Report of the Peer Consultation Meeting on Vinylidene Chloride

January 29 and 30, 2003
University of Cincinnati
Cincinnati, Ohio

Submission by:
The Dow Chemical Company for the Voluntary Children's Chemical Evaluation Program (VCCEP)

Peer Consultation Organized by:
Toxicology Excellence for Risk Assessment

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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 January 29 and 30, 2003 to conduct a peer consultation of a submission on vinylidene chloride (VDC) prepared by The Dow Chemical Company for the Voluntary Children's Chemical Evaluation Program (VCCEP). The purpose of the peer consultation meeting was to provide a science-based forum to discuss the available exposure and toxicity data on VDC and determine whether there are adequate data to characterize the risks to children, or if more data or studies are needed. The panel used the assessment submitted by the company as well as their personal expertise and knowledge to form their personal opinions regarding data needs.

Exposure Assessment

VDC is used as an intermediate in the production of polymers and is produced, distributed and consumed in closed systems. Only trace amounts of VDC are found in finished consumer products. The sponsor presented four exposure scenarios (inhalation exposure via outdoor ambient air, inhalation exposure via indoor air, oral exposure via domestic water, and oral exposure via wrapped food). The total aggregate exposure for these scenarios was 0.065 ug/kg-day (central tendency) and 0.15 ug/kg-day (high end). Ambient air was the largest single contributor to exposure. The sponsor noted that VDC could form in groundwater as a breakdown product of 1,1,1-trichloroethane and that vapor migration into the indoor air was possible in homes located above heavily contaminated groundwater. The company did not include the vapor intrusion pathway in its submission.

The panel discussed the potential pathways and sources of VDC exposure, age groupings of exposed populations, and exposure calculations. Some panel members identified potential pathways that they thought should have been addressed more extensively. These included dermal exposure, vapor intrusion, placental transfer, and breast milk. The panel discussed whether the two life-stages presented by the sponsor (0-12 years and over 12 years) completely cover prenatal and postnatal exposures, as well as exposures to prospective parents. One panelist noted that the key question is whether there are any special periods of vulnerability for VDC. While acknowledging the importance of focusing on special periods of vulnerability, the members agreed that nothing in the data indicates that any such periods exist.

Many of the panel members thought the exposure assessment was done well and the data enabled adequate characterization of exposures to children. They believed not much more would be gained from further exposure work, and they pointed out that, in some aspects, this exposure assessment went beyond a screening assessment. Some panelists wanted more explanation provided to support the exclusion of some sources and pathways from the exposure assessment.

Hazard Assessment

The sponsor presented the toxicity information on VDC and concluded that the hazard database is extensive with most Tier 1-3 categories filled with multiple studies conducted in multiple species. The company thought that study "overlap" provides adequate coverage of

immunotoxicity and neurotoxicity endpoints, and there is no evidence of unusual age-related sensitivity.

A major topic of panel discussion was whether cardiac abnormalities in laboratory animals might occur at doses lower than those causing liver toxicity. In particular, the panel discussed the results of the Dawson study (Dawson et al. 1993), which showed cardiac abnormalities in rat pups exposed *in utero*. The majority of the panel thought that, although the Dawson study did raise questions, its results were clearly inconsistent with several other earlier developmental studies that did not show these effects. Some panelists offered suggestions on actions that might clarify the results, but most panelists did not favor repeating the Dawson study at this time.

The majority of panelists were satisfied with the hazard assessment. Several noted that the totality of hazard data on VDC is voluminous and without critical deficiencies. It is a large dataset that allows setting a reference dose (RfD) and adequately characterizing the risk to children. Some panelists agreed with the sponsor that essentially all the data sought from the studies listed in the three Tiers are available because of the "overlap" from results of similar studies. While the existing studies cover limited endpoints, they do address many reproduction and developmental toxicity issues. Others noted that although nothing in the current database points to neurotoxicity as being an issue, this does not mean neurotoxicity would not be seen if a developmental neurotoxicity study had been conducted. After further discussion, most panelists concluded that the dataset (when considered overall) does not lead one to believe that effects would occur at doses lower than those producing liver effects, although some members remained concerned about the cardiac effects reported in the Dawson study.

Risk Characterization

To characterize the potential risks to children, the sponsor calculated the margins of difference between the aggregate exposure estimates and toxicity benchmarks (e.g., RfDs). Based on a central tendency estimate of exposure, the Margin of Safety (MOS) (defined here as the RfD divided by the exposure estimate) was 770 and the Margin of Exposure (MOE) (defined here as the NOAEL divided by the exposure estimate) was 71,000. Based on a high-end exposure, the MOS was 330 and the MOE was 31,000. The sponsor noted there is limited potential for exposure to children since VDC is primarily used in closed-system industrial settings, and there is insignificant residue in consumer-used polymer products. The sponsor acknowledged the potential for exposures to occur from vapor intrusion to indoor air near hazardous waste sites, but emphasized that even when the upper 95th percentile exposure levels found at vapor intrusion sites are included in total exposure estimates, the results are still below the RfD.

Most panel members agreed with the sponsor's risk characterization. They thought the health benchmarks used were appropriate. The panel also discussed the MOS and MOE concepts, with one panel member suggesting use of the Hazard Index as an alternate approach.

Data Needs

The sponsor proposed no further national exposure monitoring is warranted. The sponsor concluded that most of the Tier 1-3 toxicity categories are satisfied by the results of existing

studies and that no evidence of unusual toxicities or age-related sensitivities was observed. The existing study "overlap" is enough to negate the need for any additional studies.

Most panelists agreed that sufficient data are available to adequately understand and characterize the risks to children, particularly in light of the large margins existing between exposures and toxicity benchmarks. While several panelists noted a need for more data on the potential for exposure from groundwater plumes containing VDC or contaminants that might degrade to VDC, they did not expect the sponsor to generate these exposure data. Some panelists wanted more data on the amounts of VDC and VDC metabolites crossing the placenta and excreted in breast milk. While most panel members concluded that no further toxicity studies were necessary, several panel members suggested additional work, but not necessarily toxicity testing, be considered to resolve questions raised by the Dawson study.

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Sponsor

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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 (see http://www.tera.org/peer for information about the program and reports from meetings). Under this program, *TERA* is organizing peer consultation meetings for assessments developed under the Voluntary Children's Chemical Evaluation Program (VCCEP). This panel reviewed an assessment on vinylidene chloride (VDC), prepared by The Dow Chemical Company.

The VCCEP program is a voluntary pilot program and part of the 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 that manufacture and/or import 23 chemicals (which have been found in human tissues and the environment in various monitoring programs) to volunteer to sponsor a chemical 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 page (http://www.epa.gov/chemrtk/vccep/childhlt.htm).

To provide wide ranging scientific evaluation of the sponsor's submission and identification of data needs, 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 these meetings is to provide a science-based peer consultation on the data needs for the particular chemical, utilizing the assessment submitted by the sponsor as well as the expertise and knowledge of the panel. The panel's members have experience in various disciplines, including toxicity testing, exposure evaluation, risk assessment, and children's health. Panel members bring a wide range of views and perspectives to the peer consultations, reflecting the interest in VCCEP from a wide range of stakeholders. *TERA* selects the panel members after careful consideration of nominations from the stakeholders and public, and is responsible for convening and chairing panel meetings to discuss the sponsors' submissions. *TERA* prepares a report of each meeting and makes this available to the public at http://www.tera.org/peer/VCCEP/welcome.htm.

The Dow Chemical Company volunteered to sponsor a Tier 1 assessment for vinylidene chloride, including hazard, exposure, risk characterization, and data needs assessments, utilizing the available information and 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. If data needs are identified through this process, then the sponsor would choose whether or not to volunteer for any additional testing and Tier 2.

The VCCEP 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 are listed in one of 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 analyses. In selecting the panel *TERA* involved stakeholders by considering their nominations for panel members, and sought to have a range of perspectives on the panel. This is not a consensus-based approach; rather the individual panel members discuss their views of the existing data and their recommendations for additional data. Recommendations of the Peer Consultation Panel members regarding the need, or lack of need, for additional data apply only to VCCEP. In the meeting report opinions of the individual panel members are summarized, along with areas of agreement and disagreement.

The VCCEP Peer Consultation Panel for VDC consisted of twelve members: the nine VCCEP Core Panel members and three additional *ad hoc* members specifically selected for this meeting. Collectively, this panel has over 70 publications and/or presentations in the field of children's health risk, as well as hundreds of others on pertinent topics.

The panel includes scientific experts in toxicity testing, risk assessment, exposure assessment, and children's health. Core Panel members who participate in all panel meetings are supplemented with *ad hoc* reviewers. *TERA* received 50 nominations for the core panel 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 core group of nine scientists in June 2002.

The three *ad hoc* panel members were independently invited by *TERA* to provide additional expertise relevant to vinylidene chloride. Nominations were solicited from interested parties for *ad hoc* panelists for the vinylidene chloride panel. The *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 and VDC. *TERA* evaluated the disclosures in selecting panel members and presented the disclosures at the beginning of the meeting.

TERA developed a "charge" document that identified questions and scientific issues to guide the panel discussions. The panel members received a copy of the submission, the charge, and key references approximately a month prior to the meeting so that they had adequate time to carefully review the documents and prepare for the discussions.

Members of the public were invited to attend the peer consultation and observe the panel discussions. They were also given the opportunity to prepare brief technical comments on the assessment document and submit these in writing prior to the meeting.

TERA prepared this meeting report to summarize the sponsor's presentations, the opinions and recommendations expressed by the panel, and oral comments from the public observers. The meeting report is a summary, not a transcript. Panel members have reviewed and approved the report.

This report is organized into three major sections, which correspond to the submission's exposure assessment, hazard assessment, and risk characterization/data needs. In addition, some generic process issues and recommendations of the panel are discussed. During the discussions of the exposure and hazard assessment, the panel members identified strengths and weaknesses of the assessments, identified data gaps, and suggested possible data needs. However, the primary purpose of the peer consultation was to gather the individual members' thoughts and recommendations on data needs. Issues and concerns raised during the hazard and exposure discussions did not always translate into recommendations for additional studies or data compilations.

Introduction

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, noting that copies of panel members' biosketches and conflict of interest (COI) and bias disclosure statements were provided to all attendees. Panel members then introduced themselves and noted whether they had additions or changes in their disclosure statements. No panelists had changes or additions, and the panelists had no questions regarding one another's disclosures. See Appendix B for the panel biographical sketches and disclosure statements.

Dr. Michael Dourson, the panel chair, then described how the meeting would be run. He explained that discussions would be based around the questions found in the Charge to the Panel (Appendix C). He noted that all panelists would have the opportunity to state their own positions on the charge questions 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.

Throughout the two days of meeting, the panel members suggested a number of ideas for data organization and presentation in the VCCEP submissions and in the general VCCEP and peer consultation processes. The panel recognized there is no specified document format that the sponsors must follow for these submissions, although general guidance on content is provided in the Federal Register notice of December 26, 2000 (http://www.epa.gov/oppt/chemrtk/ts00274d.htm). Panel member suggestions regarding content and process for future submissions have been noted within the discussions captured below.

The meeting was open to the public and observers were invited to submit technical comments in writing. In addition, they were provided the opportunity to address the panel as time permitted. Three sets of written comments were received. These were distributed to the panel members and sponsors prior to the meeting, and copies were provided at the meeting for observers. These written comments are found in Appendix D.

This report is organized into three sections; exposure assessment, hazard assessment, and risk characterization and data needs. In addition, the panel discussed a number of generic and process issues related to the submissions and VCCEP process; some of these are mentioned in the panel discussions and others are in the final section of the document.

Exposure Assessment

Sponsor Presentation

A representative of the sponsor introduced its submission on VDC (see Appendix E for a copy of the presentation slides). The sponsor noted that as the first VCCEP sponsor, it faced special opportunities and challenges, including the lack of precedent for how to present the information and how many details to include. VDC is used as an intermediate in the production of polymers. VDC is produced, distributed, and consumed in closed systems; only trace amounts of VDC are found in finished consumer products, so little potential for consumer exposure exists. In addition, the physical and chemical properties of VDC tend to minimize exposure. The chain of commerce for the chemical is well understood. The company has a comprehensive stewardship program to manage the risks associated with VDC production, distribution, consumption, and disposal. As part of this program, the sponsor has conducted numerous human health and environmental health evaluations.

The sponsor summarized the approach to exposure assessment used in the VCCEP submission document. The sponsor conducted biased sampling of extensive monitoring data that exist for VDC in air and tap water and then used bounding estimates of the ambient inhalation and tap water oral distributions. In addition, bounding exposure scenarios were used where fewer monitoring data were available, such as for indoor air, food, and dermal pathways. Overall, conservatism was maximized by adding the high-end values from each distribution within each exposure scenario. The assessment approach evaluated exposure scenarios for all exposure routes. The aggregate exposure was estimated by converting exposure estimates to units of ug/kg-day, adding them, and comparing their sum to the reference dose (RfD) available from the EPA's Integrated Risk Information System (IRIS). Four exposure scenarios were aggregated by summing their exposure estimates. The four scenarios were inhalation exposure via outdoor ambient air, inhalation exposure via indoor air, oral exposure via domestic water, and oral exposure via wrapped food.

For the inhalation pathway, both outdoor and indoor airs were evaluated. Over 20,000 ambient air-monitoring samples were assessed for VDC; 90% of the samples were non-detectable. Only the 10% of the samples that were detectable were used for the exposure assessment. Air concentrations of VDC in these samples ranged from 0.02 to 69.4 ug/m^3. The inhalation reference concentration (RfC) is 200 ug/m^3.

For indoor air, air concentrations were modeled. The modeling assumed that all interior spaces are carpeted and replaced every 5 years. It also assumed that no VDC was lost from carpet backing prior to installation and that all VDC was released to interior spaces after installation.

For the oral pathway, both VDC in tap water and residual VDC in food wrap were evaluated. For tap water ingestion, 65,000 monitoring samples were used; 98.5% were non-detectable. The exposure analysis assumed exposure at the detection limit for samples with non-detectable values. In addition, a Monte Carlo analysis was used to incorporate distributions for children's exposure factors. For the first 19 years of life, the 100,000 Monte Carlo estimates of exposure from water ingestion ranged from 0.002 to 0.397 ug/kg-day, well below the RfD of 50 ug/kg-day.

An FDA screening evaluation was used to estimate exposure from VDC monomer in food wrap. The assessment assumed the maximum possible residue in food wrap, that all 3 kg food or drink consumed in a day is wrapped, and that 5% of the wrap is polyvinylidene chloride (PVDC) copolymer. Finally, the assessment used the amount of VDC that could be extracted by 212^o F peanut oil. The estimated daily intake of VDC via consumption of food that had been wrapped in PVDC copolymer film was 0.0375 ug/kg-day for a 20 kg child under the assumptions of the FDA screening evaluation. This amount is well below the RfD of 50 ug/kg-day.

The aggregate exposure for both central tendency and high-end childhood exposure was estimated for all the scenarios separately. The total aggregate exposure was 0.065 ug/kg-day (central tendency) and 0.15 ug/kg-day (high end). Ambient air was the largest single contributor.

The sponsor discussed the fact that VDC could form environmentally in groundwater as a breakdown product of 1,1,1-trichloroethane and that vapor migration into the indoor air was

possible in homes located above heavily contaminated groundwater plumes. However, the use of 1,1,1-trichloroethane has been reduced significantly with its production phased out under the Montreal Protocol, and the Clean Air Act Amendments of 1990. This effectively limits the environmental emissions of 1,1,1-trichloroethane and the subsequent environmental formation of VDC from such emissions. Among the homes over a contaminated groundwater site in Colorado, many had non-detectable air concentrations of VDC. There were no measured indoor air concentrations that exceeded the RfC of 200 ug/m^3. The sponsor did not include this vapor intrusion pathway in its estimated aggregate exposure.

After the sponsor presentation, the panel members asked a number of clarifying questions. These questions and answers have been integrated into the panel discussion below.

