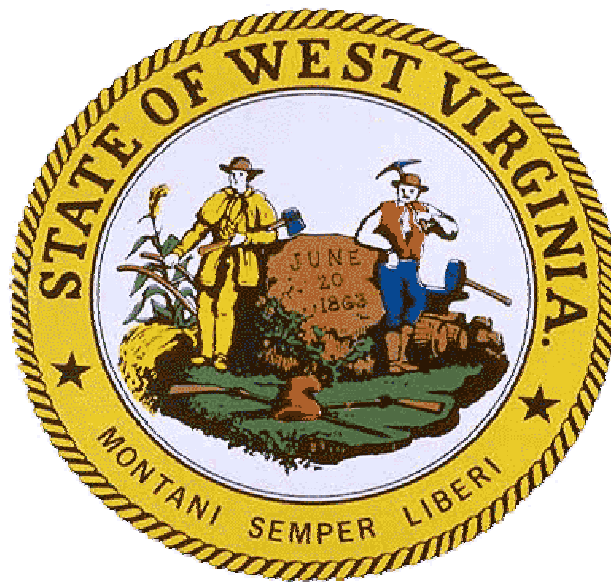# FINAL

AMMONIUM PERFLUOROOCTANOATE (C8)

ASSESSMENT OF TOXICITY TEAM (CATT) REPORT

August 2002

Department of Environmental Protection - *promoting a healthy environment*

EXECUTIVE SUMMARY

Pursuant to a consent order signed November 14, 2001 between the West Virginia Environmental Protection and Health and Human Resources departments, and E. I. Du Pont de Nemours, Inc. (DuPont) the C8 (ammonium perfluorooctanoate) Assessment of Toxicity Team (CATT) was established to:

 (1) determine risk-based human health protective screening levels (SLs) for this unregulated chemical in air, water, and soil;

(2) provide health risk information to the public; and

(3) determine an ecological health protective SL for C8 in surface water.

To date, two public meetings have been held in the vicinity of the DuPont Washington Works facility located near Parkersburg, West Virginia. Also, a team of 10 expert toxicologists have met and determined human health provisional risk factors for the oral and inhalation routes of exposure, and calculated health protective SLs based on these risk factors using Region 9 U.S. Environmental Protection Agency standard methodology. The results of the CATT's investigation are presented in summary below. The ecological SL for surface water currently is still in development. An addendum to this report is expected to be released in Fall 2002 presenting the surface water SL findings.

The methodology, overall process, and rationale utilized by the CATT to develop these risk factors and SLs are discussed, the members are listed, and a synopsis of the events leading to the consent order are presented herein. The intent of this report is to document the process and conclusions of the CATT in an effort to provide to the public a record of these activities. It is not intended to be a summary of all the toxicology information available on C8.

The risk factor or Reference Dose (RfD) for the oral route of exposure determined by the CATT for C8 was 0.004 milligrams per kilogram of body weight per day (mg/kg-day). A risk factor for the inhalation route of exposure or the Reference Concentration (RfC) of 1 micrograms per cubic meter of air ($\mu g/m^3$) was determined. The RfD or RfC is defined by EPA as an estimate (with uncertainty spanning perhaps an order of magnitude or greater) of a daily exposure level for the human population, including sensitive subpopulations, that is likely to be without an appreciable risk of deleterious effects during a lifetime. Based on the oral RfD, health protective SLs were calculated for water of 150 parts per billion (ppb), and for soil of 240 parts per million (ppm). Based on the inhalation RfC, a health protective SL of 1 $\mu g/m^3$ was derived for air.

ACKNOWLEDGEMENTS

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1.0 INTRODUCTION

The investigation described herein was conducted pursuant to the November 14, 2001 Consent Order Number GWR-2001-019 between the West Virginia Departments of Environmental Protection (DEP) and Health and Human Resources (DHHR), and E. I. Du Pont de Nemours, Inc. (DuPont). A copy of this consent order is included as Attachment I. These actions were instigated by the presence of an unregulated chemical, ammonium perfluorooctanoate commonly called C8, in the Lubeck, W.Va. public water supply which is near the DuPont Washington Works (WW) facility in Washington, W.Va. A site map is included in Attachment IIc.

The consent order established two scientific teams: (1) the C8 Assessment of Toxicity Team (CATT), and (2) the Groundwater Investigation Steering Team (GIST). The CATT was tasked with investigating the toxicity of C8; developing provisional risk factors for the inhalation, dermal, and oral routes of exposure; and establishing human health protective screening levels (SLs) for air, water, and soil; investigating the ecological toxicity of C8 and determining an ecological health protective SL for surface water; and with communicating health risk information to the public. In the consent order DuPont agreed to meet these SLs at their WW facility, once developed, and that these SLs would remain in effect until superseded by U.S. Environmental Protection Agency (EPA) guidance. The CATT's activities and findings regarding the toxicity of C8, development of risk factors and SLs are presented in detail in Section 2 of this report. Slides presented at the two public meetings held thus far are provided in Attachment II. The investigation into the ecological toxicity of C8 and surface water SL development is scheduled for completion in Fall 2002. When finished, the surface water will be presented in an addendum to this report.

The GIST was established by the consent order to determine the extent and concentration of C8 in both groundwater and surface water. The activities of the GIST continue as of the issuance of this CATT report. The GIST will issue a report on the C8 analytical data for groundwater and surface water when that work is finished, scheduled for early 2003. Interim reports are available through the DEP Division of Water Resources (DWR). The groundwater investigation focused not only on the WW plant, but also on areas where C8 had been disposed, including the Local Landfill (on WW property), Dry Run Landfill (near the WW plant), and the Letart Landfill (30 miles south of the WW plant). Maps of the one-mile radius study area around these locations are included in the presentation of interim results at the second public meeting provided in Attachment IIc.

Summarized findings to date by the GIST are compared to the health protective water SL developed by the CATT in Section 3.0. Results of air dispersion modeling efforts thus far conducted by the DEP Division of Air Quality (DAQ) are compared to the air SL in Section 3.0 as well.

Background

The DuPont WW plant is located approximately 10 miles southwest of Parkersburg, W.Va. along state Route 61 in the rural hamlet of Washington, W.Va. This facility was established in the 1940s and currently is one of the largest DuPont enclaves in the world. DuPont has used C8 at this facility for more than 50 years as a surfactant in various manufacturing processes, including the production of Teflon. "C8" is the 3M trade name for its product that contains ammonium perfluorooctanoate (APFO) (CAS # 3825-26-1).   In biologic media, APFO quickly dissociates to perfluorooctanoate, which is the anion of perfluorooctanoic acid (PFOA). The PFOA form has been identified as potentially toxic to animals. Throughout this report, C8 is used as terminology to include C8, APFO, or PFOA.

