - ↓ body weight gain and water consumption at highest dose, both sexes
      - hematologic changes at top two doses that were interpreted as mild macrocytic normochromic anemia with depressed regeneration

Tier 1

- Tissue observations in 90 day rat study:
  - **Spleen:** minimal to mild hemosiderosis, top two doses, male only
  - **Liver:** Slight (~ 5-15%) ↑ relative wt., top two doses
    - no histopathological changes in either sex
  - **Kidney:** Slight (~ 14-26%) ↑ relative wt.
    - 3400 & 1700 mg/kg/d, males; 3100 mg/kg/d, females
    - ↑ spontaneous nephropathy seen with aging
  - **Testes:** Slight (~ 20%) ↑ relative wt., no histopathological changes
    slight ↓ sperm motility & morphology, slight ↓ epididymal wt.
    - **$NOAEL_{rats}$ = 900 mg/kg/d, males; 1200 mg/kg/d, females**

Tier 1

- *<u>One generation reproductive toxicity drinking water studies</u>*
  - *Treatment of male rats (0.5%, 6 weeks; ~ 340 mg/kg/d)*
    - no effect on the number of matings, pregnancies and fetuses, or testicular weight and morphology (Larsen *et al*., 1991)
  - *Treatment of both sexes with acetone at 0.5 or 1% for nine or six weeks, respectively; ~ 340 or 680 mg/kg/d*
    - no effect on the number of matings, pregnancies, or testicular weight and morphology (Dalgaard *et al*., 2000)

Tier 2

- Reliable studies on acetone are available for the following VCCEP Tier 2 requirements
  - **90 Day repeated dose toxicity** - (Dietz *et al*., 1991)
  - **Prenatal developmental toxicity** (two species) (Mast *et al*., 1988)
  - **Genotoxicity**: *in vivo* - negative micronucleus
  - **Immunotoxicity** - 4-week drinking water study by OPPTS Test Guideline - negative (Woolhiser *et al*., 2003)
  - **Metabolism & pharmacokinetics** - extensively studied, a PBPK model for both **isopropanol** and **acetone** in several species is available (Gentry *et al*., 2003)

Tier 2

- *Inhalation developmental toxicity (Mast et al., 1988)**
  - Rats at highest exposure (11,000 ppm)
    - ↓ (~ 44%) maternal body wt. gain
    - ↓ (~14%) fetal body wt.
    - NOEL 2200 ppm
  - Mice at highest exposure (6600 ppm)
    - ↑(~ 20%) maternal liver wt. (absolute & relative)
    - ↓ (~8%) fetal body wt, increase in late resorptions
    - NOEL 2200 ppm

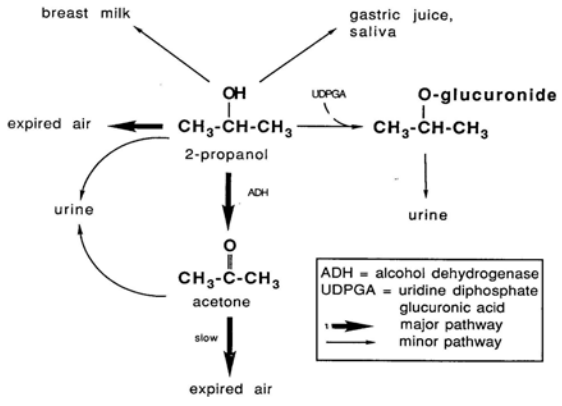
  * Key study for development of RfC & RfD using PBPK model