Panel Discussion

The panel discussion on the exposure assessment addressed these charge questions:

1. Is sufficient information provided to determine the conditions (sources, routes, frequency, duration, intensity, etc.) of exposure, and also to identify and quantify the populations of concern?

2. Is the information presented on physical/chemical properties, environmental fate, and monitoring parameters adequate?

3. Are all time periods relevant to childhood exposure (parental exposure prior to conception, prenatal development, postnatal development to the age of sexual maturation) appropriately considered?

4. Are the estimates of exposure calculated appropriately?

5. Do you agree with the conclusions of the exposure assessment?

The discussion of specific charge questions frequently expanded to include multiple charge questions; therefore, the meeting summary is organized by general topic areas, rather than by charge question. The primary topics discussed by the panel included pathways and sources of exposure, age groupings, sensitive populations, and exposure calculations.

In general, many of the panel members indicated that they thought the exposure assessment was done well and the data were sufficiently covered. Some commented that the assessment went beyond a screening assessment and preempted questions suggesting additional analyses may be needed. One panel member commended the sponsor for including Monte Carlo analyses that were of high quality and transparency. This panel member also noted that manufacturing was particularly well discussed, but, because the VCCEP is focused on children, residential levels are generally of more interest. Another panelist cautioned not to forget that children might spend long periods of time in parks and at playgrounds.

Pathways and Sources of Exposure

One member stated that in general the exposure assessment was sufficient, even though not all possible routes had been identified. Other panel members agreed, and identified additional routes and pathways. Individual panelists suggested that oral and/or inhalation exposures from drinking, washing clothes, and showering with contaminated tap water; and dermal exposure while bathing or swimming, or playing in soil were additional pathways of potential importance to children. Another member emphasized the importance of inhalation of residential air, but acknowledged that information from this exposure source may be incomplete. One panelist, noting that the sponsor is unaware of any studies of VDC in breast milk, suggested this possible exposure route needs further exploration. Several panel members emphasized that the sponsor should not be expected to address exposure pathways that were extremely unrealistic, but they wanted assurance that all reasonable pathways were considered.

Panel members stated that the submissions would have been more informative if the authors had provided rationales for accepting and rejecting pathways. Several members wanted to see data and rough calculations for the rejected pathways to be able to judge for themselves the appropriateness of dismissing them. Members agreed that future submissions might consider presenting exposure scenarios and pathways with a flow chart. They suggested sponsors begin by identifying all possible sources, and then determine which are relevant for children. Sources not relevant for children could be dropped, but data should be presented to justify dropping them. One panelist suggested an exposure continuum be shown, identifying routes of exposure and how contact with the substance might occur.

The dermal pathway was a particular concern for several members who believed that it was dismissed without adequate explanation. Individual panelists identified several potential dermal pathways, including children playing in water. They thought that adding the results of the sponsor's dermal exposure analysis would have improved completeness. The sponsor agreed that this inclusion would have improved the transparency of the document, but repeated that the dermal pathway makes no meaningful contribution to total exposure. Further, in response to this request, the sponsor prepared a rough estimate of dermal exposure to VDC from contact with food wrap film (See Appendix F). The sponsor explained that its rough estimate illustrated that potential exposure from this dermal pathway was several orders of magnitude lower than exposures from the oral and inhalation routes; therefore, dismissing this pathway for food wrap was justified. Dismissing VDC's other dermal pathways (e.g., from carpets and soil) was similarly justified, as calculations for VDC dermal exposures from these media would be calculated in the same way and the results would be similarly low. The sponsor noted that there is no plausible dermal exposure to VDC from carpets. Moreover, the sponsor emphasized that it had accounted for any potential exposure to VDC from carpets in the inhalation exposure assessment, which assumed all the VDC in carpets volatilized into the indoor air.

A major topic of discussion was how best to evaluate exposure to VDC formed in the environment from the breakdown of other environmental contaminants. This issue is of particular concern for communities affected by sites with groundwater plumes containing solvents, such as 1,1,1-trichloroethane, which have degraded to VDC. The panel expanded its discussion to include generic issues of how future submissions should deal with exposures due to

degradation of other environmental contaminants, which are unrelated to the manufacture and commercial uses of the chemicals that are the subject of the VCCEP program. One panelist stated that the sponsor cannot be held accountable for VDC from these sources, and the sponsor should not have to provide data on other source compounds. However, the existence of VDC occurring as a result of these other substances should be noted and included in the risk assessment, as the sponsor has done. A second panelist stated that discussion of VDC formation from other compounds was the sponsor's responsibility. A third noted that the VDC exposure values in the submission already accounted for all sources, including formation from other substances, because the assessment relied on empirical measurements of VDC, which may have come in part from breakdown of other chemicals. This panelist thought that the age of the studies with empirical data combined with the known decline of major VDC precursors (discussed below) tended to make the current assessment a worst-case scenario for exposure. Some panel members expressed concern that the vapor intrusion pathway resulting from contaminated ground water plumes near waste sites may result in much higher exposures (by orders of magnitude) than exposures from the consumer products pathways. One panel member expressed concern for infants and pregnant women exposed orally and dermally to contaminated water at plume sites. Another noted that there will always be instances of site-specific excursions above general situations, but risk management actions are needed to address these special situations, and risk management is beyond the scope of VCCEP.

Panelists and the sponsor discussed the fact that the worst-case scenario presented in the submission did not cover exposures from vapor intrusion sites. The number of these sites is not known, but one member noted that there are numerous Superfund sites with VDC precursors, and additional sites may be identified. The sponsor noted that there is a declining trend in the highest VDC ambient air concentration measurements. This is explained by the ban on 1,1,1-trichloroethane, which is the source of environmentally formed VDC. The sponsor believes the decline in VDC will continue as 1,1,1-trichloroethane declines. A panel member asked if it was necessary to identify the people who live above plumes and consider them as specific subpopulations. He supported this position by noting these people represent the extreme high-end of exposure and thus are the demonstrated plausible upper bound on VDC exposure. A second member agreed, suggesting that it might be valuable to compare general population exposure with site-specific subpopulations.

In response to a suggestion that it would be useful to have data on VDC air exposure from a "representative" hazardous waste site to compare to general population air exposures, a panelist stated there would be widely differing comparison values, depending on whether all houses within a site area are included in the assessment or only those directly above the plume. For example, if houses in the entire plume area at the Denver site are considered, the 50^{th} percentile VDC level is 0.67 ug/m^3 (six times the 50^{th} percentile of 0.11 ug/m^3 calculated for the general population). However, if only the houses located directly above the plume are considered (95^{th} percentile), the VDC level is 36 ug/m^3 (30 times the 95^{th} percentile of 1.2 ug/m^3 calculated for the general population). The sponsor clarified that its calculations used all 700 homes in the Denver plume area, not just those directly above the plume. The sponsor emphasized, however, that if only the homes above the plume are considered, the resulting air concentrations are still below the RfC, and the resulting total exposures are below the RfD.

In discussing the available air data, one panelist noted that air emissions from VDC residues in consumer products could not be determined from the data in the submission document. He suggested that more data are needed on VDC stability in consumer products, especially those products expected to be in contact with children. The panelist noted that most available data are for outdoor ambient air. One panelist suggested that an estimate of how much of the indoor air was from outdoor air intrusion would be helpful. Another panelist expressed concern about pregnant women who lived within plume sites inhaling air while showering. A panel member noted that using ambient air measurements included VDC evaporating from carpets and other in-home sources, and that pregnant women were included in the risk assessment. An additional panelist also agreed that ambient air measurements were conservative enough to use for inhalation exposures, because for purposes of the exposure assessment, the sponsor had used the conservative assumption that all VDC that could be present in carpeting and other home sources would volatilize.

Time Periods of Exposure and Sensitive Populations

The panel discussed the age groupings that were used in the assessment by the sponsor. Within these discussions, they also made suggestions for future submissions. A panel member noted that two life-stages (0-12 years and over 12 years) were used in the assessment and that these completely cover prenatal and postnatal exposures, as well as those to prospective parents. He noted that the exposure factors that were used were the usual ones for items like body weight and physiological parameters. While a partial assessment of newborns was done, he considered this adequate overall for a screening assessment.

Another panel member questioned whether there is a need to put children into smaller age bins for this assessment. Several panel members thought that sponsors should have flexibility in choosing how many age bins to accommodate data and whether there is something that leads one to believe that there is something different about a particular life stage and not others. A panel member noted that the key question to be asked is whether there are any special periods of vulnerability for VDC. He thought that nothing in the data indicates that any such periods exist. There is no indication that any particular age range would have special exposures – such as if VDC were used in an infant product. In addition, the conservative high-end assumptions used in the submission gave large margins of exposure. In this case, differences in assumptions regarding parameters such as body weight would not make a meaningful difference. When asked if all relevant time periods were covered for toxicity, as well as for exposure, the panelist responded that the submission covered the entire period "from gamete to grave."

Some panel members suggested that future submissions should use consistent age bins within the submission, for all data presentations and discussion. Others disagreed, saying that the age bins should be flexible, depending on the ages at which meaningful exposures occur and the ages at which important toxicities are noted. A panelist suggested that future submissions should use a more systematic, structured approach to evaluate all possible exposure pathways and relate them to age groups. For example, the panel member noted that VDC followed different age group populations for each exposure pathway (ambient air – 1-18 years; indoor air – 1-12 years; drinking water – 1-12 years; food – both 1 and 3 kg consumed) rather than defining a single age range and analyzing that same age group for all possible exposures. Other panelists considered

this comment to be appropriate as a general suggestion for future submissions, but did not think this was a major flaw in the VDC submission.

A panel member discussed the need to consider the most relevant time period for evaluating hazards for children and thought that it is more important to focus on the one-year exposure as an infant than on a whole lifetime. Given this perspective, the panel member questioned whether effects observed in a chronic study are the best choice for comparison with infant exposure. A second member asked whether the liver toxicity observed for VDC develops within one year of exposure, or whether it only develops following longer exposure. A third replied that liver toxicity was observed in the three-generation reproductive study with the same pattern as in the two-year chronic toxicity study, and that liver toxicity was monitored in young animals, thus providing confidence in the application of this endpoint to children.

Several panelists thought there might be a need to treat pregnant women as a separate subpopulation because of possibly increased exposures resulting from the life-style changes occurring in pregnancy. One panelist also questioned whether the total reliance on healthy, normal children for assessing children's exposure was adequate. Another panel member responded that the uncertainty factor for within species variability in the derivation of the RfD covers uncertainty for sensitive subpopulations, including pregnant women and susceptible children. The majority of panel members agreed with this point.

Exposure Calculations

A panelist stated that a spot check of the exposure estimates found that they were calculated correctly and the calculations in the submission could be replicated.

One panelist questioned whether the data in the exposure assessment presented the worst-case exposures if one considered spatial correlations. He wanted shorter time periods considered in order to obtain higher acute exposure values. Another member disagreed, stating that it was correct to consider data over longer time periods. The sponsor added that spatial correlations must include variations because of wind and climate changes, noting that in the real world one person cannot follow the exposure source around for an extended time period.

A panel member thought an improvement could be made on spatial correlations of data coming from fixed sites and suggested that perhaps one should consider only sites consistently above detection limits to address spatial relations. He thought questions to consider for the groundwater plumes should include whether the high air levels are near each other, what makes them high, what combinations of inputs give the maximum values, and whether these inputs likely to occur again or elsewhere. However, he added that these types of analyses go beyond a screening level assessment and are not necessary for this VDC submission.

A panel member noted that the exposure scenarios appropriately looked at central tendency, but they should also address the high-end exposures. He asked when additional data on high-end exposures should be pursued. The sponsor noted that it looked at the 90^{th} percentile of the ambient air concentration measurements showing "detects," and looked at the 95^{th} percentile of the public water system VDC concentration measurements. The sponsor considered this

consistent with the guidance for the appropriate use of such data but recognizes that; ultimately, this is a risk management and public policy decision.

Exposure Conclusions

Most of the panel members indicated that they thought the exposure assessment was done well and enabled adequate characterization of exposures to children, particularly in light of the large margins existing between exposures and toxicity thresholds. They believed not much more would be gained from further exposure work and they pointed out that in some aspects this exposure assessment went beyond a screening assessment. Many of the panel members suggested ways to improve the presentation of data in future submissions.

Hazard Assessment

Sponsor Presentation

A representative of the sponsor presented the approach to hazard assessment taken in the VDC submission. The hazard assessment was conducted using a tiered approach, highlighting the data available in each of the tiers defined by the VCCEP program.

For Tier I studies a robust database exists including both oral and inhalation acute toxicity studies, repeated-dose studies, and a three-generation reproduction study. However, many of the studies were done several years ago. VDC was positive in the Ames assay with activation, while the *in vivo* genotoxicity assays were usually negative. The target organ in repeated-dose studies was usually the liver and effects on this organ are the basis for the NOAEL and LOAEL values. In addition, kidney and lung effects have been observed, particularly in single-dose studies. No effects on reproductive, nervous, or immune system tissues have been observed.

The Tier 2 studies include tests of *in vivo* cytogenetics, repeated-dose, developmental toxicity, metabolism/pharmacokinetics, and immunotoxicity. Among the Tier 2 studies, some delayed developmental effects were noted (Short, et al., 1977). A recent paper by Ban, et al. (2003) indicated enhancement of an immunologic response seen in mouse lymph nodes. However, carbon tetrachloride, a known immunosuppressant, also gave an enhanced response in this study; therefore the biological significance of the effect reported in this paper is unknown.

Eighteen carcinogenicity studies (Tier 3) have been conducted. Although a positive mouse carcinogenicity study exists, this study has been discounted, and VDC is not classified as a carcinogen. A neurotoxicity screening battery was not conducted, but no central nervous system (CNS) or peripheral nervous system (PNS) lesions were noted in other studies that examined these tissues histologically. No clinical neurological or behavioral effects have been noted in VDC toxicity studies. A developmental neurotoxicity study has not been conducted, but no lesions have been noted in the CNS in other developmental toxicity studies. In addition, no behavioral effects were observed in neonatal rats following *in utero* exposure (Short, et al., 1977).

The sponsor specifically addressed potential age-related effects. The sponsor noted that the Dawson study (Dawson et al. 1993) reported heart malformations when VDC or trichloroethylene was administered to pregnant rats via drinking water; however, no dose-response relationship was observed for VDC. Similar findings were not observed in a more recent report (Fisher et al., 2001) that studied only trichloroethylene. Other VDC developmental studies were uniformly negative for these cardiac and other developmental effects. The sponsor concurred with the IRIS External Peer Review Panel for VDC, which concluded in 2002 that the effects observed by Dawson were not treatment-related.

The sponsor concluded that the hazard database is extensive with most Tier 1-3 categories addressed by multiple studies conducted in multiple species. Study "overlap" provides coverage of immunotoxicity and neurotoxicity endpoints and there is no evidence of unusual age-related sensitivity.

After the sponsor presentation, the panel members asked a number of clarifying questions. These questions and answers have been integrated into the panel discussion below.

Panel Discussion

The panel discussion on the hazard assessment addressed these two charge questions:

6. Is the toxicity information [including absorption, distribution, metabolism and excretion (ADME), mechanistic work, structure activity relationships (SAR), *etc.*] adequate to identify and assess potential hazards to children or prospective parents?

7. Do you agree with the conclusions of the hazard assessment?

A panelist summarized the existing data and concluded that liver toxicity is the critical effect for VDC. He said that, overall, the data presented in the hazard assessment are sufficient to characterize the hazards to the target populations. Many panel members agreed based on the large number of toxicity studies conducted on this compound. The focus of the discussion was on a number of specific topics, including potential pulmonary effects, the Dawson study, fetal exposure, and presence of VDC in breast milk, potential for carcinogenicity, and sensitive subpopulations. Panel members overall conclusions regarding the hazard assessment are summarized at the end of this section.