The DEP became aware of and began investigating the presence of C8 in the Lubeck, W.Va. public water supply in November 2000. In Spring 2001, DEP received a letter requesting a formal agency investigation into DuPont's environmental releases of C8 and the presence of C8 in the Lubeck drinking water from attorneys representing a few citizens residing in proximity to the WW plant. The Lubeck public water supply well field lies approximately 3 miles south of the DuPont WW plant. Also around this time, DEP became aware that C8 was chemically similar to perfluorooctane sulfonate (PFOS), another perfluorocarbon manufactured by 3M, and that 3M had recently removed their Scotchguard product from the marketplace because it contained PFOS. From U.S. EPA Region 3 and Headquarters, DEP learned that 3M had undertaken a significant research effort into the toxicity of perfluorocarbons, particularly PFOS and including C8; that perfluorocarbons were potentially more toxic than previously thought; that 3M was submitting the new data to EPA under the Toxic Substances Control Act (TSCA); and that these data were publicly available under Administrative Record 226 (AR226). Additionally, DEP learned that DuPont was submitting toxicity data on C8 to EPA, as well.

DEP gathered data and met with DuPont and met with citizens attorneys in Spring 2001. The DEP, which regulates groundwater in West Virginia, was joined in the investigation by the DHHR, which regulates drinking water. The DHHR requested support from EPA Region 3 to enforce the National Safe Drinking Water Act. At the request of these agencies, DuPont supplied information regarding C8 and its use in manufacturing processes, its toxicity, and emissions. After several months of investigation and discussions, a consent order was signed in November 2001. A copy of the consent order is provided in Attachment I. It describes the tasks and members of the CATT and GIST. The DEP informed the public of the consent order and scheduled a public meeting to discuss the order.

The DEP held it's first public meeting regarding C8 on November 29, 2001 at Blennerhassett Junior High School which is located near the Lubeck and Washington communities. The meeting was spearheaded by the CATT and the GIST. The purpose of the meeting was to inform citizens of: (1) the requirements of the consent order; (2) the members and activities of the GIST; (3) their assistance was required to fill out and return a water use survey if they had groundwater wells, cisterns, or springs (particularly those used for drinking water), and to allow sampling of these water sources; (4) the members and activities of the CATT; (5) the available information regarding the toxicity of C8; and (6) the known current levels of C8 in the Lubeck public water supply, which were below 1 part per billion (ppb). At this meeting, James Becker, M.D. of Marshall University spoke regarding environmental exposures and risks in general, and Dee Ann Staats, Ph.D. (DEP) explained the CATT and GIST activities, the consent order, and known toxicity of C8. The slides from both presentations are provided in Attachment IIa.

By the end of January 2002, contractors were in place to assist the CATT and the GIST in their tasks. The GIST was headed by DEP and had members from DHHR, EPA, and Dupont. The CATT was headed by DEP and had members from DHHR, EPA, DuPont and the Agency for Toxic Substances Disease Registry (ATSDR). The DEP contracted with the National Institute of Chemical Studies (NICS), a nonprofit organization, which subcontracted the human and ecological toxicology work to the Toxicology for Excellence in Risk Assessment (*TERA*) group, also a nonprofit, which subcontracted the ecological toxicology work to Menzie Cura & Assoc., Inc. (MC). Both *TERA* and MC are well respected in the field of toxicology. The NICS subcontracted the risk communications tasks to Marshall University.

In March 2002, EPA Regions 3 and 5 signed a consent order with DuPont requiring the provision of alternative water to any resident in West Virginia or Ohio with C8 in drinking water at levels above 14

ppb. The 14 ppb was an interim value in effect until the water SL was developed by the CATT. This value was taken from the final report by ENVIRON Int. Corp. (a consulting firm hired by DuPont) titled "A Hazard Narrative for Perfluorooctanoate (PFOA)", January 2002. An earlier draft, "A Review of the Toxicology of Perfluorooctanoate (PFOA)", November 2001, had proposed a drinking water value of 210 ppb. However, DEP's toxicologist, Dr. Staats, expressed concern over some of the assumptions made in the calculation of the 210 ppb to DHHR and EPA Region 3. The outcome of these discussions was a decision that a very conservative approach should be taken in the interim until the CATT water SL was developed. Therefore, 14 ppb was accepted as the interim water SL for alternative water provision. Note that this consent order was jointly signed by two regions of EPA because West Virginia is in Region 3 and Ohio is in Region 5. During the investigation, C8 had been found in the Little Hocking, Ohio public water supply. Also, note that DEP and DHHR invited Ohio EPA to join the CATT and GIST as observers, but not as members because this would have required renegotiating the consent order between West Virginia and DuPont.

TERA was assigned by DEP to review and compile the C8 toxicological information provided by DEP and to prepare for and hold a meeting of the CATT toxicologists during which the provisional risk factors and health protective SLs would be derived. The CATT toxicologists panel was comprised of 10 expert scientists with a collective span of experience of over 175 years and many specialties including endocrinology, veterinary medicine, cancer, and risk assessment.

TERA's efforts are described further in Section 2.1. By mid April 2002, *TERA* was prepared for the meeting. Also, *TERA* helped prepare the other toxicologists for the meeting by providing toxicity reports and summary information. The CATT toxicologists met on May 6 and 7, 2002 at EPA offices in Cincinnati, Ohio. The minutes of this meeting are provided in Section 2.2. The meeting lasted approximately 18 hours with roughly one-third of that time spent in discussions of C8's potential carcinogenicity. The oral provisional reference dose (pRfD) risk factor, and the two health protective SLs (for water and soil) based on this risk factor were developed at this meeting. The panel agreed that the toxicology database was insufficient to develop a dermal exposure pRfD. The inhalation provisional reference concentration (pRfC) risk factor and air SL developed at the meeting were only interim because additional data collection was necessary for their calculation. These data were collected and provided to *TERA*, who calculated the final pRfC and air SL, wrote a report describing this activity and forwarded it to the other CATT toxicologists for their approval. This document is provided in Section 2.3 as the post meeting action items. Both the meeting minutes and the post meeting action items were reviewed and approved by the panel of 10 highly qualified toxicologists.

An internal briefing for the DEP, DHHR, and EPA was held on May 8, 2002 to discuss the water and soil SLs. Rather than withhold this information while the meeting minutes report was prepared, DEP released the water and soil SLs so that the public would be informed of the status of their drinking water, and decisions could be made regarding the provision of alternative water supplies. In that spirit, DuPont and the public were informed – via a meeting with the above regulators and a press release, respectively - of the water and soil SLs on May 9, 2002.