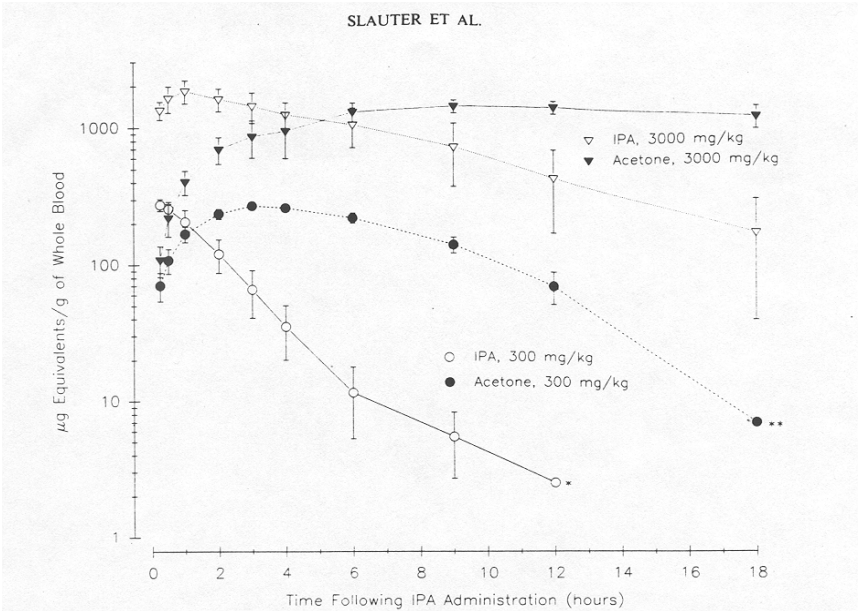
Tier 2

- Acetone is one of three ketone bodies produced as a result of acetyl coenzyme A catabolism within the liver - normal endogenous production occurs in all humans
  - **blood levels of acetone increase during exercise and fasting without ill effect, also present in breast milk as well as many foods**
  - **endogenous production higher in children - no indication that children have a greater sensitivity to acetone**
    - ketogenic diets shown to have beneficial effect in the treatment of epileptic children (Musa-Veloso *et al.*)
  - **eliminated *via* metabolism or in exhaled air or urinary excretion**
    - elimination by metabolism predominates under normal conditions, three metabolic pathways to pyruvate after hydroxylation by acetone monoxygenase

Tier 2

Isopropanol is extensively metabolized to acetone





Tier 2

- Reliable studies on isopropanol fulfill the two-generation reproduction study requirements of VCCEP Tier 2 for acetone
  - *Two generation reproductive toxicity drinking water studies (Bevan et al., 1995)*
    - ↓ mating index in P_2 male at 1000 mg/kg/d
      - (73% *vs* 93% in controls)
      - NOAEL - 500 mg/kg/d; $BMDL_{10}$ = 416 mg/kg/d

Tier 3

- Reliable studies on isopropanol or acetone fulfill the requirements of VCCEP Tier 3 for acetone
  - **Chronic Toxicity/Carcinogenicity:** inhalation of isopropanol up to 5000 ppm was negative for oncogenicity in mice & rats (Burleigh-Flayer *et al*., 1997)
  - **Neurotoxicity screening battery**
    - no "dying back" neuropathy with acetone (Spencer *et al*., 1978)
    - no histopathological effects on nervous tissue with acetone (Dietz *et al*., 1991) or isopropanol (Burleigh-Flayer *et al*., 1997)
    - negative SCOB study with acetone (Christoph *et al.,* 1997)
  - **Developmental neurotoxicity:** gavage up to 1200 mg/kg/d, negative in rats for isopropanol (Bates *et al*., 1994)

Conclusion

- Reliable studies on acetone or isopropanol fulfill all VCCEP requirements for acetone
  - RfC and RfD derived using PBPK model of Gentry *et al.* based on Mast *et al.* developmental toxicity study:
    - RfC - 29 ppm
    - RfD - 8.7 mg/kg/d
    - RfD (IRIS) based Dietz *et al.* = 0.9 mg/kg/d

Acetone VCCEP

EXPOSURE ASSESSMENT FOR ACETONE

Presented by:
Paul Price M.S.