Pulmonary Effects

One panelist stated that, regardless of dose route, VDC was exhaled and therefore the lung was a target organ. She pointed out that although VDC metabolism in the lungs is higher in rodents than in humans, reactive intermediates are formed in the human lung (Dowsley, et al., 1999). Agents causing lesions in Clara cells are known. An observer commented, using trichloroethylene as an example, that dosing mice for five days will affect Clara cells, but the effect is reversible with time. He said humans have fewer Clara cells than mice and less cytochrome P450 (CYP) so they are less responsive than mice. The sponsor noted that in 30 longer-term studies, lung pathology was never observed, not even in Clara cells. Panelists

discussed the effects of perfusion on the ability to detect Clara cell damage. It was suggested that the reason toxicity studies have not shown pulmonary effects except with acute bolus dosing may be that the longer-term studies used lower doses than acute studies, and lung toxicity has a relatively high threshold compared to those of other organs.

Metabolism

One panelist thought the hazard assessment did not adequately address mechanistic factors. She noted, for example, that mice with high levels of the CYP isoform 2E1 (CYP2E1) have more damage than those with less CYP2E1, and humans are known to have variations in CYP2E1 due to their ethnicity and also from effects of environmental agents (Forkert and Boyd, 2001; Forkert, Boyd, and Ulreich, 2001; Forkert, et al., 1994). When asked if a link existed between CYP2E1 and teratogenicity, the panelist said a good correlation exists between CYP2E1 levels and metabolism and damage. Another panelist added that active metabolites might cross the placenta and cause fetal damage. In response to a question of when CYP2E1 becomes functional, the sponsor answered that CYP2E1 is not present in the human fetus, and does not become fully active until two years of age. [Note: After the peer consultation, additional information about CYP2E1 was identified from publications and from a symposium held at the 2003 Society of Toxicology meeting. This information indicates that CYP2E1 may be detectable at low levels in some, but not all, human fetuses, and that CYP2E1 expression increases in humans at the time of birth.]

An observer offered a comment regarding the similarities between trichloroethylene and VDC metabolism. He noted that for VDC, as for trichloroethylene, metabolism is flow limited at low doses and a 15-fold increase in CYP activity results in a two-fold increase in metabolites. A panelist asked, if given a 0.02 mg/kg-day dose of VDC whether the entire dose would be metabolized and would parent VDC get into the bloodstream. The observer indicated that the dose would be metabolized, but that there would also be parent compound in the blood. The observer also indicated that in diabetics, a 10-fold increase in enzyme activity will result in a much lower than 10-fold increase in metabolite production. Another panelist asked if glutathione was measured in the study and which metabolites were measured. The observer replied that he did not know about the glutathione, but that it probably was not depleted. He further noted that he was referring to a physiologically based pharmacokinetic (PBPK) study, not a metabolism study, so no specific metabolites were measured.

Regarding the metabolism discussion, one panelist thought that a mechanism of VDC toxicity involving CYP2E1 was an interesting hypothesis, but he thought the overall data do not necessarily support it, and many reasons exist to doubt it. He emphasized that the teratogenicity studies are negative.

Dawson, et al. (1993)

The panel discussed whether reproductive toxicity showing cardiac abnormalities could occur at doses lower than those doses that caused liver toxicity. In particular, the panel discussed the results of the Dawson study, which showed cardiac abnormalities in rat pups exposed *in utero*. A panel member noted that if the Dawson study were used as the basis of the RfD, then the RfD

for VDC would be lower than that currently on IRIS. He thought that the effect was biologically significant even though there was no dose response.

A panelist noted that while evaluating VDC, the IRIS External Peer Review Panel identified significant problems with the reporting of the methods and dosing in the Dawson study. The study authors were contacted directly in order to obtain enough information to estimate the actual exposure of the animals. The IRIS Panel concluded this study should not be used to derive the RfD.

One panelist suggested the study should be repeated and combined with a more general developmental toxicity study, taking into account that the placenta has CYP2E1. She suggested more studies of reproduction also are needed to explore a recent finding that trichloroethylene damages mouse epididymides (Forkert et al., 2002), and she noted that a human study (Forkert et al., 2003) with eight subjects showed a link with infertility. She also noted that placental metabolism has not been evaluated. She further noted that the toxic entity has not been resolved, although she thinks the epoxide is likely to be the reactive form of the chemical.

Another panelist noted that, although many of the negative developmental studies were done in the 1970s, the techniques used at that time are still considered valid today. He emphasized that the sectioning procedures used in those earlier studies would have shown cardiovascular defects if they existed, but none were reported. Another panelist was not convinced that the earlier developmental toxicity studies had been designed to detect the effects reported by Dawson, but he acknowledged the functional significance of the Dawson findings is unclear. He noted that the Dawson study looked at the cardiac tissues using a very detailed exam with a dissecting microscope. This panelist noted that there have been other developmental toxicity studies with fetal exposure that had no evidence of cardiac effects. He said that when the weight of evidence is considered, the Dawson study is clearly an outlier.

One panelist did not think that the statistical analysis in the Dawson study was appropriately conducted. Using individual fetal hearts gave the study more statistical resolving power than is justified because effects among littermates are often correlated. Rather, the incidence of cardiac abnormalities in litters should have been evaluated. Another panelist agreed, but said that doing this may not have made a difference in the outcome.

A panelist thought the main problem with the Dawson study was the group housing of the animals, which made it impossible to determine the drinking water dose each animal received. Another problem was that the volatility of VDC from the drinking water was not measured, so the concentration of VDC in the drinking water was unknown.

Another panelist asked whether VDC metabolism to an active form might be occurring in neonates and whether VDC present in the mother might lead to fetal cardiac terata. Despite these questions, this panelist concluded that the toxicology studies viewed as a whole support the liver as the critical organ in rat pups. He added that this conclusion is strengthened by noting that the study by Short et al. (1977) was via inhalation; therefore, the dams' livers were not protecting the fetus. He cannot explain the results of the Dawson study, but he finds it difficult

to accept them given the results of five other developmental studies that do not show these cardiac effects.

Several panelists, comparing the Dawson and the Fisher studies, concluded that since the study protocols appeared to be substantially different and the Fisher study tested trichloroethylene and not VDC, it could not be said that Fisher fails to replicate Dawson. The sponsor noted that the Fisher study did largely duplicate the methodology of Dawson, and methodology is the key issue in question.

One member suggested a number of actions to try to resolve questions regarding the Dawson results. He suggested that contacting the Dawson study authors (P. Johnson in particular because she was a coauthor on both the Dawson and Fisher studies) might help determine whether the results of these studies differed because of methodology. The authors could also be asked for a rationale of why the incidence at the low-dose was similar to the incidence in the 1000-fold higher dose. This panelist also suggested trying to obtain pictures (histology) of the cardiac tissues or the tissues themselves for further examination. A second member agreed, and also suggested trying to obtain the raw data from Dawson for statistical reanalysis.

While agreeing that these suggestions would help provide some clarity, another panelist thought the weight of evidence supported the conclusion that VDC is not a cardiac developmental toxicant. He believed the doubts raised about several aspects of the Dawson study are sufficient to discount this study as showing that VDC is a cardiac teratogen. Another member noted there are many questions regarding the validity of the Dawson work and suggested that the panel avoid asking for non-essential testing. Another panelist thought that additional studies are not essential and will not result in helping to protect children.

To summarize the discussion of the Dawson paper, the panel majority thought that, although the study does raise questions, the results are clearly inconsistent with several other developmental studies done earlier. Rather than repeating the Dawson work at this time, some panelists favored reanalyzing and attempting to clarify the results of the original study. Others did not think any additional work was needed.

Fetal Exposure and Breast Milk

One panelist questioned whether sufficient data were presented on placental transfer or prenatal exposure. He reminded the panel that VCCEP is focused on children and involves the public's right to know; therefore, there should be information on how much of the mother's exposure reaches the fetus. Another panelist said studies were needed to measure the placental transfer of VDC at concentrations equal to the effect levels used to derive the RfD, in order to compare the dose to the liver with the dose to the fetus. This panelist believed that, since the issue of cardiac developmental toxicity was not resolved, studies would be necessary to determine if significant exposure to the fetus occurred. He said that repeating the Dawson work was not justified, but other approaches to obtain further information should be considered. A third panelist agreed that more information about the exposure factors of pregnant women would be useful. Another panelist disagreed, stating that for exposure analyses the mother is the intermediary in both animal and human studies. Few studies exist on fetal kinetics, and, for those that do, the animal

data may not relate to humans. He said that even if measurable levels of VDC were detected in the fetus, this would still not answer the question of whether these levels of VDC would cause cardiac abnormalities.

Several panelists discussed the possibility of VDC occurring in breast milk. One panelist indicated that the physical properties of VDC make it unlikely to be found in breast milk, and a study to look for it there may not be justified. Another panelist said VDC would likely partition into octanol rather than water. While VDC is not lipophilic, it is not hydrophilic either, so a study may be warranted. A third panelist added that VDC could not be excluded from being in breast milk because it is biphasic with a 20-minute half-life and is lipid soluble. A member suggested that it might be possible to do a screening estimate of the amount of VDC in breast milk, based on physical properties. She noted further that there is a PBPK model that could be used to estimate breast milk concentrations. The discussion ended with panelists having varying opinions on the necessity to further explore the presence of VDC in breast milk.

One panel member wanted studies to be done to identify the dose of VDC that that would be present in the fetus and in breast milk. He said that finding VDC would suggest the need for further research. A second panelist disagreed, stating that having this information would not change the overall weight of evidence for VDC, nor would it change how VDC would be managed. Studies to determine possible fetal doses would not provide useful information because we know other developmental and reproductive toxicity studies have found effects, so we know that VDC is being transferred to the fetus. Even if cardiac effects were confirmed, it is unlikely that there would be a change in the conclusions drawn regarding VDC because the MOEs for this chemical are so large. The first panelist stated he did not believe the data from the developmental and reproductive studies provided convincing evidence that the fetus is actually exposed to VDC. Nearly all of the fetotoxicity observed could easily have been caused by the significant maternal toxicity observed, rather than by the direct effect of VDC transferred to the uterine compartment.

Potential Carcinogenicity

One panelist described the cancer study of VDC in Swiss mice (Maltoni, et al., 1984). The EPA IRIS document concluded the study results provided suggestive evidence of carcinogenicity but the findings were not sufficient to justify providing a quantitative estimate of cancer risk. An increased incidence of tumors was found in kidneys, mammary glands, and lungs. For tumors in mammary glands and lungs, the highest incidence was at the lower of the two exposures used in the study. In each case, the incidence declined at the higher exposure. However, the absolute increase in mammary and lung tumors was statistically significant at both exposures. The researchers discounted the significance of the tumors in the mammary gland and lung. Tumors in the kidney were found only in one gender (males) at the highest exposure tested. No kidney tumors were found in the control or low exposure or in females at either exposure. Since the publication of the bioassay results, new data on metabolism of VDC suggest that the increase in the kidney tumors in male mice might be a species- and gender-specific response. The panel member stated that these data, however, are not sufficient to conclude that the kidney tumor response in male mice has no relevance for a human health risk assessment.

The panel discussed whether children are more sensitive to carcinogens than adults are. A panelist mentioned that the VDC database includes populations exposed, beginning prenatally, and so young animals are included in these studies. One panelist stated that the mechanism of carcinogenicity for a given chemical is the key factor in determining if children would be more susceptible than adults would. Another panelist noted that for some agents, like radiation exposure, children are more sensitive to carcinogenicity than are adults. Two panelists noted that any difference between children and adults would be expected to be quantitative, not qualitative. Since VDC has not been classified as a carcinogen, children are not considered to be at risk.

Other Issues

The panel discussed the relative sensitivity of mice versus rats. Although mice may be somewhat more sensitive than rats to the chronic effects of VDC, this is not known for sure because most long-term studies in mice used gavage exposure, while most long-term studies in rats used exposure from drinking water. Therefore, a direct exposure-response comparison between mice and rats is not possible. EPA used the studies in rats with exposure from drinking water to derive the RfD because this route of exposure is more relevant for humans. One panelist noted that the liver microsomes of humans are more active than those of either rats or mice.

A panelist noted that VDC exposure can be influenced by nutritional status and questioned the implications of this for U.S. society with its obesity problems. CYP2E1 induction is increased in the diabetic state, and in starvation or fasting, which could indicate that bulimic children are another potentially sensitive population. He noted further that data suggest malnourished or protein deficient children are more susceptible to liver disease and questioned whether this issue was adequately considered in the submission. Another panelist noted that in the diabetic state, P450 levels are elevated and individuals with juvenile diabetes may be more susceptible to VDC. Another panelist agreed that while these issues identify data gaps, he did not consider them to be substantial deficiencies in the hazard assessment. The sponsor added that overly nourished populations appear to be less susceptible to VDC effects than malnourished populations. In addition, in the available chronic studies with malnourished animals, the animals are not malnourished for a long duration. The fact that multi-dose studies are not routinely conducted on malnourished animals complicates this issue.

In response to the question of whether data are available on the variability of baseline levels of glutathione in children, a panelist replied that it is essentially impossible to deplete glutathione completely with VDC. Another panelist agreed, noting that in the first few months of life, there is a large store of reducing power. A third panelist indicated that VDC-glutathione conjugation is not mediated by glutathione transferase; therefore, the levels of this enzyme are not an issue.

In response to a question regarding use of epidemiology data, the sponsor noted that the Ott study (Ott et al. 1976) study is discussed in the submission. Because of its small base size and confounding factors from other chemicals being present, the Ott work does not allow cause and effect conclusions and is not of sufficient quality to be used in risk assessment. In response to a public comment on epidemiology studies (see Foos comment in Appendix D), it was noted that

only two such studies have been done and they are both confounded due to the presence of other chemicals.

Panelists discussed the study by Ban (Ban et al. 2003), which reported immune effects. One panelist had questions about the length of exposure, dose estimation, significance of the observed effects, and how comparable the immune effects were to liver effects. Others responded that the exposure in this study was believed to be 6 hours at 15 ppm (100 mg/m^3). One panelist noted that hypersensitivity, which is the effect noted in the Ban study, is not an immunotoxic response; therefore, this study does not really provide any hazard data. There was general agreement with this statement among the panel members.

Hazard Assessment Conclusions

The panel provided some general overall comments about the data in response to the charge question regarding whether they agreed with the hazard assessment conclusions.

One panelist stated that the totality of hazard data on VDC is voluminous and has no important deficiencies. He said it is an impressive dataset that allows setting the RfD and adequately characterizing the risk to children. He noted that all the data sought from the predefined, requested studies in the Tiers have been generated, due to "overlap" of results of similar studies in the data set.

Another panelist agreed saying a three-generation study has been done that addresses the reproduction and developmental toxicity issues, and that the critical effect, liver toxicity, was monitored in young animals. A third member reminded the panel that the three-generation study covers limited endpoints, and that, looking broadly at the toxicity studies, it is important to realize that all the clinical observations and histopathology data obtained from the existing studies do not necessarily indicate that no neurotoxicity will be observed if a developmental neurotoxicity study is conducted. She acknowledged, however, that when considered overall, nothing in the dataset points to neurotoxicity as being an issue. The dataset does not indicate any effects occurring at doses lower than those that produce liver effects. Issues have been identified regarding items that are unknown, but conducting additional studies is not likely to reduce the uncertainty. Even if the effects of the Dawson report are accepted as real and the RfD is lowered to account for cardiac effects, that may not make any real difference in the risk characterization of VDC. However, another member thought that reconciling the different results of the Dawson and Fisher studies needs more attention.

The majority of panelists stated their approval of the hazard assessment when viewed in total, but several expressed varying degrees of concern about the results of the Dawson work, even though most panelists did not recommend the Dawson study be repeated at this time.