A second public meeting was held at Blennerhassett Junior High School on May 15, 2002, to inform the public of the details of the SL development and of the groundwater C8 concentrations that had been detected at that point. Dr. Becker first spoke regarding environmental health risks in general. Dr. Staats described the process used by the CATT toxicologists to arrive at the water and soil SLs. Finally, David Watkins (DEP, GIST chairman) presented the C8 analytical data for private and public water sources. Slides of the presentations given at this meeting are provided in Attachment IIb.

2.0 DEVELOPMENT OF RISK FACTORS AND SCREENING LEVELS

TERA was assigned to prepare for, host and document the meeting of the CATT toxicologists during which the provisional C8 risk factors (pRfDs and pRfC) would be developed by the group. The activities undertaken by *TERA* to prepare for the meeting are presented in Section 2.1. The actual minutes of the meeting are provided in Section 2.2., and the tasks conducted by *TERA* to develop the final air SL after the meeting at the direction of the panel are described in Section 2.3.

2.1 Pre Meeting Action Items

TERA is a nonprofit [501(c)(3)] corporation dedicated to the best use of toxicity data for the development of risk values. This organization is very well known and respected in the toxicology arena for their professionalism, wealth of knowledge, experience, and unbiased approach to deriving risk factors. All the non-*TERA* toxicologists on the CATT, whether from government agencies or industry, were in unanimous support of including *TERA* in this project.

TERA was tasked with compiling and reviewing the available toxicological data for C8. A literature search and review of these data was in draft by EPA Headquarters, this document was provided to *TERA*. The 3M submittals to AR-226 were provided to *TERA* by DEP. These data grew from a total of seven compact discs to 10 during the time period of this project. The AR-226 continues to grow with 3M submittals currently. The index of the first seven discs are provided in Attachment Va. Additionally, DEP conducted a literature search of C8 toxicity data on the National Library of Medicine's Medline and Toxline databases in June 2001. The results of these searches were provided to *TERA* by DEP as well. Also, documents submitted to DEP from DuPont in response to the EPA Region 3 request for information was made available to *TERA* by DEP, first by mailing relevant toxicology documents identified by Dr. Staats, and then by physically delivering all these documents to their Cincinnati office for *TERA* to sort and identify those deemed relevant and necessary for their work. Therefore, little literature searching or data retrieval was required of *TERA*.

After reviewing the existing C8 toxicology data, *TERA* selected studies that would be suitable for derivation of risk factors for the oral, dermal, and inhalation route of exposure. A list of the potential key studies was prepared. An indepth review of these studies was then conducted, and the details of the studies were summarized in tabular format. Next, *TERA* prepared a condensed table of these studies including critical effects and exposure levels identified by *TERA*, and blank columns for the other criteria necessary in the risk factor development process, such as the uncertainty factors. The documents listed below were provided to the other CATT toxicologists approximately two or three weeks prior to the meeting. *TERA* also prepared tables of suggested uncertainty factors, risk factors, and resulting SLs to DEP. These documents were discussed with Dr. Staats but were not distributed to the other toxicologists prior to the meeting in an effort not to influence their decisions, and not to give the false impression that the decisions on risk factor development had already been made and that the panel's purpose was simply to review *TERA*'s work. Rather, *TERA*'s suggestions would be presented at the meeting as a starting point for panel discussions and the development of the risk factors and SLs would be done as a group. The pre-meeting documents provided to the rest of the panel by *TERA* and DEP are contained in Attachment III. Also in Attachment III is a more detailed description of the decisions and methodology used by *TERA* in suggested risk factor development.

2.2 CATT TOXICOLOGISTS MEETING MINUTES

Meeting of C8 Assessment of Toxicity Team (CATT) Toxicologists

May 6 and 7, 2002

Andrew W. Breidenbach Environmental Research Center, Cincinnati, Ohio

Attendees:

Voting Team Members

John Cicmanec, D.V.M., M.S., ACLAM, USEPA Office of Research and Development
Joan Dollarhide, M.S., M.T.S.C., J.D., Toxicology Excellence for Risk Assessment (*TERA*)
Michael Dourson, Ph.D., D.A.B.T., *TERA*
Gerald Kennedy, E. I. Du Pont de Nemours, Inc.
Andrew Maier, Ph.D., C.I.H., *TERA*
Samuel Rotenberg, Ph.D., USEPA Region 3
Jennifer Seed, Ph.D., USEPA Office of Pollution Prevention and Toxics (may abstain from voting)
Dee Ann Staats, Ph.D. (Chairperson), West Virginia Department Environmental Protection (DEP)
John Wheeler, Ph.D., D.A.B.T., Agency for Toxic Substances Disease Registry (ATSDR)
(representing West Virginia Department of Health and Human Resources [DHHR])
John Whysner, M.D., Ph.D., D.A.B.T. (consulting for DuPont)

Invited Guests

John Butenhoff, Ph.D., 3M Company (study director)
Jim Sferra, M.S., Ohio EPA (observer)

Note taker

Daniel Briggs, Ph.D., D.A.B.T., *TERA*

Introduction

The toxicologists on the C8 Assessment of Toxicity Team (CATT) met on May 6 and 7, 2002, to develop provisional reference doses (pRfDs) and screening levels (SLs) for ammonium perfluorooctanoate (C8) as specified in Consent Order GWR-2001-019 between the West Virginia Department of Environmental Protection, the West Virginia Department of Health and Human Resources, and E. I. Du Pont de Nemours & Co., (DuPont) dated November 14, 2001. These screening levels apply only to DuPont at their West Virginia facilities as specified in this consent order. Any use of these pRfDs or SLs for any other purpose or by any other regulatory agency is solely their choice and responsibility.

The meeting opened with Dr. Staats announcing that this meeting was being held pursuant to the above-cited consent order as part of an enforcement action and was therefore closed to the public. Dr. Staats noted that, except for Dr. Butenhoff and Mr. Sferra who were invited guests, the panelists were named as part of the consent order and were free to enter into discussions and vote on issues. It was noted that Dr. Seed could abstain from voting at any time. The rules for the meeting were set forth as follows:

- The panel would strive for unanimous consensus, but if such consensus could not be reached, then the majority of votes would rule.
- The panel was expected to be cooperative and courteous with each other.
- The risk factors and screening levels would be developed together as a group, rather than simply by reviewing the work and suggestions of *TERA*.
- Votes would be taken at each decision point. After panel discussion on each point, a motion would be made on the floor. The chair would then repeat the motion and verbally poll each panel member individually. The chair would always vote last in order to not influence the voting.