Peer Consultation Panel for the US EPA Voluntary Children's Chemical Evaluation Program

Developed by
AMEC Earth & Environmental

Scope of the Exposure Assessment

- Assessment focuses on relevant endogenous and exogenous sources using child-centered approach
- Endogenous exposures product of metabolism
  - age related
  - characterized by appreciable inter- and intra-individual variability
- Exogenous exposures
  - chain of commerce (evaluated quantitatively)
  - non-chain of commerce (evaluated qualitatively)

2

Production, Use, and Release of Acetone

- U.S. production was 4 billion pounds in 2002
  - industrial uses (chemical intermediate and solvent)
  - commercial uses (surface coatings, cleaning fluids, adhesives)
  - consumer products (nail products, solvent)
- Industrial emissions in 1993 totaled 134 million pounds/yr
- Non-chain of commerce releases
  - vegetative releases (9 million tons/yr)
  - biomass burning (10 million tons/yr)
  - vehicle exhaust, photo-oxidation of hydrocarbons

3

Endogenous Production of Acetone - Introduction

- Acetone found in most human tissues and organs
- Produced when fats and lipids are metabolized for energy
- Primarily formed in the liver
- Can be monitored in plasma, whole blood, urine and breath

4

Endogenous Production of Acetone - Variability

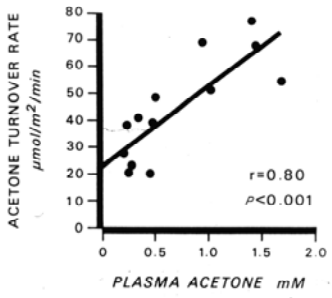
- Inter-human and intra-human variability
  - changes in physiological conditions (e.g. pregnancy, dieting)
  - disease states (e.g. diabetes, alcoholism)
  - differences in age, activity level, and daily diet

Subject	Blood Level (mg/L)
Normal adult	11
Fasting adult	44
Moderate diabetic	90
Severe diabetic	189

5

Endogenous Production of Acetone - Relating Blood Levels to Dose

- Children's serum acetone levels from Peden (1964)
- Endogenous production (Turnover Rate) vs. plasma acetone from Reichard et al. (1979)
- Linear relationship when plasma acetone concentration is less than 5 mM



Note: Figure from Reichard et al., 1979.

6

Endogenous Production of Acetone – Age Specific One-Day Doses

Endogenous production levels under normal conditions

Age Group	Plasma Concentration (mg/L)		Acetone Production (mg/kg-day)	
	Mean	Maximum	Mean	Maximum
Infant	16	140	120	390
1 to 5 Years	14	37	94	140
6 to 13 Years	13	37	72	100
14 to18 Years	9	34	55	83
Adults	11	28.6	41	72

7

Ambient Air (Indoor and Outdoor)

- Natural and anthropogenic sources
- Exposure concentrations based on typical values in ATSDR
- Conservative default activity pattern from EFH
  - 21 hours/day indoor and 3 hours/day outdoor

Ambient Air: Concentrations & range of doses among age groups

Environment	Concentration (ppb)	Avg. Daily Dose (mg/kg-day)
Indoor Air	8	<0.005
Outdoor air - urban	7	<0.0006
Outdoor air - rural	3	<0.0003

8

Food and Water

- Agricultural commodities naturally contain acetone
  - acetone found in raw cow's milk (0 to 11.6 mg/L)
  - trace levels in onions, grapes, cauliflower, tomatoes, beans
  - Generally Recognized as Safe in food additives
- Dose from ingestion of milk and food containing milk quantified using Lifeline Version 2.0 (model tracks all milk products)
- Tapwater not a significant source of exposure

Food: Range of one-day and average daily doses among age groups

One-Day Dose (mg/kg-day)		Average Daily Dose (mg/kg-day)	
Median	95th	Median	95th
0 to 0.092	0.026 to 0.41	0.012 to to 0.13	0.026 to 0.16

9

Human Milk

- Acetone detected but not quantified in human milk
- Concentration varies with endogenous production
- Non-occupational and occupational estimates
  - Non-occupational: milk conc. = avg. population blood level
  - Occupational: milk conc. = PBPK blood level at 500 ppm TLV

Human Milk: Concentrations & infant doses

Infant group	Concentration (mg/L)	Avg. Daily Dose (mg/kg-day)
Non-occupationally exposed mother	11	1.5
Occupationally exposed mother (250 days of work per year)	80 (work day) 11 (non-work day)	7.9