Risk Characterization and Data Needs

Sponsor Presentation

A representative of the sponsor presented a summary of the risk characterization presented in the submission as well as the sponsor's conclusions regarding the data needs for VDC (see Appendix E for a copy of presentation slides). The sponsor used monitoring data whenever these data were available; when not available; the estimates incorporated highly conservative assumptions. The sponsor noted that due to the physical properties of VDC, estimated exposure to VDC is expected to be very low. Because the effects observed after VDC exposure are systemic, and not dependent on the portal of entry, the sponsor added exposure from the oral and inhalation routes together to estimate an aggregate exposure. This compounded the conservatism of the estimates with the assumption that one person is exposed from all potential pathways. When this aggregate exposure is divided into the U.S. EPA RfD on IRIS (50 ug/kg-day) the result is an estimate of a Margin of Safety (MOS). The aggregate exposure divided into an estimated $BMDL_{10}$ (4600 ug/kg-day) would result in an estimate of a Margin of Exposure (MOE). Based on a central tendency estimate of exposure, the MOS was 770 and the MOE was 71,000. Based on a high-end exposure, the MOS was 330 and the MOE was 31,000.

The sponsor noted that extensive monitoring for VDC has occurred over a long period of time. In addition, there is limited potential for exposure to children since VDC is primarily used in closed system industrial settings and there is insignificant residue in consumer-used polymer products. The sponsor acknowledged the potential for exposure from occurrence at hazardous waste sites, but considered these exceptional cases, the impact of which on children must be analyzed as separate from the impact of the VDC chain of commerce. The sponsor noted that indoor air measurements at vapor intrusion sites resulted in concentration values below the RfC. The sponsor concluded no further national exposure monitoring is warranted, but that site-specific monitoring near disposal sites with contaminated groundwater may provide useful information.

Regarding characterization of hazard, the sponsor noted that most of the Tier 1-3 categories are satisfied with multiple studies and that no evidence of unusual age-related sensitivity has been observed. The existing study "overlap" is enough to negate the need for any additional studies. Finally, the risk characterization indicates that an adequate margin of safety exists to protect children. Therefore, the sponsor believes no further hazard evaluation or exposure studies are necessary.

Panel Discussion

The panel discussed the risk assessment/characterization and data needs for vinylidene chloride. The panel addressed a number of charge questions. In discussing these questions, the panel members discussed again many of the same issues that have been presented in previous sections. For clarity in this meeting report, much of the previously recorded discussion will not be repeated here; rather this section will focus on the panel members' conclusions regarding risk characterization and data needs, given the information and discussion on hazard and exposure.

Questions Regarding the Risk Characterization

8. Are the hazard and exposure data appropriately interpreted and used to identify and assess potential risks to children and prospective parents?

9. Does the risk characterization use the appropriate information; for example risk values such as RfDs or dose-response patterns of key effects?

10. Can the Margin of Exposure and Margin of Safety for vinylidene chloride be used (in part) to support the data needs conclusions?

11. Are the underlying assumptions, uncertainties, strengths, and weaknesses of the risk characterization adequately discussed?

12. Do you agree with the conclusions of the risk characterization?

Questions Regarding the Data Needs Assessment

13. Does the Data Needs Assessment identify all the additional information needed to adequately characterize the potential hazards, exposures, and risks to children and prospective parents?

- Are any additional toxicity studies from the next Tier needed? If so, explain their value.

- Are any additional exposure data or analyses from the next Tier needed? If so, explain their value.

Risk Characterization

The panel discussed the risk characterization presented in the submission. Specific topics discussed included calculation of the aggregate exposure and the MOE/MOS approach taken in the document.

A panelist said that putting the toxic effects in terms of human exposure is informative, and in this case, it shows toxicity would occur only at very high doses, and children are not subjected to these high exposures. The panelist also noted that the suggestions for mechanistic work described for VDC in the hazard assessment may be a good investigative model, but the data do not indicate a risk to children, given the estimated exposures.

Two members noted that although some uncertainty exists regarding immunotoxicity and neurotoxicity effects due to limited data in these areas, the data that are available do not suggest that any issues exist. They said that because the MOE for VDC is so large, this lack of data has no effect on the risk assessment and uncertainty, nor would it change the overall conclusions.

A panel member agreed that the sponsor used appropriate health benchmarks and that RfDs were used appropriately. In addition, the sponsor appropriately assessed the aggregate exposure given the same systemic effect was observed following both oral and inhalation exposures. This member disagreed, however, with the sponsor's use of California EPA methodology that uses the ratio of body weight to breathing rate for exposure assessment. He said the California EPA guidance recommends estimating internal dose from inhalation exposure by using the ratio of inhalation rate to body weight. This is an over-simplification because the absorption of VDC across the lung is not a simple function of inhalation rate and body weight. A more accurate approach would be to adjust by the blood:air partition coefficients and in pharmacokinetics/metabolism of VDC in the liver of the rat and human. However, not all of the data for these corrections are available. The panel member noted that the development of the RfC following EPA guidance would account for these parameters, and therefore comparing inhalation exposure directly to the RfC would take these differences into account.

As an alternative approach, he suggested using a Hazard Index (HI) approach similar to that used by EPA's Superfund Program in which the total oral exposure is divided by the RfD to arrive at an oral Hazard Index, and the total inhalation exposure is divided by the RfC to arrive at an inhalation Hazard Index. Then the two HIs are added to get the Hazard Quotient, which represents the aggregate exposure. An HI for dermal exposure could also be included. He noted however, that using this approach will not change the overall conclusions because aggregate exposure would continue to be well below a level of concern. Another panel member cautioned that the use of the suggested HI approach might lead to less use of available data for secondary exposure routes, such as dermal, when no formal benchmark value is available.

Several panel members had questions on the meaning of the terms "Margin of Exposure" (MOE) and "Margin of Safety" (MOS) and how these terms were related to the Hazard Index approach discussed above. A panelist clarified this issue by explaining that EPA's definition of MOE is the NOAEL of the critical effect divided by the estimated exposure dose (Barnes and Dourson, 1988); MOS is the term that EPA and others used before MOE. The sponsor uses the definition of MOE correctly in their text. As the sponsor defines the MOS, it is the inverse of the Hazard Quotient, which is the estimated exposure dose divided by the RfD. One panelist indicated that, if the RfD is exceeded, he would use the MOE to evaluate specific exposure scenarios, and that the MOS is not needed. A second agreed, adding that "safety" was too subjective a word to use. Another member endorsed the use of RfDs for evaluating children's health, but acknowledged that the MOE and MOS concepts are not always understood. However, he thought that because VDC has such a large margin between estimated exposures and the RfD, there is no need to get into the more difficult questions involved with selecting the best approach.

Most panel members agreed with the sponsor's risk assessment and characterization conclusions.

Data Needs

Most panelists agreed with the sponsor's conclusion that sufficient data are available to adequately understand and characterize the risks to children. Several panelists mentioned the large margins existing between exposures and toxicity thresholds and thought that little would be gained from further exposure work. One panelist noted that, although she believes more data on

the potential for exposure from groundwater plumes are needed, she would not expect the sponsor to generate these exposure data. Another panelist added that the sources of VDC in the groundwater plumes are decreasing, so this issue would become less important in the future.

Two panelists wanted more data regarding the amounts of VDC and VDC metabolites (a) crossing the placenta and entering the fetus, and (b) possibly being in breast milk. They identified both of these items as exposure data needs. They suggested that once these additional data were obtained and evaluated, further toxicity work might be indicated.

Panel members repeatedly noted that there are many toxicity studies on vinylidene chloride. One panelist in agreeing with the sponsor that no additional hazard data are needed noted that there are multiple studies that overlap and adequately cover the required toxicity endpoints. The panelist added that the VCCEP program is not intended to be a forum for suggesting areas of basic research, such as studies on mechanism of action. Other panelists voiced their agreement with this position.

In summary, the majority of the panel concluded that no further toxicity studies were necessary. However, other panel members suggested considering work to resolve the questions raised by the Dawson study (e.g., redoing the statistics, re-examining the tissues, and interviewing the investigators regarding study methodology.)

Commenting on the panel's data needs discussion; an observer asked that the report of the VCCEP Peer Consultation Panel meeting be clear in stating that the recommendations of the VCCEP panelists apply only to the VCCEP program.

General VCCEP Program Issues

During the course of discussing the VDC submission, the panel raised numerous generic and process issues that go beyond this first assessment. Issues presented below include the scope of the submission, preferred ways to present data and analyses, the role of the sponsor, use of the RfD and MOE concepts, and age groupings for populations of interest. Some panel discussions of process issues were captured in the main body of the report above.

Panel members discussed the need for flexibility in the submission and peer consultation process to meet the particular needs and situation of the chemical. For example, one thought that presenting hazard information before exposure would be preferable, while another thought the opposite. Another panelist pointed out this is an iterative process and so the order of presentation likely will not make much difference.

The panel discussed the desirability for submissions to systematically identify potential sources of exposure. For example, one could quickly dismiss some scenarios based on properties of the compound (e.g., compound is volatile; therefore, the dermal route will not likely be a problem). It was thought that a systematic approach would help insure that important exposure pathways and scenarios are not missed and avoid pursuit of sources/pathways that are extremely unlikely.

By clearly laying out the assumptions used for identifying meaningful exposures, readers can alter assumptions and determine for themselves what might happen.

Several panel members questioned how far beyond typical risks a sponsor should look. One stated that what is needed from the sponsor submissions is what happens in manufacturing and use of the materials and where exposures would occur; to the extent site specific situations are known they should be addressed. The panel member noted that the purpose of these assessments should be to provide information about safety for children under foreseeable scenarios.

The sponsor's submission utilized the RfD as a benchmark and compared VDC exposure estimates to it. In discussing the appropriateness of using the RfD for this purpose, one panel member noted that, in general, there could be two approaches for evaluating exposure. The first would be to evaluate acute, high-end exposure as representative of infant exposure. The second would be to evaluate chronic exposure as representative of a longer-term childhood exposure. This panelist was not convinced that the RfD was always the appropriate benchmark for evaluating the acute type exposures and suggested developmental toxicity studies would be a more appropriate benchmark. A second panel member stated that the concept of the RfD and RfC is to predict a dose that is safe for all life stages, but the RfD and RfC do not predict where or when the effect will develop. If the program requires that risk assessors specifically predict at what time during the lifecycle an effect will occur, then a benchmark different than the RfD will be needed. For example, if a short-term exposure period is of concern, then a benchmark developed from a short-term toxicity study will be needed. A third panel member indicated that a starting point would be to compare childhood exposure to the RfD. If the exposure is lower than the RfD, then there is no cause for concern because the RfD is developed to account for missing data, including data from studies of young animals. However, if childhood exposure were above the RfD, then perhaps a more specific benchmark would be needed.

Panel members discussed and had some disagreement regarding whether it is the sponsor's responsibility to include pathways from environmental formation of the compound of interest that occur as the result of the degradation of other chemicals. One member expressed concern that the panel was asking the sponsor to carry its assessment too far beyond the scope of the program, and, for VDC, thought the plume issue should be dealt with separately. Another replied that the sponsor is responsible for the final text of the document, and therefore, should describe all possible routes of exposure. There is a regulatory precedent for having to account for total exposure from all sources of a particular chemical. Risks to children cannot be adequately characterized without information on all sources, not just manufacturing sources. This panelist indicated that it is not necessarily the responsibility of the sponsor to do research on, or take steps to address, general environmental issues with a sponsored chemical. The first panel member disagreed, stating that the suggestion to include this information would lead to the public perception that the general environmental issues are the sponsor's fault and responsibility. A third member noted that the goal is to determine how to best serve the Right-to-Know requirements, but said the sponsored chemical in commerce should not be equated with the chemical resulting from environmental contamination due to degradation of other chemicals. The role of the sponsor needs to be defined in general for the entire VCCEP process, whether sponsors are to be viewed as overall stewards for the chemical of interest or simply as an interested party with the most technical expertise. Another panel member thought that since this

is a Right-to-Know program, it is the sponsor's responsibility to include all technical issues in the report, even if these issues are outside the program area.

The panel discussed preferred age ranges or "bins." A panel member asked if there was an EPA policy on what is the appropriate age group for evaluating children. Other panel members noted that although there is no EPA policy, the age group of 0-6 years is typically chosen rather than 1-12 or 1-18 years. A panel member thought that the important consideration is to use the same age group throughout the analyses of all exposure pathways. A different member noted that the choice of age group might be both chemical and route-specific, so that it is difficult to establish a blanket policy on the issue. However, this panelist agreed that the 1-18 year group is not appropriate, and suggested that future submissions should explain how and why target age ranges were chosen. Yet another panelist suggested that chemical- and route-specific age groups be determined first and then the remaining ages could be combined. It was noted that the Food Quality Protection Act (FQPA) has evaluated these issues. Another panel member noted that it is also important to combine the route and chemical issues with the toxic effects of concern and the timeframe for development of those effects. It was also noted that even if a chronic two-year study is used for the RfD, it does not mean that the critical effect only developed at the end of the two-year exposure, it could have developed (and often is) at an earlier time point.

A panel member asked the panel to consider, as a larger program issue, how much uncertainty is tolerable. In addition, this member cautioned the panel about recommending additional studies unless they are critically needed. Otherwise, when they do recommend a study, their recommendations will not be given credence.

One panelist raised the issue of access to confidential business information (CBI) data that cannot be made public. He suggested that a way be found to ensure that someone other than the sponsor has access to this information so that critical information may be independently verified.

References

Ban M, Hettich D, and Bonnet P. 2003. Effect of inhaled industrial chemicals on systemic and local immune response. Toxicology. 184(1): 41-50.

Dawson BV, Johnson PD, Goldberg SJ, and Ulreich JB. 1993. Cardiac teratogenesis of halogenated hydrocarbon-contaminated drinking water. J Am Coll Cardiol. 21: 1466-72.

Dowsley TF, Ulreich JB, Reid K, Petsikas D, and Forkert, PG. 1999. Cytochrome P450 bioactivation of 1,1-dichloroethylene to a reactive epoxide in human lung and liver microsomes. J Pharmcol Exp Ther 289: 641-648.

Fisher JW, Channel SR, Eggers JS, Johnson PD, MacMahon KL, Goodyear CD, Sudberry GL, Warren DA, Latendresse JR, and Graeter LJ. 2001. Trichloroethylene, trichloroacetic acid, and dichloroacetic acid: do they affect fetal rat heart development? Int J Toxicol. 20(5): 257-67.

Forkert PG and Boyd SM. 2001. Differential bioactivation of 1,1-dichloroethylene in A/J, CD-1 and C57BL/6 mice. Drug Metab Dispos. 29: 1396-1402.

Forkert, PG, Redza ZM, Mangos S, Park SS, and Tam SP. 1994. Induction and regulation of CYP2E1 in murine liver after acute and chronic acetone administration. Drug Metab Dispos. 22: 248-253.

Forkert PG, Boyd, SM, and Ulreich JB. 2001. Pulmonary bioactivation of 1,1-dichloroethylene is associated with CYP2E1 levels in A/J, CD-1 and C57BL/6 mice. J Pharmacol Exp Ther. 279(3): 1193-200.

Forkert PG, Lash L, Nadeu V, Tardif R, and Simmonds A. 2002. Metabolism and toxicity of trichloroethylene in epididymis and testis. Toxicol Appl Pharmacol. 182(3): 244-54.

Forkert PG, Lash L, Tardif R, Tanphaichitr N, Vandevoort C, and Moussa M. 2003. Identification of trichloroethylene and its metabolites in human seminal fluid of workers exposed to trichloroethylene. Drug Metab Dispos. 31(3): 306-11.

Maltoni C, Cotti G, and Chieco P. 1984. Chronic toxicity and carcinogenicity bioassays of vinylidene chloride. Acta Oncol. 5(2): 91-146.

Ott MG, Fishbeck WA, Townsend JC, and Schneider EJ. 1976. A health study of employees exposed to vinylidene chloride. J Occup Med. 18(11): 735-38.

Short RD, Minor JL, Winston JM, Ferguson B, Unger T, and Lee C. 1977. The developmental toxicity of vinylidene chloride inhaled by rats and mice during gestation. U.S. Environmental Protection Agency. Office of Toxic Substances. EPA-560/6-77-022.