TERA recorded the official minutes for the meeting. However, the chair recorded supplemental notes, which were provided *TERA* to assist in the preparation of the final Meeting Minutes Report. It was noted that specific discussion comments or votes would not be attributed to panel members (i.e., no names would be used) in the meeting report in order to facilitate full and open discussion among the team. It was also noted that *TERA* would distribute a draft meeting report to the CATT panel for their review and incorporate panel comments as appropriate. Each panel member would be asked to sign a statement agreeing that the meeting report is an accurate representation of the discussion and conclusions of the CATT Team. The original signatures will remain on file with the DEP.

The sequence of discussion on Monday, May 6 was oral noncancer assessment; dermal noncancer assessment and on Tuesday, May 7 was cancer assessment; inhalation noncancer assessment; oral screening level; and interim inhalation screening levels. (Note that Dr. Seed left the meeting at 2:30 pm on Tuesday, May 7, 2002; she was present and joined in all discussions through the cancer assessment.) However, for clarity, the meeting report is organized according to noncancer (oral, dermal, inhalation) assessment, cancer assessment, and screening levels. Below, under each heading is a brief description of *TERA*'s opening comments, followed by the panel discussion, and then the outcome of the panel discussion.

Noncancer Assessment: Review of the Oral Studies

Prior to the meeting, *TERA* evaluated the available human and animal health effects studies for C8. (A list of the documents and studies included in *TERA*'s prior review is provided in the Attachments). *TERA* evaluated the pool of available studies to identify the key studies that could be selected by the CATT panel as the basis for the pRfD. In narrowing the list of available studies, the available data were evaluated weighing considerations such as observed effect levels, study duration and quality, and applicability to human health. The judgments were made in a manner consistent with hazard identification and dose-response assessment practices used in current U.S. EPA risk assessments. Studies were generally given greater consideration as potential principal studies if they were at least of subchronic duration; identified NOAEL/LOAEL boundaries on the low end of the range provided by all the data; and had robust design (e.g., diverse array of endpoints, sufficient number of animals). From the total pool of available studies, *TERA* developed detailed summary tables for each of the key

studies having potential for being selected as the principal study for derivation of the pRfD. The resulting detailed summary table of key studies was provided to the panel members prior to the meeting to facilitate the selection of the principal study by the CATT panel and is attached. Therefore, discussion of the oral studies at the meeting focused on the tables presented in the attachment which identified those studies of sufficient duration, content, and quality to merit consideration as the bases for deriving a pRfD. The tables present *TERA*'s selection of critical effect levels, and highlight the study data for key parameters that showed treatment-related changes.

At the opening of the meeting, the panel discussed whether all adequate studies had been included and whether any potential key studies were missing. One panelist asked why the 90-day Rhesus monkey study (Goldenthal, 1978b) had not been included. *TERA* responded that the Rhesus study was not considered to be as useful as the cynomolgus monkey study (Thomford et al., 2001) because it had fewer animals per group, and suggested a higher NOAEL/LOAEL boundary; however, findings from the Rhesus study would be discussed together with the cynomolgus study as supporting data. The panel confirmed that, to the best of their knowledge, the table included all of the toxicity work that should be considered in selecting principal studies for deriving the pRfD for C8.

After agreeing that all of the potential critical studies had been identified, the panel then discussed the merits of each of the studies, and the appropriate No-Observed-Adverse-Effect-Levels (NOAELs), Lowest-Observed-Adverse-Effect-Levels (LOAELs), and lower bounds on the benchmark doses (BMDLs) for each study.

Human Studies (Olsen et al. 2000; Olsen et al. 1998; Gilliland and Mandel 1996; Gilliland and Mandel 1993; Ubel et al. 1980)

TERA initiated the discussion by providing a brief synopsis on the potential utility of the available human health effects studies for deriving the pRfD. Two cohort mortality studies were available: (1) Ubel et al. (1980) reviewed the records of 180 deceased 3M employees for a period of 30 years (1948-1978) and found no significant difference between observed and expected mortality rates; (2) Gilliland and Mandel (1993) found no increases in mortality rates from liver cancer or liver disease in 3,537 (2,788 males and 749 females) exposed 3M workers for 35 years (1947 – 1983). Note that since the CATT meeting, a new epidemiological study on almost 4,000 (80% male) 3M workers has been completed which found no increase incidence of cancer in C8 exposed workers. Several cross-sectional studies of 3M workers (111, 80, and 74 males in 1993, 1995, and 1997, respectively) were available. However, these studies were noted as being limited for use in deriving the pRfD, since workers were exposed to unknown amounts of C8 for varying time periods, and no clear signs of toxicity (such as elevated serum levels of liver enzymes were reported). The mixed findings regarding changes in hormone levels were noted. It was noted that many of these studies provided data on serum levels of C8 (or serum fluorine levels), which could serve as a measure of exposure. However, the current toxicokinetics data were not viewed as sufficiently developed to conduct a quantitative extrapolation from the reported serum levels to equivalent oral doses in humans. Based on this introduction, the panelists were asked to comment on the human data and its usefulness for deriving the pRfD.

Key Panel Discussion Points: Panelists noted that, although limited, the existing human data are consistent with the animal data when exposure levels are considered. Although weaknesses in the epidemiology data were noted, one panel member commented that the human data are useful for hazard identification purposes, and provide some level of comfort in conducting the assessment since they do not identify adverse effects in chronically exposed workers. It was noted that a few of the

human subjects had C8 serum levels comparable to those observed in animal studies [20 parts per million (ppm) or greater]. Other panel members described gaps in the human studies. Regarding the absence of effects observed in the epidemiology studies, the panel noted that the small number of female subjects and uncertainties in exposure levels for workers prevents the existing data from being used to rule out human toxicity. For example, the very small numbers of women in the studies prevent drawing a conclusion regarding female reproductive effects. One panelist noted that the increased blood level of estradiol reported in some subjects is not clinically significant. In addition, no adjustments were made for body mass index (BMI) variations among subjects. Since BMI is known to affect estradiol levels and in this study BMI was the only parameter to correlate with hormone levels, it was noted that it is unlikely that C8 exposure was related to increased estradiol levels. The panel discussed Gilliland and Mandel (1986), which reported six prostate cancer deaths overall and four among exposed workers. One panel member commented on the update to this study (no study report was provided), which showed no indication of increased risk of prostate cancer. This follow up study demonstrated that only one of the four workers with prostrate cancer were determined to have been exposed when work history records and blood levels of C8 were examined.

It was suggested that it might be possible to correlate C8 serum concentrations with lack of observed toxicity to estimate a human NOAEL. However, it was noted that the lack of clear exposure levels in the human studies precluded this type of analysis. Although C8 half-life determinations were conducted in some of the human studies, this information cannot be used to determine exposure doses because some exposure to the subjects may still be occurring. However, it is clear that humans do not have the major sex-related half-life difference that exists in rats. It was noted that a physiologically-based pharmacokinetic (PBPK) model is being developed, which may be useful in estimating exposure concentrations from human serum C8 levels. However, a panel member familiar with the status of this current toxicokinetic modeling effort, noted that the data are not sufficiently developed to use for quantitative risk assessment purposes at this time.