10

Exposure from Consumer Products - Introduction

- Wide variety of consumer products contain acetone
  - Sack et al. (1992) GC/MS survey of consumer products
  - EPA Source Ranking Database
  - current material safety data sheets
- Assessment focused on those consumer products believed to have greatest potential for resulting in appreciable exposure to children
  - frequency of use inside the home
  - weight content
- Four scenarios selected
  - residential pure solvent use as a nail tip remover (dermal, inhalation)
  - residential nail polish remover (inhalation)
  - residential spray painting (inhalation)
  - residential pure solvent use as a spot remover (inhalation)

11

Exposure from Consumer Products - Methodology

- Modeling completed using EPA models or guidelines
  - EPA Dermal Exposure Assessment: Principles and Guidelines
  - EPA EFAST, MCCEM & IAQX Models (2-Zone IAQ Models)
- User and non-user groups assigned based on product type
  - all age groups except infants assumed to use nail polish remover
  - only teenagers and adults assumed to use other products
- Non-users assumed to not enter the room of use
- Typical and upper bound differentiated by usage amount or usage time (nail tip removal only)
- Conservatively small room of use volume assumed (20 m^3)
  - accounts for close proximity of user to product being used
- Open window assumed in accordance with product labeling
  - exposure estimates also provided for active ventilation with window fan

12

Exposure from Consumer Products – Dose Estimates

- Consumer products usage results in short term but not chronic doses
- 1 and 8 hour TWA exposure concentrations available in report for spray paint and spot remover

Consumer Products: Range of one-day and annual average doses among age groups and typical and upper bound uses

Scenario	One-Day Dose (mg/kg-day)	Annual Avg. Dose (mg/kg-day)
Nail polish	0.1 to 0.6	<0.05
Spray paint – open window	0.7 to 5	<0.05
Spray paint – exhaust fan	0.2 to 1	<0.02
Spot remover – open window	0.3 to 4	<0.2
Spot remover – exhaust fan	0.1 to 1	<0.05
Nail tip removal	0.3 to 3	<0.03

Exposure Assessment Summary

- Endogenously produced acetone is the dominate source of exposure to children and females of child bearing years
- Acute exposure
  - Consumer product usage results in one-day doses that are an order of magnitude lower than endogenous doses
- Chronic exposure
  - Dietary (milk) exposures are the highest exogenous exposure for most children and adults
  - Air, water and consumer products are minor chronic sources of exposure to children and females of child bearing years
  - Nursing mothers with occupational exposures to acetone can result in elevated exposures to infants

14

Acetone VCCEP

RISK CHARACTERIZATION
and
DATA NEEDS ASSESSMENT

Presented by:
Dr. John Waechter
Paul Price M.S.

Peer Consultation Panel for the US EPA
Voluntary Children's Chemical Evaluation Program

American Chemistry Council Good Chemistry Makes it Possible

Responsible Care®

Acetone Risk Characterization

Risk Characterization Overview

- Evaluated chronic, one-day acute and short term exposures
- Chronic doses compared to Gentry *et al*. PBPK RfD of 8.7 mg/kg-day using hazard index
- Acute one-day doses compared to estimates of age-specific endogenous production
- Short term exposure concentrations compared to 1-hr and 8-hr draft Acute Exposure Guideline Level (AEGL-1)

Acetone Risk Characterization

Potential for Unique Susceptibility of Children to Acetone

- Gentry RfD and RfC represent safe doses for population lifetime exposures, including susceptible subgroups such as children
- Available toxicity data do not indicate children are more susceptible
- Children have higher endogenous levels than adults
- Ketogenic diet (KD) used to treat refractory epilepsy in children with no adverse effects (*KD breath levels are 100-fold higher than non-KD breath levels*)

Acetone Risk Characterization

Chronic Hazard Evaluation

- Children's risk evaluated using hazard quotient approach
- Background exposure includes air, water, food (milk)