APPENDIX A

List of Attendees (January 29-30, 2003)

Appendix A. List of Attendees

Dr. Katherine Anitole
US EPA
Office of Pollution Prevention and Toxics

Mr. Matthew Barkhurst
Toxicology Excellence for Risk Assessment

Dr. Craig S. Barrow
The Dow Chemical Company

Dr. Christopher Bevan
BP

Dr. Dan Briggs
Toxicology Excellence for Risk Assessment

Mr. Robert Campbell
Great Lakes Chemical Corp

Dr. Paul H. Dugard
Halogenated Solvents Industry Alliance (HSIA)

Mr. Chuck Elkins
Chuck Elkins & Associates

Ms. Brenda Foos
US EPA
Office of Children's Health Protection

Mr. William Greggs
Procter & Gamble

Dr. Bert Hakkinen
Toxicology Excellence for Risk Assessment

Dr. A Michael Kaplan
DuPont - Haskell Laboratory

Mr. Patrick Kennedy
US EPA
Office of Pollution Prevention and Toxics

Dr. Karen Kohrman
Procter & Gamble

Dr. Greg Lawrence
ENVIRON

Mr. Richard W. Leukroth, Jr.
U.S. Environmental Protection Agency

Dr. Phillip K. McKittrick
Rohm and Haas Company

Ms. Patricia Nance
Toxicology Excellence for Risk Assessment

Ms. Julie Panko
AMEC Earth & Environmental

Ms. Jacqueline Patterson
Toxicology Excellence for Risk Assessment

Dr. Kenneth A. Poirier
Kendle International, Inc.

Ms. Bebe Raupe
The Bureau of National Affairs

Ms. Lee Salamone
American Chemistry Council

Dr. Chad B. Sandusky
Physicians Committee for Responsible Medicine

Mr. Donald H. Seiler
The Dow Chemical Company

Ms. Diana Waid
Rohm and Haas Company

APPENDIX B

Panel Biographical Sketches and Disclosure Statements

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/COIPolicy.htm 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 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 twelve 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 which they may be associated. This peer consultation panel is a distinguished group with many years experience in a wide range of disciplines.

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 this chemical 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 vinylidene chloride and its Sponsor, the Dow Chemical Company.

Dr. John Balbus

Dr. John Balbus is currently the Director of the Environmental Health Program for Environmental Defense, where he is working on projects related to antibiotic resistance, health impacts of urban sprawl and transportation policy, and chemical testing and right-to-know. Prior to his current position, he served as the founding Director of the Center for Risk Science and Public Health, as well as an Associate Professor at the George Washington University Medical Center. Dr. Balbus' research activities at the Center for Risk Science and Public Health included addressing susceptibility in risk assessment and risk management, children's susceptibility to waterborne contaminants, and health impacts of climate change. Dr. Balbus was a founding co-director of the Mid-Atlantic Center for Children's Health and the Environment, one of 11 Pediatric Environmental Health Specialty Units funded by the USEPA and ATSDR.

Dr. Balbus received his M.D. from the University of Pennsylvania, an M.P.H. from the Johns Hopkins School of Hygiene and Public Health, and an A.B. in Biochemistry from Harvard University. He completed residencies in internal medicine at Pennsylvania Hospital and in occupational and environmental medicine at Johns Hopkins School of Hygiene and Public Health. Dr. Balbus has also held a variety of additional academic appointments that include: Assistant Professor of Medicine at George Washington University Medical Center, Clinical Fellow in Medic ine at John Hopkins School of Medicine, Assistant Professor in Medicine at Uniformed Services University of the Health Sciences, and Clinical Instructor in Medicine at the University of Pennsylvania School of Medicine.

Dr. Balbus is currently certified by the American Board of Internal Medicine, and the American Board of Preventive Medicine, specialty in Occupational Medicine.

In addition to Dr. Balbus' extensive professional and academic career, he has published numerous articles relating to a variety of topics in risk assessment, public health, and environmental health.

DISCLOSURE:

Dr. Balbus is a VCCEP Core Panel member. He is employed by Environmental Defense. Environmental Defense has taken public positions on chemicals included in the VCCEP pilot program and on the VCCEP program itself.

Dr. Robert Benson

Dr. Robert Benson is a toxicologist for the Drinking Water Program, U.S. Environmental Protection Agency, Region 8, Denver, Colorado. His current responsibilities include interpreting data on the health effects of drinking water contaminants, providing risk assessments for contaminants of concern, and recommending actions necessary to protect the public health. He represents EPA on policy matters regarding these subjects through testimony in public hearings and meetings. He also serves as a peer reviewer for the World Health Organization (WHO) and is a member of EPA's National Advisory Committee to Develop Acute Exposure Guideline Levels for Hazardous Substances. In addition, he serves as the Superfund representative to the Agency for Toxic Substances and Disease Registry's Minimal Risk Level Work Group.

Dr Benson was the lead author of the EPA's recent IRIS (Integrated Risk Information System) document on vinylidene chloride (VDC) that was finalized in August 2002. He also was the author of the VDC International Programme on Chemical Safety – Concise International Chemical Assessment Document (CICAD) sponsored by the WHO. He has authored numerous other documents, including assessments for WHO, toxicological reviews for EPA, reports for the Food and Drug Association, as well as articles in many scientific journals.

Dr. Benson received his Ph.D. in Biochemistry from the University of California at Los Angeles and was a post-doctoral fellow at the University of Washington and the University of California at San Francisco. He served as Assistant Professor in the Schools of Medicine and Dentistry at the University of Louisville. Before joining the EPA, Dr. Benson held positions in the Food and Drug Administration including Acting Director, Consumer Safety Staff, Center for Veterinary Medicine. While at FDA, he received the agency's Award of Merit for individual contributions.

DISCLOSURE:

Dr. Benson has been selected to serve as an *ad hoc* panel member for vinylidene chloride. He is employed as a toxicologist by the U.S. EPA, Region 8, in Denver. 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. EPA recently has prepared an IRIS toxicological review and summary document on vinylidene chloride. Dr. Benson was the author of these documents.

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*, Field Editor for *Teratogenesis, Carcinogenesis and Mutagenesis*, 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 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. Michael 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. *TERA* has worked on acetone, decabromodiphenyl ether, methyl ethyl ketone, and toluene. *TERA* has done work for Dow, but that work was not related to vinylidene chloride or to the VCCEP.

Dr. Poh-Gek Forkert

Dr. Poh-Gek Forkert is a professor in the Department of Anatomy and Cell Biology at Queen's University, Kingston, Ontario, Canada. Her current research areas include toxicology, pathology, and chemical metabolism. She has published extensively on vinylidene chloride and related chemicals, and is an international expert on vinylidene chloride's pulmonary effects, mechanisms of toxicity, and metabolism. She recently published a review article providing an overview of the mechanisms of vinylidene chloride-induced cytotoxicity in lung and liver.

Dr. Forkert received her Ph.D. in Anatomy from the University of Manitoba. She was a Postdoctoral Fellow at the Laboratory of Chemical Pathology at the University of Texas Medical Branch in Galveston, Texas. Dr. Forkert has received numerous awards from institutions including the U.S. National Institutes of Health, the Ontario Ministry of Health, the Southwest Environmental Health Sciences Center at the University of Arizona, and the Canadian Association of Anatomy, Neurobiology and Cell Biology.

Dr. Forkert's professional activities include membership in numerous scientific societies and participation on many university committees. She also reviews manuscripts for journals in physiology, pharmacology, and toxicology and is an active reviewer of grants for agencies in Canada and for NATO. She is a consultant to the Canadian Environmental Law Association, and a reviewer for Health Canada, and the U.S. EPA. She has recently served as a member of the expert panel for the U.S. EPA's workshop for the IRIS summary and supporting documentation for 1,1-dichloroethylene (vinylidene chloride). She has presented numerous invited lectures for a variety of government agencies in Canada and the U.S., for colleges and universities, and for international organizations.

DISCLOSURE:

Dr. Forkert has been selected to serve as an *ad hoc* panel member for vinylidene chloride. She is a Professor in the Department of Anatomy and Cell Biology at Queen's University in Ontario, Canada. She has published extensively on vinylidene chloride metabolism and toxicology. Dr. Forkert was an External Peer Reviewer for the EPA IRIS toxicological review on vinylidene chloride, and participated in the Peer Review Workshop on vinylidene chloride for the IRIS document.

Dr. Elaine 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 was an External Peer Reviewer for the EPA IRIS toxicological review on vinylidene chloride, and he participated in the Peer Review Workshop on vinylidene chloride for the IRIS document.

Dr. R. Jeffrey Lewis

Dr. R. Jeffrey Lewis has been a Scientific Associate with ExxonMobil Biomedical Sciences, Inc. since 1990. He is responsible for designing and conducting epidemiological studies of ExxonMobil employees, and advising the Corporation regarding environmental health issues. He also interacts with regulatory agencies regarding 1,3-butadiene, ethylene, and propylene scientific issues, participates in scientific trade association activities, and manages and plans research budgets and programs. Dr. Lewis is also an Adjunct Assistant Professor of Occupational Health at the University of Texas, School of Public Health.

Dr. Lewis received his Ph.D. and a M.S. in Epidemiology from the University of Texas, School of Public Health's Health Science Center. He earned an M.B.A. from Rutgers University.

Dr. Lewis has over 15 years experience in designing, conducting, analyzing, and publishing epidemiology studies. He currently serves as the Chair for the Endocrine Group of the Children's Health Coordinating Group, the American Chemistry Council's Epidemiology Work Group, and the International Institute of Synthetic Rubber Producer's Epidemiology Subcommittee. He is also currently a member on the International Institute of Synthetic Rubber Producer's Environmental Health Committee. He has served as a member on the European Center for Ecotoxicology and Toxicology of Chemical's Propylene Task Force, as well as a organizing and editorial/publication committee member for an international symposium on 1,3-Butadiene, Isoprene, and Chloropene Health Effects in 2000.

Dr. Lewis is a current member of the American College of Epidemiology, the Society for Epidemiological Research, and the American Association for the Advancement of Science. He has a variety of publications in the area of toxicology and human health assessment.

DISCLOSURE:

Dr. Lewis is a VCCEP Core Panel member. He is employed by ExxonMobil Biomedical Sciences, Inc. and is Adjunct Assistant Professor of Occupational Health at the University of Texas Health Science Center, School of Public Health. Exxon Mobil is sponsoring the VCCEP pilot chemicals benzene, methyl ethyl ketone, m-xylene, o-xylene, and toluene. Dr. Lewis, therefore, has a conflict of interest with these chemicals and will recuse himself from participating in the Peer Consultation Meetings for these chemicals. Dr. Lewis is active on several committees, work groups, and task forces associated with the American Chemistry Council.

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. 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. Susan Youngren

Dr. Susan Youngren is a Senior Managing Scientist with the legal firm of Bergeson & Campbell, PC, having recently moved there from a similar position with Exponent, Inc. (formerly Novigen Sciences, Inc.). Her previous assignments include positions at EA Engineering, Science, and Technology, Inc, and the ILSI Risk Science Institute. Dr. Youngren is responsible for assessing a variety of scientific issues for the clients of Bergeson & Campbell, PC for both regulatory actions as well as product stewardship. This work ranges from assessments for registration and re-registration of pesticides to labeling issues for consumer products in the area of company responsibilities to their customers.

Dr. Youngren received her Ph.D. in Environmental Biology and Public Policy from George Mason University, her M.S. in Environmental Sciences and Engineering from the Virginia Polytechnic Institute and State University, and her B.S. in Microbiology and Public Health from Michigan State University .

Dr. Youngren has over 15 years experience in risk assessment, with particular emphasis on exposure assessment. She has conducted many types of risk assessments, such as residential, dietary, microbial, occupational, and hazardous waste sites. She has assessed dermal, oral, and inhalation exposures for paints, indoor and outdoor foggers, and for products used on carpets, turf, and home gardens. Her work has included development of project-specific algorithms, data analysis, determination of the applicability of surrogate data, development of distributional data, and complex distributional analysis.

Dr. Youngren is a Councilor and member of the International Society of Exposure Analysis. She also belongs to the Society of Risk Analysis, the Society for Occupational and Environmental Health, and the American Association of University Women. She has numerous publications in the areas of risk assessment and exposure, such as a risk assessment for children playing on lawns treated with pesticide. She also has made many presentations on topics such as children's exposure to pet products, choosing distributional forms for use in Monte Carlo exposure assessments, and advancing exposure assessment in the residential environment.

DISCLOSURE:

Dr. Youngren has been selected to serve as an *ad hoc* panel member for vinylidene chloride. She is employed as a senior scientist by the law firm of Bergeson & Campbell. She previously worked for Novigen Sciences, Inc. As a part of her responsibilities for her present and previous employers, she has been in contact with scientists at Dow on issues unrelated to vinylidene chloride or to VCCEP. While Dr. Youngren was with Novigen, her employer did work for the American Chemistry Council regarding appropriate databases to be used for selecting the chemicals for VCCEP. This work did not include recommending selections of any specific chemicals.

APPENDIX C

Charge to Panel

Vinylidene Chloride Panel Charge Questions

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. The Panel is not required to reach a consensus position on this issue. 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 submitted to EPA.

To help the Panel discuss the sponsor's submission and address whether a chemical has been adequately characterized, *TERA* has prepared these Charge Questions. Most are generic questions intended to be used at each Panel meeting. They are supplemented with other questions that address issues specific to the Vinylidene Chloride assessment being reviewed. The questions are consistent with the directions for VCCEP submissions given in the December 26, 2000, Federal Register: http://www.epa.gov/oppt/chemrtk/ts00274d.htm.

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 charge questions based upon experience gained at the VCCEP peer consultation meetings.

Questions Regarding the Exposure Assessment

1. Is sufficient information provided to determine the conditions (sources, routes, frequency, duration, intensity, etc.) of exposure, and also to identify and quantify the populations of concern?

2. Is the information presented on physical/chemical properties, environmental fate, and monitoring parameters adequate?

3. Are all time periods relevant to childhood exposure (parental exposure prior to conception, prenatal development, postnatal development to the age of sexual maturation) appropriately considered?

4. Are the estimates of exposure calculated appropriately?

5. Do you agree with the conclusions of the Exposure Assessment?

Questions Regarding the Hazard Assessment

6. Is the toxicity information (including ADME, mechanistic work, SAR, etc.) adequate to identify and assess potential hazards to children or prospective parents?

7. Do you agree with the conclusions of the Hazard Assessment?

Questions Regarding the Risk Characterization

8. Are the hazard and exposure data appropriately interpreted and used to identify and assess potential risks to children and prospective parents?

9. Does the Risk Characterization use the appropriate information; for example risk values such as RfDs or dose-response patterns of key effects?

10. Can the Margin of Exposure and Margin of Safety for vinylidene chloride be used (in part) to support the data needs conclusions?

11. Are the underlying assumptions, uncertainties, strengths, and weaknesses of the Risk Characterization adequately discussed?

12. Do you agree with the conclusions of the Risk Characterization?

Questions Regarding the Data Needs Assessment

13. Does the Data Needs Assessment identify all the additional information needed to adequately characterize the potential hazards, exposures, and risks to children and prospective parents?

14. Are any additional toxicity studies from the next Tier needed? If so, explain their value.

15. Are any additional exposure data or analyses from the next Tier needed? If so, explain their value.

APPENDIX D

Premeeting Observer Comments

Pre-meeting Public Comments
Vinylidene Chloride VCCEP Assessment
January 2003

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Voluntary Children's Chemical Evaluation Program

Comments on Dow Chemical Co.'s VCCEP Submission for
1,1-DCE (Vinylidene Chloride) Dated Nov. 2002

Comments by
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January 13, 2003

This VCCEP submission concludes that there is no reason for further testing of 1,1-DCE on the basis that exposures to children are anticipated to be low, well below non-cancer health benchmarks referred to from the USEPA and from the State of California. However, the VCCEP submission overlooks important rationale for juvenile animal testing that can help decrease key uncertainties regarding children's health risks from this compound. This rationale is in two areas: 1) greater children's exposure potential than what was presented in the VCCEP

submission; and 2) considerable uncertainty regarding potential genotoxic and carcinogenic risks in early life stages. These points are elaborated below.