Outcome: The panel agreed unanimously that the human studies were not adequate to be used for quantitative dose-response determinations. The human studies have many substantial data gaps, such as low numbers of subjects and unknown exposure concentrations. No LOAEL was established and the exposure uncertainty does not allow identification of a clear NOAEL. In final comments made during polling of the panel, one panel member agreed with the group, but noted that the data could be used to develop a bounding estimate. A second panel member added that some evidence suggests the endocrine system as a target for C8 effects, and therefore, the human data might support the animal toxicity studies.

Definition of Adverse Liver Effect

TERA noted that in all experimental animal studies liver effects occurred. For the purposes of conducting this assessment, *TERA* defined adverse liver effects as the presence of histopathology (moderate grade hypertrophy would be considered sufficient) in addition to statistically significant absolute or relative weight changes, or a liver weight change of 10% or greater. A doubling of serum levels of liver enzyme activity (e.g., alkaline phosphatase (ALP), aspartate aminotransferase (AST), or alanine aminotransferase (ALT)) would also indicate an adverse liver effect. These adverse effects are used by other health organizations as well. The panel unanimously agreed with this general definition of adverse for liver effects, but noted that individual studies could demonstrate a continuum of liver effects that could be considered biologically significant.

Palazzolo et al. 1993

This is a 90-day study in male rats in which animals received C8 at doses of 0, 0.05, 0.47, 1.44, and 4.97 mg/kg-day in feed. The major finding in this study was increased liver weight with histopathological findings such as moderate hypertrophy. Panelists were asked to comment on the data from this study; on the selection of study adverse effect levels; and on the usefulness of this study as the basis for deriving a pRfD.

Key Panel Discussion Points: The possible role of peroxisome proliferation in the observed liver effects was discussed. The panel discussed uncertainty in the relevance of this mechanism to humans. One panelist stated that when considering the relevance of peroxisome proliferation, it is important to consider both qualitative and quantitative issues. This panelist suggested that peroxisome proliferation may potentially occur in humans because the cellular receptor that modulates this reaction in rodents has been found in humans, but that this mode of action should be considered to be only qualitatively relevant to humans because the receptor is far less expressed in humans, and humans have not been shown to manifest a peroxisome proliferation response. It was noted that USEPA has an on-going project to investigate the relevance to humans of rodent peroxisome proliferation effects, but at this time EPA has no official policy on the significance of peroxisome proliferation for humans. It was also noted that IARC has also considered the issue of peroxisome proliferation and concluded that this mode of action is not relevant to humans if it has not been demonstrated to occur in human cells or primates treated with the chemical in question. (Note that the panel discussed the role of peroxisome proliferation as a potential mode of action for tumor formation later in the meeting. The results of this discussion are documented in the section on Cancer Mode of Action)

Discussion occurred regarding the usefulness of relative versus absolute liver weight in determining adverse effect levels. One panelist stated that changes in both of these parameters are preferred before designating a dose as an adverse effect level. However, most panelists considered a change in relative liver weight to be sufficient to designate a dose level as an adverse effect level. It was noted that liver weights in dosed animals in this study were comparable to control values after an 8-week recovery period; however, the panel agreed that this recovery should not influence selection of the NOAEL and LOAEL values.

Outcome: The panel agreed unanimously that 1.44 mg/kg-day is the LOAEL for this study because at this level statistically-significant increases in relative liver weight and CoA oxidase activity occur. In addition, hepatocellular hypertrophy of minimal severity or greater is observed in 14 of 15 animals at this dose, and in 2 of 15 animals at grade 2 or higher. The panel recommended that benchmark dose modeling be performed for the data based on grade 2 or higher hepatocyte hypertrophy. This modeling was conducted during the course of the meeting, resulting in a BMDL estimate of 1.3 mg/kg-day. It was noted that this BMDL is essentially the same as the LOAEL found in this study. Most panelists believed 0.47 mg/kg-day is the NOAEL because at this dose there are no statistically significant changes in either absolute or relative liver weight and only a "minimal" severity of hepatocellular hypertrophy is reported at this dose. However, one panel member preferred to call this a "minimal LOAEL" rather than a NOAEL, noting that dose-related changes in critical liver parameters had been established at the lower dose levels and suggesting that these could be part of the continuum of effects that might be considered a minimal LOAEL.

Goldenthal 1978a

This is a 90-day study in male and female rats in which animals received C8 in their feed at doses of 0, 0.56, 1.72, 5.64, 17.9, or 63.5 mg/kg-day for males and 0, 0.74, 2.3, 7.7, 22.4, or 76.5 mg/kg-day for females. This study is limited by the small number of animals (5/sex) in each dose group. Therefore, this study was not considered to be a key study. However, it was presented for the panel's consideration and comments because it includes female as well as male animals and the data on relative liver weights allow a BMD to be calculated.

Key Panel Discussion Points: One panelist noted that a sex difference was observed in this study. Another mentioned that this study demonstrates the importance of internal dose (C8 serum level), as compared to the administered dose.

Outcome: The panel agreed with the proposed NOAEL, LOAEL, and BMDL as presented by *TERA*. However, the panel also agreed unanimously that the study was not adequate to serve as the basis for deriving a pRfD because of limitations in the study (e.g., the small number of animals).

York 2002

This is a two-generation reproduction study in which male and female rats received C8 doses of 0, 1, 3, 10, and 30 mg/kg-day by gavage in distilled water. Parental animals were exposed through cohabitation and gestation to weaning of F1 animals, approximately 6 weeks. F1 animals were exposed from weaning until weaning of the F2 generation. The primary findings were increased liver weight and liver pathology in P and F1 generation male animals; however, it was noted that histology was conducted only when gross effects had been observed, and therefore liver histopathology data were not available for the control and low-dose F1 generation males.