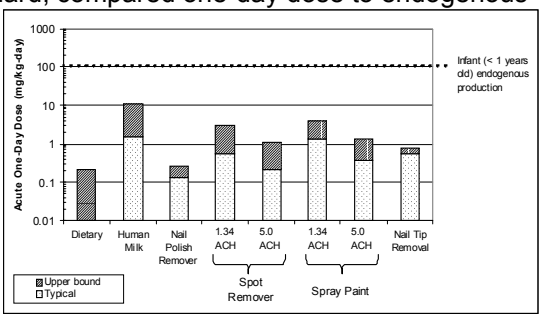
Exposure	Hazard Indices (HI = ADD/RfD)	
	Infant	Other ages
Urban background	0.18	< 0.02
Background + microenvironment (nail polish, nail tip, paint or spot remover)	0.18 to 0.19	< 0.03
Background + occupationally exposed mother	0.92	
Background + microenvironment + occupationally exposed mother	0.92 to 0.93	

- Note: Use of IRIS RfD also results in HI < 1 except for nursing infant

Acetone Risk Characterization

One-Day Dose Evaluation

- Evaluated for dietary exposures (milk) and consumer products
- No regulatory standards for general population acute exposures
- In absence of standard, compared one-day dose to endogenous production
- For all age groups, upper bound exogenous doses are 1 to 2 orders of magnitude lower than endogenous dose



Typical Result: Infant

Acetone Risk Characterization

Short Term Exposure Concentrations

- Evaluated for spray paint and spot remover
- Short term exposure concentrations compared to acetone draft acute exposure guideline level (AEGL-1: Slight sensory irritation) of 200 ppm for 10-minute to 8-hour intervals
- Typical 1-hr and 8-hr concentrations less than 122 ppm
- For users, upper bound spot remover and spray paint 1-hr exposure concentrations (309 and 394 ppm, respectively) exceed AEGL-1 when adequate ventilation not used

Acetone Risk Characterization

Risk Characterization Summary

- Hazard assessment and exposure assessment did not indicate unique susceptibility to acetone in children
- Quantitative risk characterization indicates children's exposure to acetone from ambient background and consumer product sources unlikely to pose health risks
- Typical and upper bound acute one-day exogenous doses are 1 to 3 orders of magnitude lower than endogenous dose
- Short term air concentrations not expected to exceed AEGL-1 with adequate ventilation

Acetone Risk Characterization

Risk Characterization: Uncertainty & Variability

- Uncertainty in hazard
  - RfD based on PBPK model w/ cumulative UF of 30, but true NOEL likely higher than that used.
  - AEGL-1 level based on subjective human responses (slight irritation)
- Uncertainty in exposure
  - Exact estimates of endogenous production have not been fully documented in the literature but the approach used is believed to be conservative
  - Human milk acetone content (conservatively set equal to blood level)
  - Activity patterns and usage amounts (based on EPA guidance)
  - Used models to predict personal exposure (EPA and publicly available models)
- Conclusion of risk characterization not sensitive to hazard and exposure uncertainties

Acetone Data Needs Assessment

Hazard Assessment

- Extensive hazard database on acetone
- Most Tier I-II categories filled with multiple studies in multiple species
  - Coverage of two generation reproduction provided by IPA study
- Tier III coverage of carcinogenicity, neurotoxicity and developmental neurotoxicity endpoints by either “overlap” in other acetone studies or IPA studies

Acetone Data Needs Assessment

Hazard Assessment (*continued*)

- No evidence of unusual age-related sensitivity, including clinical information and developmental neurotoxicity studies
- Data adequate to allow for development of an RfD and RfC using a PBPK model
- *Further studies & use of animals not warranted for VCCEP hazard assessment*

Acetone Data Needs Assessment

Exposure Assessment

- Additional exposure assessment work is certainly possible
- The sources and exposure pathways that have not been assessed are believed to be minor and to not significantly contribute to children's total doses
- Therefore, additional exposure assessment work is not warranted

Acetone Data Needs Assessment

Risk Assessment (*Risk = Exposure x Hazard*)

- Extensive hazard data and human clinical data indicate a very low toxicity for acetone and do not indicate an unusual sensitivity of the young.
- Exposure analyses indicate that exogeneous exposure of children to acetone is very low relative to endogeneous production.

Quantitative estimates of risk indicate that typical or upper-bound estimates of acetone exposure do not represent a health risk to children – on this basis, no further studies, exposure measurements or risk analysis are warranted for purposes of VCCEP.