1) Children's Exposure Potential. The VCCEP submission mentioned in passing the potential for 1,1-DCE to enter indoor air due to its influx into buildings from subsurface contamination. However, this pathway was not analyzed. 1,1-DCE is highly volatile and migrates readily from groundwater into soil vapor and then into indoor air. It can form from the biodegradation (reductive dechlorination) of several solvents commonly used in industrial degreasing or commercial dry cleaning activities, 1,1,1-TCA, trichloroethylene (TCE), and tetrachloroethylene (PERC) (ATSDR Tox Profile for 1,1-DCE, 1994). The VCCEP submission acknowledges 1,1-DCE formation from 1,1,1-TCA, but dismisses this pathway due to the phasing out of this solvent. This dismissal is premature given the large number of 1,1,1-TCA subsurface releases in the past, with this historic contamination leaving considerable 1,1-DCE source material in groundwater. Additionally, 1,1-DCE's formation from TCE and PCE, solvents which are still in industrial/commercial use, indicate that there will continue to be new opportunities for the environmental formation of 1,1-DCE. In Connecticut, indoor air testing has become more common at solvent-impacted sites to check on the validity of vapor intrusion models that predict health risks. Such surveys have found 1,1-DCE to be a common indoor air contaminant at these sites, even though 1,1-DCE was typically not directly used or released into groundwater. While concentrations vary depending upon the type of building (size, ventilation system), location of the building (proximity to source and to groundwater), and based upon the time of year (highest indoor air concentrations tend to be in cold, wet weather), levels of 1,1-DCE in the 1-10 ug/m3 range are not unusual (e.g., USEPA, Region I, 2000). These are likely due to subsurface sources rather than indoor sources (e.g., carpet backing) as concentration decreases as one samples at higher levels of the home (e.g., 2^{nd} floor vs. 1^{st}).

   Our testing experience in Connecticut makes it clear that the VCCEP submission underestimates the potential for indoor air exposure to children in homes which overlay solvent-impacted groundwater. The submission only considers inhalation exposure to 1,1-DCE emanating from carpet backing, the high end concentration estimate being 0.063 ug/m3 (Table 7.3.2, page 73 of submission). This would appear to be 1 to 2 orders of magnitude too low for what is plausible at impacted sites. The lack of data discovery in this area makes the submission underestimate children's exposure and overestimate the margin of safety when comparing back against the RfD (Table 7.3.2). While CTDPH has not done the thorough literature search, we are aware that 1,1-DCE is also a common groundwater contaminant in other states, with very high concentrations found in groundwater and indoor air at a particular location in the Denver area (Krasnoff et al., 2002). Thus, a more complete literature evaluation and analysis of this pathway is needed for the 1,1-DCE VCCEP submission.

2) Uncertainties Regarding Carcinogenic Hazard to Children. The VCCEP submission does not consider the important uncertainties that surround the issue of children's cancer risk from 1,1-DCE. This chemical has tested positive in a wide variety of mutagenicity and clastogenicity test screens, in a manner generally consistent with, but less potent (and somewhat less consistently positive) than vinyl chloride (USEPA/IARC Genetic Activity Profile database). While the VCCEP submission acknowledges the genetic activity of 1,1-

DCE, it relies upon the cancer bioassay database to allay concerns about carcinogenic risk. Inhalation carcinogenicity testing with 1,1-DCE has produced equivocal results due largely to inconsistent findings and inadequate study designs (see attached table). Oral cancer bioassays have produced negative results. USEPA considers the inhalation database to be uncertain and insufficient for calculation of a cancer unit risk factor (USEPA, 2002). This uncertainty becomes particularly important in the area of children's cancer risks because children are suspected of being more susceptible to carcinogenic agents (Anderson, 2000). This is particularly true for genotoxic carcinogens given that enhanced cell proliferation rates in the rapidly growing tissues of young animals are associated with a greater risk for DNA adducts (Laib et al., 1989) and carcinogenesis than in adult animals. While this has been shown in perhaps the most detail for vinyl chloride (Maltoni, 1981; Laib, 1989; USEPA/IRIS file), it has also been borne out for a wide array of other genotoxic carcinogens (McConnell, 1992; Ginsberg, in press).

1,1-DCE has not been subjected to juvenile animal cancer bioassay testing (standard cancer bioassays begin with sexually mature, 4-6 week old rodents), so we don't know if the genotoxic potential of this chemical will translate into a carcinogenic risk for early life stages (children). This datagap is made particularly significant by the uncertainties in the 1,1-DCE inhalation cancer bioassay database and by the genotoxic action of this chemical. While juvenile animal cancer bioassays do not typically detect carcinogens that went undetected in adult-only bioassays (McConnell, 1992), that conclusion is true for agents which are clearly negative in adults and which are not genotoxicants. This is different than 1,1-DCE's profile and begs the question regarding the outcome of the standard newborn mouse cancer bioassay with 1,1-DCE. This test system has been well-developed over many years, showing good concordance with adult bioassay results, but usually with greater potency and much shorter latency (Flamming, 1997; Fuji, 1991). In fact, there are numerous examples of single dosing or very short-term dosing in this test system yielding clearly positive tumor responses, indicating that long-term chronic exposure is not a prerequisite for carcinogenisis in early life (Vesselinovitch, 1979; Toth, 1968; Ginsberg, in press). Therefore, this is a reasonably short-term (6 months sacrifice) and sensitive test system for achieving a key goal: to decrease uncertainties in the cancer risk assessment for 1,1-DCE exposure in children. I would recommend that vinyl chloride be used as a positive control, with the relative potency to vinyl chloride (if a response is found at all) serving as an index of the overall carcinogenic potential of 1,1-DCE to children. This is because vinyl chloride is the only compound for which a formal cancer risk assessment for children has been developed; this assessment resulted in a child-specific unit risk approach (USEPA/IRIS File). Vinyl chloride is also a close structural analogue of 1,1-DCE.

In addition to generating tumor data following newborn mouse exposures, it would also be helpful to obtain toxicokinetic and DNA adduct data in the newborn mouse system for both 1,1-DCE and the positive control agent. This would facilitate interpretation of the tumor data regarding its meaning for children's risk assessment.

In summary, there is a substantial potential for children's exposure to 1,1-DCE on a daily, subchronic basis due to its intrusion into homes that overlay solvent-impacted groundwater. This is in addition to the background exposures characterized in the VCCEP submission. The carcinogenic hazard associated with these scenarios is not adequately characterized due to the

fact that the cancer bioassay database for 1,1-DCE has no data involving exposures to newborn or juvenile animals. This data gap compounds the uncertainty that already exists in the adult-only inhalation bioassay database (equivocal results in the face of positive genotoxicity data). This backdrop makes 1,1-DCE a natural candidate for testing in the sensitive and relevant newborn mouse cancer bioassay screen.

References

(Note: references in attached table are already in VCCEP submission and so are not reproduced here).

Anderson, L.M., Diwan, B.A., Fear, N.T., and Roman, E. (2000) Critical windows of exposure for children's health: cancer in human epidemiological studies and neoplasms in experimental animal models. Environ. Health Persp. 108, Suppl. 3: 573-594.

Fujii, K. (1991) Evaluation of the newborn mouse model for chemical tumorigenesis. Carcinogenesis 12: 1409-1415.

Flammang, T.J., von Tungeln, L.S., Kadlubar, F.F. and Fu, P.P. (1997) Neonatal mouse assay for tumorigenicity: alternative to the chronic rodent bioassay. Reg. Tox. Pharm. 28: 230-240.

Ginsberg, G.L. (2003) Assessing cancer risks from short-term exposures in children. Risk Analysis 23, No. 1, in press.

Krasnoff, P.M., Morris, P.E., and Roat, R.E. (2002) Estimating indoor air exposure to VOCs from subsurface releases – field methods and model limitations. Proceedings: Indoor Air International Conference, Monterey, California, pp 908-913.

Laib, R.J., Bolt, H.M., Cartier, R., and Bartsch, H. (1989) Increased alkylation of liver DNA and cell turnover in young versus old rats exposed to vinyl chloride correlates with cancer susceptibility. Toxicol. Lett. 45: 231-239.

Maltoni, C., Lefemine, G., Ciliberti, A., et al. (1981) Carcinogenicity bioassays of vinyl chloride monomer: a model or risk assessment on an experimental basis. Environ. Health Persp. 41: 3-29.

McConnell, E. E. (1992) Comparative responses in carcinogenesis bioassays as a function of age at first exposure. In: (Guzelian, P.S., Henry, C.J., and Olin, S.S., eds.) Similarities and Differences Between Children and Adults: Implications for Risk Assessment. ILSI Press, Washington D.C. pp. 66-78.

Toth, B. (1968) A critical review of experiments in chemical carcinogenesis using newborn animals. Cancer Res. 28: 727-738.

USEPA, Region I (2000) Final Report - Residential Indoor Air Study, Stratford, CT June 2000. US EPA Office of Site Remediation and Restoration and US EPA Office of Environmental Measurement and Evaluation.

USEPA (2002) Toxicological Review of 1,1-Dichloroethylene. EPA/635/R02/002.

Vesselinovitch, S.D., Rao, K.V.N., and Mihailovich, N. (1979) Neoplastic response of mouse tissues during perinatal age periods. NCI Mongraph 51: 239-250.

Table 1. Overview of Findings and Limitations in 1,1-DCE Inhalation Cancer Bioassays

Study/Species	Dose Range	Cancer Findings	Design Limitations
Maltoni, 85; mice	0, 10, 25 ppm	Increased mammary and pulmonary tumors; mammary dose response not progressive.	Exposure only 4 hr/d and only for 1 yr
Quast, 86; rats	0, 25, 75 ppm	Increased mammary tumors at low but not high dose; no other increases	Changing doses during bioassay; very marginal demonstration that MTD achieved
Cotti,88; Maltoni,85;rats	0, 10 to 150 ppm	Some evidence for mammary and leukemia tumors, particular from prenatal exposure	Unusual embryo exposure design in one study; only 52 wks of exposure in the other
Lee, 1977, 78; rats, mice	0 or 55 ppm	Several hemangiosarcomas in treated groups	Only 1 yr of exposure; small N (18/sex/dose)
Hong, 81; rats, mice	0 or 55 ppm	Suggestion of mammary tumor increase	Only 6 months of exposure; small N (12/sex/dose)
Viola & Caputo, 77; S-D rats	0, 75, 100	No tumor increases	Small N (30/sex/grp); poor documentation of dosing and findings
Viola & Caputo, 77; Wistar rats	0, 200 ppm	No tumor increases	Small N (37/sex/grp); only 1 yr of dosing; change in dose during study; poor documentation

Written Comments for the VCCEP Vinylidene Chloride (VDC) Peer Consultation
US EPA Office of Children's Health Protection
Brenda Foos

We are pleased to have this opportunity to share our comments on the VDC VCCEP submission provided by Dow Chemical Company. We have reservations as to whether this assessment provides "data to enable the public to understand the potential health risks to children associated with certain chemical exposures," as is the stated goal of the VCCEP program[*].

Exposure:

1. The information/parameters used for eliminating and assessing exposure scenarios are largely unreferenced, or are referenced to internal memos, notes, and unpublished notes of the Dow Chemical Company, which are not publicly available and were not available for consideration in the review of this submission. A few examples (there are many) are:

No reference:
- "an EPA scientist's review of risk associated with VDC" (page 9)
- "It has been determined that there is no potential for VDC to be present in [flame retardant] clothing" (page 21)
- "VDC is not detectable in CAC" (page 22; note, CAC is used in agricultural and pharmaceutical products, which children come into contact with)
- "there is essentially no potential for VDC exposure through [the use of urethane foam in automotive interiors]" (page 22)

Unpublished references:
- Lickly, TD. The Migration of Residual Monomers and Additives from Saran Wrap Household Film under Microwave Oven Temperatures. Unpublished report of the Dow Chemical Company ES-1086 (August 31, 1988)
- Fontaine, DD. (2002). Unpublished Research Note of the Dow Chemical Company.

Very little information is available on the data or the methods of data collection that was used in producing a large portion of the exposure assessment; therefore, the estimates can not be considered reliable or protective. US EPA, with the goals of objectivity, utility, and integrity[†], will likely have great difficulty considering unreferenced and unpublished data. Without revision, it is unclear how the overall exposure scenarios and outcomes could be used to inform the Right-to-Know.

Toxicity:

1. The repeated statement that there is no indication that VDC is associated with developmental toxicity is incorrect. The Dawson, et al. studies indicate increased fetal cardiac malformations. The data available from these studies are not adequate for quantitative estimates

[*] www.epa.gov/opptintr/chemrtk/childhlt.htm

[†] www.epa.gov/oei/qualityguidelines/EPA-OEI-IQG-FINAL-10.2.pdf

of the oral reference dose; however, there is a difference between there being no developmental toxicity and there being developmental toxicity observed in studies that are not adequate for quantitation. Section 6.7 of the submission document incorrectly quotes the draft IRIS *Toxicological Review* (2000), as the final *Toxicological Review* is now available (2002)[‡]. The quoted statement regarding changes in cardiac morphology having little or no consequence has been replaced with statements indicating that the fetal cardiac malformations were of unresolved biological significance. Cardiac birth defects are not of unresolved human significance, as the March of Dimes estimates 25,000 infants are born in the US each year with congenital heart defects[§]. It is important to note that the Dawson et. al studies did more thorough investigations of alterations in cardiac development than other studies available, and also dosed throughout pregnancy (not done by Fisher et al. 2001 in their examination of TCE, as cited on page 57), which is a more human-relevant exposure scenario. It would seem that resolving such outstanding developmental concerns could be an important role for Right-to-Know.

3. If epidemiological studies are going to be included (Section 6.13), then the epidemiological studies of birth defects associated with VDC should also be reviewed, as they are relevant to children than the occupational studies in section 6.13. Epidemiological studies of birth defects associated with VDC include:

Swan, S; M. Deane, J. Harris, R. Neutra. Pregnancy Outcomes in Relation to Water Contamination, 1980-1981, San Jose, CA. In: Pregnancy Outcomes in Santa Clara County 1980-1982: Reports of Two Epidemiological Studies. CA Department of Health Services, 1985.

Goldberg, S.J.; M.D. Lebowitz; E.J. Graver. An association of human congenital cardiac malformations and drinking water contaminants. Journal of the American College of Cardiology 16:155-164 (1990).

Bove, F; M Fulcomer; J Klotz; J Esmart; E Dufficy; and J Savrin. 1995. *Public Drinking Water Contamination and Birth Outcomes*. American Journal of Epidemiology 141(9): 850-862.

Data Needs:

1. We disagree with the conclusion that no further study of VDC is warranted. Examples of further necessary information include:

- Confirmation of the Dawson, et al. cardiac development studies. In order to resolve this concern, the drinking water study would need to be repeated with appropriate dose groups, duration of exposure (full pregnancy), cardiac analyses, and data analysis. Mode of action information would also be useful. Such data would make it possible to rule out the association of cardiac defects and VDC exposure, or would make it possible to quantify this outcome for use in the oral reference dose.
- Clarifying, publishing, and making available references for unpublished and unreferenced exposure information.

[‡] www.epa.gov/iris/toxreviews/0039-tr.pdf

[§] www.modimes.org

- Development of superior VDC monitoring and biomonitoring data sets. Section 2 is critical of the available data, but does not identify or provide superior information.

Conclusions:

In conclusion, we have identified several concerns related to the VDC exposure and hazard assessment, as well as the additional data that would be needed to resolve these concerns. Whether the collection of the needed data fits into the VCCEP pilot is yet to be determined; however, in an effort "to provide data to enable the public to understand the potential health risks to children associated with certain chemical exposures"[1], such information is clearly important.