Key Panel Discussion Points: One panelist stated that this was study was of excellent quality because it was conducted according to OPPTS guidelines for 2-generation studies. Two panelists noted that the degree of F1 generation exposure to C8 while *in utero* and while nursing was uncertain and may not have occurred at all because of rapid elimination of C8 from the systemic circulation of the female rats after it was administered via gavage. Therefore, the lack of reproductive toxicity in this study may not be meaningful. Other panelists agreed, but stated that the fact of rapid clearance resulting in decreased fetal exposure may not be relevant for humans because women do not have the same active secretory mechanism for C8 that exists in the female rat. Another panelist noted that rodent placenta provides less of an anatomical barrier than exists in primates. Another panelist observed that studies with radiolabeled C8 demonstrated that C8 could cross the placental barrier in rats. One panelist wondered whether female rat pups at weaning have developed the active secretory mechanism for C8 that exists in the mature females. Another panelist recalled data showing that weanling female rats were able to clear C8 faster than males, but not as fast as mature females. One panelist recommended that delayed sexual maturation and increased frequency of estrous cycles be included in the adverse effects noted for females for this study. A panelist pointed out that this study indicated a critical difference in the toxicity of C8 versus the structurally similar perfluorocarbon PFOS; in that PFOS caused fetal death at birth in a similarly designed study, while in this study C8 administration was associated with only a slightly statistically significant increase in fetal death at the post-weaning timeframe.

Outcome: The panel concluded that the LOAEL for males is 1 mg/kg-day. The males showed statistically-significant increases in liver and kidney weights at 1 mg/kg-day. No histology was conducted on liver and kidney at this dose level because no gross lesions were seen. However, given

the substantial histopathology noted at the next higher dose level (3 mg/kg-day), the panel believed pathology does exist at the 1 mg/kg-day level; therefore this level meets the agreed-upon definition of an adverse effect. The panel concluded that the LOAEL for females is 30 mg/kg-day. The females showed several adverse effects at this dose level, including increased mortality and decreased body weight. No NOAEL was identified for males; the NOAEL for females is 10 mg/kg-day. All of these values apply to both the P and F1 generation animals. Two panel members reviewed the BMDL modeling results, and agreed with the selection of 0.42 mg/kg-day as the study BMDL.

Riker Laboratories 1983

This is a chronic, 2-year study in male and female rats in which animals received C8 in feed at doses of 0, 1.3, and 14 mg/kg-day for males and 0, 1.6, and 16 mg/kg-day for females. The primary findings in this study are liver effects in male rats. However, it was noted that this chronic study also reported non-hepatic effects (ovarian stromal hyperplasia and ataxia) in female rats. Although this effect was not found in the subchronic study that included females (Goldenthal, 1978), the small number of animals in that subchronic study (n=5) may have limited the power of the study to observe these effects.

Key Panel Discussion Points: One of the panelists identified some copying errors in the tables (incidences of mammary fibroadenomas, Leydig cell adenomas, and ALT activity in the control group) and these values were corrected prior to the panel discussion (the attached table presents the corrected values). The panel disagreed with the study author's conclusion stated in the study report that the testicular vascular mineralization was a "spontaneous change occurring in aging rats" and that the ovarian stromal tubular hyperplasia was "equivocally related" to C8 administration because it did not progress. The panel considered both these effects to be biologically significant and relevant for determining adverse effect levels. One panelist stated that ovarian stromal hyperplasia is not commonly found in rats and noted that in this study the incidence of ovarian stromal hyperplasia in the control animals is zero. The panel discussed the relevance of the ataxia observed in females, but did not reach any conclusions about its possible biological significance. One panelist noted that at the time this study was conducted, the term "hepatic megalocytosis" was synonymous with the term "hepatic hypertrophy" currently in use. It was noted that the BMDL of 0.73 mg/kg-day calculated based on liver effects in males is consistent with the NOAELs for liver effects observed in other rat studies. In the initial summary table from which the panel was working it was noted that no BMDL was estimated for ovarian stromal tubular hyperplasia, since an adequate fit to the data was not achieved. One reviewer suggested that a model fit might be possible using log-transformed data, since the study results showed a clear log-related response curve. This approach was applied during the meeting, and resulted in a best estimate of the BMDL of 1.6 mg/kg/day.

Outcome: The panel agreed unanimously to the proposed NOAEL of 1.3 mg/kg-day for males, with a corresponding LOAEL of 14 mg/kg-day based on the following adverse effects: increased liver weight, hepatic cystoid degeneration, increased ALT enzyme activity, and testicular vascular mineralization. The panel agreed that the LOAEL in females was 1.6 mg/kg-day based on a statistically significant increase in the incidence of ovarian stromal tubular hyperplasia, and that this study did not identify a NOAEL for females. The panel further agreed that the estimated BMDL from this study is 0.73 mg/kg-day based on liver effects in males as the benchmark response.

Thomford et al., 2001

This is a 26-week study in cynomolgus monkeys, in which animals received C8 at doses of 0, 3, 10, or 30/20 mg/kg-day by gastric intubation of gelatin capsule. Gastric capsule intubation was chosen as the method of C8 administration to avoid emesis, which had occurred in the earlier Rhesus monkey study (Goldenthal et al., 1978b). Even so, several animals had problems tolerating the highest C8 dosing; as a result, the high dose was either reduced or in some cases, discontinued. Afterwards, time-weighted average doses were used to approximate the C8 dose given to the high-dose group. One animal died in the high dose group; primary findings included clinical signs and altered liver weight. *TERA* presented that altered liver weight was not considered an adverse finding.

Key Panel Discussion Points: At least two panelists believed that the degree of absolute liver weight increase (30%) noted at the 3 mg/kg-day dose should be sufficient to identify this dose as the LOAEL. Other panelists responded that this weight increase resulted from mitochondrial proliferation, and therefore was an adaptive response, not an adverse effect. They also pointed out that, unlike laboratory rodents, cynomolgus monkeys routinely exhibit large genetic variations. As a result, large differences in organ weights among these animals is relatively common and a 30% difference between groups – especially small groups, as in this study – is not necessarily biologically meaningful. Some panelists attempted to compare this study with the study conducted in Rhesus monkeys in order to help define the LOAEL, but this was not possible due to the uncertainty of dosing caused by the emesis that occurred in the Rhesus study. One panelist asked if the dosing technique (gastric intubation of the drug contained in gelatin capsules) might have contributed to a large range of C8 blood levels because of differences in capsule disintegration rates. Another panelist responded that this was unlikely because, while the data sometimes demonstrated large inter-animal variations in blood levels, the intra-animal variation over several dose administrations was small. It was noted that C8 serum levels were essentially the same in the low and mid-dose groups: 74, 80, and 120 μg/mL at 3, 10, and 30/20 mg/kg-day, respectively. The panel concluded that the similarities in serum C8 levels may explain the very similar effects observed between the 3 and 10 mg/kg-day dose groups. One panelist noted that protein-binding saturation was similar between the monkey and human.

Outcome: The panel agreed that the LOAEL is best described as "from 3 to 10 mg/kg-day" based on 30% increased absolute liver weight, and that a NOAEL does not exist for this study. At all three dose levels, statistically significant increases in absolute and relative liver weights occurred, but without accompanying histopathology. No clinical or histopathological evidence of organ damage occurred at any of the three dose levels. Dose-related trends toward lower T3 and T4 levels were observed, but these failed to achieve statistical significance, even at the highest dose. The panel concluded that these data are insufficient to identify any single dose as a LOAEL or NOAEL. Since the serum C8 levels were essentially the same for both the 3 and 10 mg/kg-day doses, the panel believed that designating a range of 3 to 10 mg/kg-day for the LOAEL is the best way to describe the study results.

Noncancer Assessment: Oral Hazard and Dose-Response Characterization
(Note: Dr. Seed abstained from voting during this part of the meeting.)

Critical Study and Point-of-Departure

The summary of NOAELs, LOAELs, and BMDLs unanimously agreed to by the panel is presented in Table 1 below. The individual study adverse effect levels were discussed by the panel for the purpose of selecting a critical study and effect level for derivation of the pRfD.

Key Panel Discussion Points: The primary target organ for C8 is the liver, and males are clearly more sensitive to this effect than female rats. One panelist observed that the liver effects in rats may be related to peroxisome proliferation, and therefore may not be quantitatively relevant for humans. For this reason, the liver effects in rats might not be an appropriate critical endpoint   Another panelist responded that, because of this, it was important to note that the monkey and rat LOAELs are in the same range, and since the liver effects in monkeys may not be related to peroxisome proliferation, liver toxicity might also be a relevant endpoint for humans. The observation of ovarian effects in female rats at the same LOAEL as liver effects in males was noted as a second reason to consider the rodent studies as an appropriate basis for deriving the pRfD.

Table 1. Summary of NOAELs, LOAELs, BMDLs, and Critical Effects for Key and Supporting C8 Studies						
	Species	Sex	NOAEL	LOAEL	BMDL	Critical Effect
Key Studies						
Palazzolo et al. (1993)	Rat	M	0.47	1.44	1.3	Liver
York et al. (2002)	Rat	M	None	1	0.42	Liver
Riker Laboratories (1983)	Rat	F	None	1.6	1.6	Ovary
		M	1.3	14	0.73	Liver
Thomford et al. (2001)	Monkey	M	None	3-10	None	Liver
Supporting Studies						
Goldenthal et al. (1987a)	Rat	M	0.56	1.72	0.44	Liver
Goldenthal et al. (1987b)	Monkey	M,F	3	10	Not done	Clinical signs

Some panelists favored choosing the monkey study as the critical study, due to the closer biological relationship with humans as opposed to rats. It was also noted that the observed increase in liver weight in monkeys may not be related to peroxisome proliferation and, therefore, may be more relevant for human health risk assessment. Other panelists disagreed, pointing to the uncertainties in dosing and effects, the small number of animals per dose group, and the unclear boundary between NOAEL and LOAEL values. Also, it was noted that the monkey study could not be considered the critical study because the 90-day, two-generation, and two-year rat studies all have LOAEL, NOAEL, and /or BMDLs below the LOAEL range identified in the monkey study, and therefore based on selection of the critical study with the lowest adequate NOAEL/LOAEL boundary would support the use of the rodent studies.

The panel considered whether it would be better to base the pRfD on a NOAEL or on a BMDL. Some panelists thought a NOAEL basis is a simpler concept and would be easier to explain to the public. Others responded that the BMDL captures more information from the entire study (e.g., reflects information from the full dose-response curve, and variability in the dose-response data) and therefore is the better choice as the basis for the quantitative dose-response assessment. Another panel member mentioned that a NOAEL is not a "no effect" level, rather it reflects the proportion of the responding population that can physically be observed in an experimental situation. Therefore, the size of the population is important. The panel agreed to not rule out using either a NOAEL or BMDL, but instead to focus on the quality of each study and the lowest critical effect level it provided.

The panel noted the unusually good agreement of the NOAELs and LOAELs from all the studies. The lowest NOAEL observed in one of the potential key studies was 0.47 mg/kg-day, from the 90-day rat study by Palazzolo et al. (1993). The lowest LOAEL observed in a key study was 1 mg/kg-day from the rat two-generation study (York et al., 2002). This study did not test doses low enough to identify a NOAEL; however, the BMDL value estimated for this study, 0.42 mg/kg-day, was essentially the same as the observed NOAEL from the 90-day study. Therefore, the panel agreed that the BMDL was an appropriate NOAEL surrogate for the two-generation study. The ovarian stromal hyperplasia reported in the chronic rat study (Riker Laboratories, 1983), provided a higher LOAEL than the two-generation study, and the BMDL for this effect resulted in the same value as the LOAEL. This demonstrates that the liver endpoint is the critical effect, because it occurs at lower doses.

Outcome: Because of the consistency in NOAELs/LOAELs and critical effect in all the key studies, the panel concluded that all studies could be considered co-critical studies and that all provide important information for human risk assessment. However, the panel unanimously agreed that the NOAEL surrogate from the two-generation study, a BMDL of 0.42 mg/kg-day, should serve as the point-of-departure for the pRfD. This value was selected since it represented the lowest NOAEL or BMDL, and provided the added consideration of having evaluated reproductive and developmental effects.

Uncertainty Factors

If adequate human data are available, these data are used as the basis for noncancer risk factor development. Otherwise, animal study data are used, along with a series of professional judgments that are incorporated into the risk factor as "Uncertainty Factors" and account for an assessment of the relevance and scientific quality of the experimental studies. There are five different uncertainty factors commonly used to address issues of biological variability and uncertainty. Two factors (Interspecies and Intraspecies) are used to address variability or heterogeneity that exists between animals and humans, and within different human populations. Three factors (Subchronic, LOAEL, Database) are used to address lack of information. Typically, the maximum total uncertainty factor that EPA will apply is 3000. If all five areas of uncertainty/variability are present warranting a total UF of 10,000, then EPA generally concludes that the uncertainty is too great to develop an RfD. The panel discussed each area of variability or uncertainty separately. A short introduction to each area of uncertainty is provided below to aid the reader in evaluating the discussions of the panel.

Intraspecies Variability (UF_H): This factor accounts for the natural differences that occur between human subpopulations and for the fact that some individuals may be more sensitive than the average population. This factor is composed of two subfactors – one to account for toxicokinetic differences (how the body distributes and metabolizes the chemical) and one to account for toxicodynamic differences (how the body responds to the chemical). If no information is available on human variability, then a default value of 10 is used. If adequate information is available on one of the two subcomponents, then this information is used along with a default value of 3 for the remaining subfactor. If data are available to adequately describe human variability in both subfactors, then actual data may be used to replace default values. In addition, if a RfD is based on human data gathered in the known sensitive subpopulation, a value of 1 may be chosen for this factor.