16th January, 2002

From: Onyemaechi C. Nweke, MPH
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Office of Policy Economics and Innovation
USEPA, 1200Penn. Ave. NW (MC 1809)
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To: VCCEP Pilot Vinylidene Chloride Peer Consultation Panel

Written comments on Dow Chemical's submission for Vinylidene Chloride (1,1-Dichloroethylene) under the VCCEP Pilot.*

Thank you for the opportunity to comment on the VCCEP assessment for Vinylidene Chloride (hereinafter referred to as VDC) under the Voluntary Children's Chemical Evaluation Program. We have prepared comments to correspond to the extent possible with the charge questions. We hope our comments are helpful.

Exposure Assessment

Charge question 5: Do you agree with the conclusions of the exposure assessment?
We do not support the conclusions of the exposure assessment on the basis that the analysis is incomplete without consideration of all known data on VDC exposure, particularly at contaminated sites. See below for details.

Include more data in the exposure assessment: An analysis of indoor exposure to VDC via vapor intrusion is lacking in the assessment. VDC has been found in the indoor environment in a number of field studies conducted by some states. We are aware of data that might be insightful on this issue in the New England area, e.g. Connecticut, and in the state of Colorado. In Colorado, subsurface groundwater contaminated with VDC have yielded sufficient indoor VDC levels to trigger mitigation of houses, even when the water concentration of VDC is at very low levels.**** Thus some measured indoor air levels of VDC may be high enough to present margins of safety of concern when compared to reference values. These data are relevant to the eventual outcome of the exposure assessment and should be included in the analysis.

Frequency of detection of VDC at a few non-representative sites is not a robust measure of all exposures to VDC: The emphasis on the "frequency" of detection of VDC in the different indoor air and breath studies is misleading. These studies were not conducted in areas contaminated with VDC or its precursors. Therefore measurements of exposure from these areas cannot be representative of persons resident in areas experiencing such contamination. Given the current

* Disclaimer: The views presented here are the personal opinions of the authors. They are not in any way representative of the position of the United States Environmental Protection Agency or the USEPA's Office of Policy, Economics and Innovation.

** Personal Communication with Edgar Ethington, (2003) Colorado Dept of Public Health and Environment. Email: Edgar.Ethington@state.co.us

** Very low levels = less than the MCL.

information on vapor intrusion as a means of exposure to volatile organics, any measurements of VDC exposure in affected areas/homes is more likely to result in a high frequency of detects. Discussions on the frequency of detects therefore should at best be contextual rather than definitive.

Differential Exposure in Children: On the issue of increased exposure of children given their unique physiology, the submission states that the implication of greater relative inhalation in children is unclear. (page 39) This implies that there is some data inadequacy that precludes any further conclusions about the relevance or irrelevance of this increased exposure for children of a certain age. This *lack of data* is the rational behind the VCCEP program. Our expectation is not to assume "no harm" because there is no data, but to pursue the development of data so that these issues can be scientifically resolved. Unfortunately, this is an issue that will persist through other assessments of respirable substances. Therefore this pioneer review should engineer some fruitful discussions about the type(s) of data that can resolve these issues, the true relevance of such data and the feasibility of acquiring such data.

Nomenclature**:** The Dow submission refers to the seasons in the NJ study in numerical terms i.e. first, second and third seasons. This document benefits the public in general that have no understanding of the nomenclature used herein. Our suggestion is to reflect more common names for the seasons (i.e. winter, summer etc).

Hazard Assessment

Charge Question 6: Is the toxicity information (including ADME, mechanistic work, SAR etc) adequate to identify and assess potential hazards to children or prospective parents?
Charge Question 7: Do you agree with the conclusions of the hazard assessment?
Charge 8: Are the hazard and exposure data appropriately interpreted and used to identify and assess potential risks to children and prospective parents?

The toxicity information is incomplete in key areas. Because these data are not included in the analysis, they are not interpreted and the conclusions in the assessment are not drawn with full knowledge of the data. These data comprise information that we propose are potentially influential to the outcome of this assessment. See detailed comments below.

Metabolism Studies:

Omitted studies: A number of relevant VDC metabolism studies are not included in this review (studies by Poh-Gek Forkert[i,ii] and the Dowsley group). Some of the studies are cited below. Hopefully, these omissions are an oversight because some of these data appear to be very informative about species differences in toxicity.

Interpretation of omitted data: The validity of rats as a preferred species for toxicity testing appears to be an issue of concern given the findings from a number of metabolism studies:

1. Acute toxicity data on DCE indicates an increased sensitivity of mice compared to rats. The LD_{50} for mice is 7-fold lower than the same for rats.[iii](Note that this is not one of the omitted or metabolism data)

2. VDC-epoxide has been identified as causing liver toxicity (www.epa.gov/IRIS). It appears that mice produce more of this epoxide compared to rats (6-fold difference).[iv] This trend correlates with the toxicity observed in the acute study.

3. The mean levels of the VDC-epoxide formed from *human liver* samples (measured as its glutathione conjugates) is only 1.8 fold higher than levels in mice liver.[v] This data suggests mice and humans are more alike in terms of VDC metabolism.

From the presented data, mice are a more sensitive species to VDC toxicity, they have a higher rate of VDC metabolism, and humans appear to metabolize VDC at comparable rates. Given this data, it appears reasonable that the mouse model is a more appropriate model of toxicity. Thus, knowledge on VDC toxicity in mice is critical. Our analysis of the database presented (in the submission) is that mice studies are in the minority in the database (see table 1). This in our opinion is a reflection of the non-robust nature of the VDC database. Unless there is some scientifically based rational for preferring the rat model, much of the toxicity data in the database used to determine the toxicity of VDC may not be very representative of toxicity in humans. We suggest discussions within the panel on the interpretation of some of the data from mice because they could be very helpful to the outcome of the VDC risk assessment (e.g. application of adjustment factors etc).

Table 1

Study Type	**# Mouse studies/# rat studies+mice studies**	**More sensitive species from toxicity doses**
Acute Oral Toxicity	1/5	Mice
Acute Inhalation	4/11	Mice
Subacute, Subchronic and chronic repeated dose studies - **Inhalation**	5/13	Detailed information unavailable from submitted table
Subacute, Subchronic and chronic repeated dose studies – **oral**	2/9	Detailed information unavailable from submitted table
Developmental - **inhalation**	1/4	Not clear from summary
Developmental - **oral**	0/2	N/a
Carcinogenicity - **inhalation**	3/8	Not clear from presented data
Carcinogenicity - **oral**	1/5	No difference

Metabolism and teratogenicity: Dichloroacetic (DCA) acid was reported (Costa and Ivanetich, 1984) as a probable metabolic product of *"in vivo or hepatocyte"* metabolism of VDC.[vi] Unfortunately, it is difficult to verify/confirm this finding because specific attempts at isolating this compound are not obvious in similar metabolism studies, and the methods employed in most of the other studies do not seem comparable to the methods employed by this duo (i.e. whole cell incubation in Costa and Ivanetich versus microsomal oxidation in some of the other studies). We

think it is important to clarify whether DCA is an *in vivo* metabolite of VDC. DCA has been identified as a cardiac teratogen (although at high doses), and cardiac defects are one of the controversial observed adverse effects of VDC exposure. It is also a metabolite of sister compound Trichloroethylene.

Developmental Toxicity: Our opinion of the developmental toxicity database is that the data are inconclusive regarding cardiac teratogenicity, and more data is required to resolve this issue with some level of certainty. The Dawson studies (1990 and 1993) are the only studies that report findings of cardiac defects in rats exposed to VDC throughout pregnancy. These data were dismissed in EPA's IRIS review of VDC. Reasons presented include methodology (*"a much more thorough investigation than is done in standard developmental toxicity protocols"*), statistical attributes of the data (*"no information on the background rates of these cardiac changes.."*, incidence data on pups rather than litters was reported), and non-reproducibility of the findings by other studies.

> *Reproducibility:* None of the studies has the same exposure pattern in the Dawson study in which exposure occurred throughout pregnancy. This difference was noted in the IRIS assessment - "*…however, in this study exposure to 1,1-DCE did not occur throughout pregnancy*. Exposure timing during pregnancy is critical because of the different windows of susceptibility that may vary with individual chemicals. The only way to avoid speculation about the relevance of this difference is to duplicate this study. The Fisher et al (2001) study (the strongest opposition to the Dawson study) does not duplicate the exposure pattern in the Dawson study.
>
> *Methodology and statistical analysis:* These are data quality issues. Resolution will require acquisition of *better quality* data – nothing short of duplicating the Dawson study and collecting the data the correct way.

The EPA after much deliberation during the IRIS review for VDC wrote that *"….EPA cannot conclude that the observed cardiac changes were caused by exposure to DCE"*. (www.epa.gov/IRIS) This statement does not say or imply that the EPA concludes VDC is not a teratogen. Rather it implies the agency is unable to make a definitive statement regarding this issue because of the data inadequacy.

The VCCEP program is a clear opportunity to resolve the Dawson findings. There are a number of ways to do this, all of which will require data acquisition/further testing. Given that this program specifically addresses risks to children, the risk characterization and data needs assessment cannot conclude that there is no risk or need for data when we clearly lack sufficient data.

Cancer: The review of the data on cancer is incomplete in the submission. Maltoni et al (1985) exposed Swiss male mice via inhalation to 0, 10 and 25ppm of VDC for 4hrs/d, 4-5days/wk for 52 weeks.[vii‡] They found pulmonary adenomas. The incidence data were statistically significant in both genders (combined, males and females). The data as presented in the IRIS file is as follows:

Gender	Dose	Incidence (%)	p-value
Combined	0, 10, 25ppm	12/331 (3.6%); 14/58 (24.1%); 41/288 (14.2%)	<0.01
Females	same	3/185 (1.6%); 6/30 (20%); 16/148 (11%)	<0.01
Males†††	same	9/190 (4.7%); 8/30 (26.7%); 25/150 (16.7%)	?

The dose-response curves in these incidence data are atypical (non-linear) and it was determined in the IRIS assessment on this basis that *"a clear dose response curve"* was not available. Given that the epoxide is produced in the clara cells[2], the consistency across gender and the statistical significance of the pulmonary adenomas, it is unlikely that these results are by chance. We recommend a review of this study because it might be relevant to the interpretation of cancer risk.

Charge 12: Do you agree with the conclusions of the risk characterization?
We disagree with the conclusions of the risk characterization for reasons discussed above. Summarized, our reasons are data gaps and incomplete analysis and interpretation of existing data. Also, the Margin of exposure analysis cannot be complete without consideration of all possible exposure scenarios.

Charge 13: Does the data needs assessment identify all the additional information needed to adequately characterize the potential hazards, exposures, and risks to children and prospective parents?
No. Refer to other comments.

Charge 14: Are any additional toxicity studies from the next tier needed? If so explain their value.
Yes. Additional toxicity studies, e.g. developmental toxicity, metabolism and pharmacokinetics (Tier2) are needed. Also the submission refers to standard protocol studies that evaluate neurotoxicity but have no references for these studies. These references should be cited and discussed in section 6.11 of the submission. This is particularly important because the IRIS assessment states that *" there are no focused studies on neurotoxicity, but no indication from chronic, developmental and reproductive assays in rats and mice by oral or inhalation exposure that neurotoxicity is an important toxic endpoint"*. Our reading of this statement is the *unfocused* studies did not pick up exaggerated (compared to subtle) neurotoxicity. ATSDR also concluded that *"Studies by the inhalation, dermal and oral routes as well as tests for neurological impairment in animals, might provide information that could be relevant to humans"*.[viii] (Section 2.9.2 – data needs) This suggests they did not identify neurotoxicity data.
We acknowledge the Dev. Neurotox study by Short et al (1977) cited in the submission might address some of the data needs (inhalation exposure in particular) for VCCEP. However we

†Data for males was not available in the IRIS file. However, # of males was derived by subtracting incidence (numerator in females) from incidence in the "combined" group. The denominator used is the original number of male animals per dose group at onset of study.
‡This piece of literature (more importantly data) is not included in the submission.

would like clarification on whether it is a straight substitute for the neurotoxicity test. We suggest that if there is specific mention by the authors of other studies alluded to in the submission of having evaluated defined neurotoxicity endpoints, such information should be included and cited. Otherwise, at least one study evaluating this endpoint is necessary.

Charge 15:Are any additional exposure data or analyses from the next tier needed? If so explain their value.

Not sure which tier the exposure data discussed on page 1 refers to but we recommend acquisition of exposure data from contaminated sites.

Minor corrections.

Page 70, section 7.2, the USEPA IRIS file used is the 2001 file, not 2000. It became an official document in 2001.

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[i] Forkert, PG. (1999) In vivo formation and localization of 1,1-Dichloroethylene epoxide in murine liver: Identification of its glutathione conjugate 2-S-Glutathionyl Acetate. J. Pharm Exp Ther. 290 (3):1299-1306

[ii] Forkert PG (2001) Mechanisms of 1,1-Dichloroethlyene-induced cytotoxicity in lung and liver. Drug Metab. Rev. 33 (1):49-80

[iii] Jones BK and Hathaway DE (1978) The biological fate of Vinylidene chloride in rats. Chemico-biological Interact 20:27-41

[iv] Dowsley, TF et al. (1995) Reaction of Glutathione with the electrophillic metabolites of 1,1-Dichloroethylene. Chemico-biological Interact. 95:227-244

[v] Dowsley TF et al. (1999) Cytochrome P-450 dependent bioactivation of 1,1-dichloroethylene to a reactive epoxide in human lung and liver microsomes. J. Pharm Exp Ther. 289(2):641-648

[vi] Costa AK and Ivanetich KM (1984) Chlorinated Ethylenes: their metabolism and effects on DNA repair in hepatocytes. Carcinogenesis 5:1629-1636.

[vii] Maltoni, C, Lefemine, G, Cotti, G., et al. (1985) Experimental Research on Vinylidene Chloride In: Maltoni, C., Mehlman MA. Eds. Archives of Research on Industrial carcinogenesis. Vol III. Princeton, NJ: Princeton Scientific

[viii] ATSDR (1994). Toxicological Profile for 1,1-Dichloroethene

APPENDIX E

Sponsor Presentation Slides

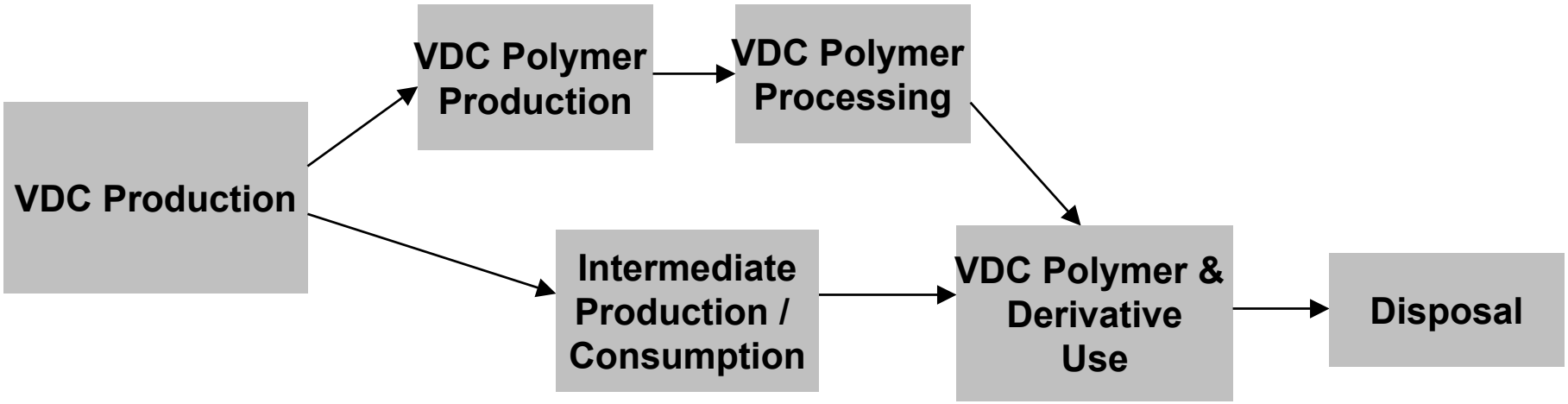
Vinylidene Chloride (VDC) VCCEP Review

Connie L. Deford

Global Environment, Health & Safety Manager

Industrial Chemicals

Vinylidene Chloride: VCCEP Review



- VDC is produced, distributed and consumed in closed systems
- Physical/chemical properties minimize potential for VDC exposure
- Chain of commerce for VDC is well understood; single producer and few users limits ability to share details
- Comprehensive product stewardship program exists to manage risks associated with VDC production, distribution, customer consumption & disposal

As part of Dow's ongoing commitment to product stewardship, Dow has previously evaluated VDC for its effects on human health & the environment; through participation in VCCEP, Dow has updated these health & environmental assessments

Exposure Assessment for Children's Health - Vinylidene Chloride (VDC)

Don Fontaine Ph.D.

Chronic Risk Assessment and Math Modeling

Toxicology, Environment, Research, and Consulting

Our Approach

- Biased sampling of the extensive monitoring data
  - Exaggerated estimates of the ambient inhalation and oral tap water exposure distributions.
- Exaggerated exposure scenarios where less monitoring was available (indoor air, food, dermal).
- Compounded the conservatism by adding the extremes of the exposure distributions from each exposure scenario.

Exposure Routes Considered in the Analysis

- **Inhalation**
  - Ambient air (20,000 measurements)
  - Indoor air (Exaggerated Carpet Backing Scenario)
    in lieu of measurements in 125, 14*, and 691* homes.
- **Oral**
  - Public water supplies (65,000 measurements)
  - Food (Exaggerated Food Wrap Scenario)
- **Dermal**
  - Contact with a product made of a polymer that contains residual monomer

*Data obtained from comments after the submission.

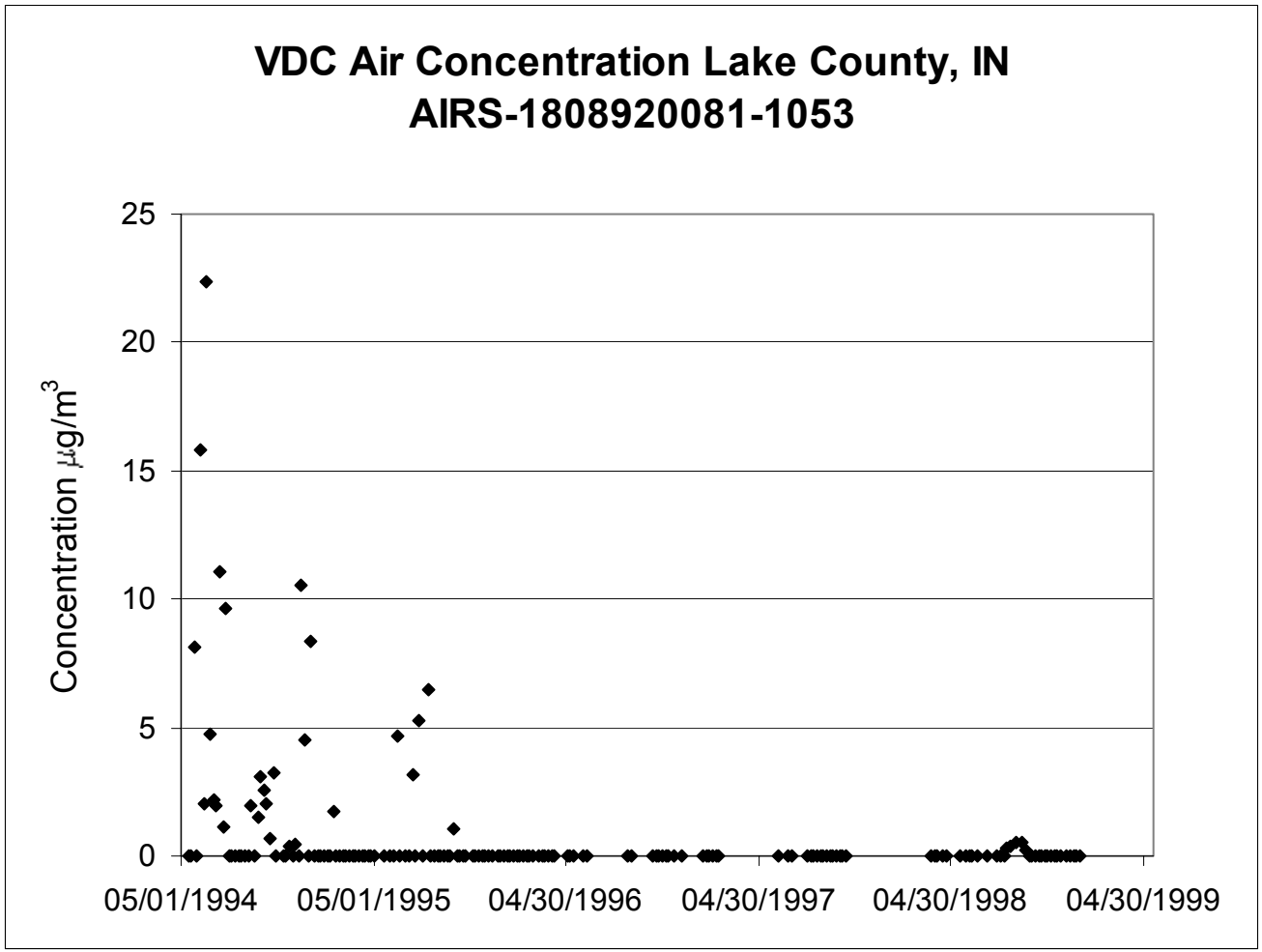
Aggregate Exposure

- Screening - Exposures from different routes are put on a common basis and added.
- Air Concentrations ($\mu g/m^3$) are converted to dose (μg/kg-day), assuming 100% absorption and appropriate inhalation rates.
- Aggregated exposure is compared to the RfD guidance level (50 μg/kg-day) to give a margin of safety or the $BMDL_{10}$ (4600 μg/kg-day) to give a margin of exposure.

Outdoor Ambient Air - Inhalation

- Vast majority of the 20,000 monitoring values are extremely low, and 90% are nondetectable.
- Detectable values occur sporadically.
- Analysis biased by using only the 10% of the data that were above the detection limits (range 0.02 to 69.4 $\mu g/m^3$).
- Monte Carlo Analysis using regulatory guidance for distributions for children's exposure factors.
- Every estimated exposure is far less than the regulatory guidance (RfC 200 $\mu g/m^3$) for safe exposure.

Outdoor Ambient Air - Inhalation



Oral - Tap Water Ingestion

- Vast majority of the 65,000 monitoring values are extremely low, and 98.5% are nondetectable.
- Detectable values occur sporadically.
- Exposure Analysis assumed exposure to at least the detection limit.
- Monte Carlo Analysis using regulatory guidance for distributions for children's exposure factors.
- Every estimated exposure is far less than the guidance (RfD) for safe exposure.

Indoor Air - Inhalation

- Modeled indoor air - residual monomer in Carpet Backing
  - Maximum residual monomer in latex backing and an above average amount of latex in carpet.
  - All interior space carpeted, replaced every five years.
  - No loss prior to installation.
  - All lost to interior space after installation.
- Estimated exposure is far less than the guidance (RfC) for safe exposure.

Oral - Residual Monomer in Food Wrap

- FDA screening calculation to estimate exposure.
  - Maximum residual monomer in food wrap.
  - All 3 kg food/drink is wrapped. 5% of wrap is PVDC copolymer.
  - 212º F peanut oil extract - less than detection limit.
  - Assume wrapped food extracts the detection limit.
- Estimated exposure is far less than the guidance (RfD) for safe exposure.

Scenario Aggregate Childhood Exposure Estimate

	Central Tendency Exposure ug/kg-day	High End Exposure ug/kg-day
Ambient Air (20% of time)	**0.024**	**0.072**
Indoor Air – Carpet (80% of time)	**0.023**	**0.027**
Drinking Water	**0.008**	**0.014**
Oral - Food Wrap	**0.010**	**0.0375**
Total Exposure	**0.065**	**0.15**

RfD = 50 μg/kg-day

Exceptional Cases

- Vapor migration into indoor air above contaminated ground water plumes.
- Many homes nondetect (98/691@ 0.04 $\mu g/m^3$ LOD and 4/14 @ 0.4 $\mu g/m^3$ Reporting Limit)
- No air measured in homes exceeded the RfC (200 $\mu g/m^3$)

Conclusion

- Robust Exposure Analysis
  - Extensive monitoring data combined with children's specific exposure factors.
- Exposure for children is uncommon and at a very low level.
- Rare exceptions are associated with groundwater containing methyl chloroform (banned in 1995).

VDC Hazard Data

TIERED APPROACH

TIER I

- Acute Oral & Inhalation Toxicity Studies
- *In Vitro* Gene Mutation Assays
- *In Vitro* and *In Vivo* Cytogenetics Assays
- Repeated Dose Toxicity Studies (no effects on reproductive, nervous or Immune system tissues)
- 3-Generation Reproduction Study

TIER II

- *In Vivo* Bone Marrow & Erythrocyte Cytogenetics Assays
- Repeated Dose Toxicity (Subchronic) Studies (no effects on reproductive, nervous or Immune system tissues)
- Developmental Toxicity Studies (2 species)
- Metabolism & Pharmacokinetics Studies

Immunotoxicity Study

TIER III

- Chronic Toxicity & Carcinogenicity Bioassays

Neurotoxicity Screening Battery

Developmental Neurotoxicity Study

TIER II

Immunotoxicity:

- Ban *et al*. (2003) reports minimal enhanced local LN & splenic PfC response.
  - Enhanced response is not “immunotoxicity” (OPPTS)
  - Same response with known suppressant, CCl_4.
  - Variable data - suggests a response to irritation.
- No lesions in immune system tissues from multiple repeated dose toxicity studies.

TIER III

Neurotoxicity Screening Battery:

- No lesions in CNS or peripheral nervous system tissues from multiple repeated dose toxicity studies.
  - Subacute, subchronic & chronic duration
  - Multiple species developmental toxicity Studies
- No clinical effects noted in multiple studies.

TIER III (Con't.)

Developmental Neurotoxicity Study:

- No developmental lesions in CNS (or decreased survival) reported following *in utero* exposure.
  - Multiple developmental toxicity studies
  - 3-Generation reproduction study
- No behavioral effects observed in neonate rats (pd 1-21) following *in utero* exposure to toxic levels (≤283 ppm) on gd 8-20 (Short *et al*., 1977).

Potential Age-Related Effects

- Developmental Toxicity - Reported increases in heart malformation (total) rate (Dawson *et al*.).
  - Previous work in chick embryos & *in utero* infusion
  - No dose-response, high control levels
  - Not reproducible (trichloroethylene work)
  - Not supported by other VDC developmental studies
  - IRIS Scientific Review Board could not conclude a treatment-related effect

CONCLUSIONS

Extensive Hazard Database

- Most Tier I-III categories filled with multiple studies in multiple species.
- Study “Overlap” provides coverage of immunotoxicity and neurotoxicity endpoints.
- No evidence of unusual age-related sensitivity, including behavioral studies of pups.
- Further use of animals or resources not warranted.

Risk Assessment for Children's Health - Vinylidene Chloride (VDC)

Don Fontaine Ph.D.
Chronic Risk Assessment and Math Modeling
Toxicology, Environment, Research, and Consulting

Exposure Summary

- Biased sampling of the extensive monitoring data and exaggerated scenarios were used to provide exaggerated estimates of exposure. The estimated exposure is at a very low level.
- Consistent with properties and use as an intermediate, primarily for the manufacture of polymers.

Aggregate Exposure

- Screening - Exposures from different routes are put on a common basis and added. Compounded conservatism.
- Aggregated exposure is compared to the RfD guidance level to give a margin of safety or the $BMDL_{10}$ to give a margin of exposure.

Guidance Levels

- USEPA IRIS RfD chronic oral exposures - noncancer effects. 50 μg/kg-day
- Minimal effect level for critical effect in chronic tox studies - $BMDL_{10}$ - 4600 μg/kg-day
- USEPA IRIS RfC chronic inhalation exposures - 200 $\mu g/m^3$.

Margins of Exposure and Safety

Typical Childhood Exposure - Margin of Safety

	Central Tendency Exposure ug/kg-day	Margin of Safety RfD/Exposure	Margin of Exposure $BMDL_{10}$/Exposure
Ambient Air (20% of time)	0.024	2100	190,000
Indoor Air – Carpet (80% of time)	0.023	2200	200,000
Drinking Water	0.008	6250	575,000
Oral - Food Wrap	0.010	5000	460,000
Total Exposure	**0.065**	**770**	**71,000**

Margins of Exposure and Safety

High End Childhood Exposure - Margin of Safety

	High End Exposure ug/kg-day	Margin of Safety RfD/Exposure	Margin of Exposure $BMDL_{10}$/Exposure
Ambient Air (20% of time)	0.072	690	64,000
Indoor Air – Carpet (80% of time)	0.027	1900	170,000
Drinking Water	0.014	3600	330,000
Oral - Food Wrap	0.0375	1300	120,000
Total Exposure	**0.15**	**330**	**31,000**

Conclusions

- Margins of Safety for children are large, typically greater than 770.

- Margins of Exposure for children are very large, typically greater than 71,000.

VDC VCCEP Review

Data Needs Assessment

Risk = Exposure x Hazard

Exposure Characterization

- Extensive monitoring effort over a long period.
- Limited potential for child exposure.
  - Primarily “closed system” industrial use
  - Insignificant residue in polymer products
  - Minimal loss to the environment
- Not warrant further, specific VDC, monitoring.

Risk = Exposure x Hazard

Extensive Hazard Database

- Most Tier I-III categories filled with multiple studies in multiple species.
- Study “Overlap” provides coverage of immunotoxicity and neurotoxicity endpoints.
- No evidence of unusual age-related sensitivity, including behavioral studies of pups.
- Not warrant further use of animals or resources.

Risk = Exposure x Hazard

Risk Modeling

- Primary contact scenarios evaluated.
- Employ very conservative assumptions.
- Theoretical exposures many orders of magnitude lower than acceptable “safe” levels.
- Exceptional exposure scenario less than RfC.
- Not warrant further, specific VDC, monitoring.

No further specific exposure monitoring or hazard evaluation studies of VDC are warranted because:

- **Extensive exposure data indicate minimal potential exposure of children *in utero* or as neonates.**
- **Extensive hazard data do not suggest an unusual sensitivity of children either *in utero* or as neonates.**
- **Modeling of risk under exaggerated conditions do not suggest a potential risk of children.**

APPENDIX F

Dow Rough Estimation of Dermal Exposure from Contact with Food Wrap Film

Dermal Contact Exposure Estimate
Food Wrap Film

Assumptions:

Residual Monomer — 5 ppm — $\frac{5\ \mu g\ \text{monomer}}{g\ \text{film}}$

Density of food wrap film
— $0.02\ g/in^2$ film

Dislodgeable residue of monomer on surface
— 1% of monomer content

Number of hand contacts/day — 100

Fraction absorbed — 100%

Area of hand contact — $10\ cm^2$

from carpet no plausible exposure scenario

100% was released into air

Daily Dose

$$5\left(\frac{\mu g\ \text{monomer}}{g\ \text{film}}\right)\left(10\ \frac{cm^2}{\text{contact}}\right)\left(100\ \frac{\text{contacts}}{\text{day}}\right)\left(\frac{0.02\ g/in^2\ \text{film}}{6.45\ \frac{cm^2}{in^2}}\right)(0.01)$$

~~0.00~~0.16 $\frac{\mu g\ \text{monomer}}{\text{day}}$

for 70 kg adult

$\approx 0.002\ \mu g/kg\text{-day}$