The panel discussed the lack of available data describing human variability. One panelist suggested a comparison of human C8 blood levels and values from the animal studies. The highest human serum C8 level reported was 111 ppm, but the average was approximately 5 ppm. No effects were noted in the human subject with the highest blood level. Thus, at least some people achieved serum C8 levels equivalent to those that resulted in adverse effects in animal studies.

As noted in the discussion of the human data above, the panel acknowledged gaps in the data on human variability and inability to define the most sensitive subpopulation, and therefore concluded that the default value of 10 was appropriate for this factor.

Interspecies Variability (UF_A): This factor accounts for the differences that occur between animals and humans and is also thought to be composed of subfactors for toxicokinetics and toxicodynamics. If no information is available on the quantitative differences between animals and humans, then a default value of 10 is used. If information is available on one of the two subcomponents, then this information is used along with a default value of 3 for the remaining subfactor. If data are available to adequately describe variability in both subfactors, then actual data may be used to replace default values. In addition, if a RfD is based on human data, then a value of 1 is appropriate for this factor.

One panelist mentioned that EPA has often used a UF_A value of 3 in other assessments when extrapolating monkey data to humans, because the kinetics and dynamics of monkeys are assumed to be similar to humans. This assumption is based on the fact that rhesus monkeys and macaques share a 92% genetic homology with humans and because monkey studies are able to detect a much broader range of clinical findings and more specific histopathology than rodents. In addition, studies on other chemicals in which a good database exists in rodents, monkeys and humans demonstrate that results in monkey studies parallel the human effects more closely than results in rodent studies.

Another panelist agreed and said the half-life of chemicals in monkeys was usually closer to humans than to rats. Other panelists responded that for C8, the half-life in monkeys is about 30 days; and this is much less than the C8 half-life in humans, which is estimated to be greater than one year. It was noted, however, that data on C8 half-life in humans is limited.

Because no data are available to warrant moving from the default, the panel unanimously agreed that a UF_A value of 10 is appropriate with either the rat or monkey toxicology studies.

Subchronic to Chronic Extrapolation (UF_S): Because the RfD protects for a lifetime exposure, this factor is applied when the database lacks information on the health effects of the chemical following a chronic exposure. Two issues are considered when making judgment on the use of this factor – are there data demonstrating that different health effects are expected following chronic exposure than subchronic exposure, and are there data demonstrating that the observed health effects progress in severity as exposure duration increases? If the database contains no information on chronic exposure, a default value of 10 is often applied, unless other data suggest a lack of progression with exposure duration. If the database contains adequate chronic bioassays, then a value of 1 is appropriate. If there are data addressing only one of the two issues, then a default of 3 may be applied.

It was noted that the database for C8 contains an adequate chronic rat study (Riker Laboratories, 1983). In addition, a second chronic study (Biegel et al., 2001) was available, although this study focused primarily on tumorigenic mechanisms in rats. In addition, for the purpose of evaluating uncertainty factors, the human occupational studies were considered by the panel to be informative on the response (or lack thereof) of humans following long-term exposure. The database demonstrates that liver

toxicity was the more sensitive endpoint in both subchronic and chronic studies. In addition, the database clearly demonstrates that liver toxicity does not progress in severity following chronic exposure. This conclusion is supported by the observation that the subchronic studies identified lower NOAELs for liver toxicity than the chronic studies. One panelist noted that the liver effect in rat progresses to cancer. However the panel concluded that the cancer effect was due to the peroxisome proliferation mechanism (as discussed below in the discussion of the cancer risk assessment). Based on these considerations, the panel unanimously agreed that a UF_S value of 1 is appropriate for the rat studies.

The panel also discussed whether a different value for UF_S would be appropriate if the monkey study had been used as the critical or co-critical study. One panelist observed that there were no data in monkeys regarding the progression beyond 26 weeks; another responded that there was no reason to think the effects in monkeys would be any more progressive than those in rats. Another panelist suggested that the toxicity of C8 in humans does not appear to be progressive. However, the panel agreed that there was some inherent uncertainty in the monkey study to justify use of the value of 3 for UF_S if the monkey study were the critical study.

LOAEL to NOAEL Extrapolation (UF_L): Because the RfD is considered to be a subthreshold value that protects against any adverse health effects, this factor is applied when the database lacks information to identify a NOAEL. If the database does not identify a NOAEL, then a default of 10 is used for this factor. If a NOAEL is used, a value of 1 is appropriate. Often, if the database does not identify a NOAEL, but the adverse effects observed are of minimal severity, then a default of 3 will be considered appropriate for use of a "minimal LOAEL". [1]

Several of the studies considered as co-critical identified NOAELs; the lowest NOAEL is 0.47 mg/kg-day from the 90-day study. Also, the BMDL estimated for the two-generation study was essentially the same as the observed NOAEL from the 90-day study. These NOAELs and BMDLs were based on well-conducted studies and their use as a basis of the pRfD is consistent with standard practice. Therefore, the panel had confidence that the C8 database has identified the threshold for toxicity in rats, and it unanimously agreed a UF_L value of 1 is appropriate for the critical effect in the rat studies.

The panel also considered the value of UF_L that would be appropriate if the monkey study were to be used as the critical study.   Because there is no clear NOAEL value, the panel agreed that a value of 1 was not appropriate. However, because the effects seen at the low dose were limited to mild increases in liver weight without accompanying changes in histopathology, or any other effect, the low dose was considered to be a minimal LOAEL. Therefore, the panel agreed that a UF_L of 3 would be appropriate if the monkey study were to be used as the critical study.

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[1] EPA is currently discussing the application of UF_L when using a BMDL. A BMDL value represents the lower limit on the dose that should cause 10% of the experimental animals to respond with the effect that is being modeled. Because animal studies typically cannot detect a response less than 10%, an experimentally derived NOAEL also represents the dose that causes 10% of the animals to respond. For this reason, EPA has historically considered a BMDL to be a NOAEL surrogate and selected a UF_L value of 1 when a BMDL is used. Although EPA does not have official guidance on this issue, recent discussions in the agency suggest that if the effect being modeled for the BMDL is adverse, then the BMDL should be considered as a LOAEL. Currently, BMDLs are being evaluated on a case-by-case basis, considering the nature of the effect being modeled and the relationship of the estimated BMDL to observed NOAELs.

Database (UF$_D$): The database for deriving a high confidence RfD includes two chronic bioassays by the appropriate route of exposure in different species, one two-generation reproductive toxicity study, and two developmental toxicity studies in different species. The minimal database required for deriving a RfD is a single subchronic bioassay, that includes a full histopathology examination. The database factor is used to account for the fact that a potential health effect may not be identified if the database is missing a particular type of study. This factor may also be used if the existing data indicate the potential for a heath effect that is not fully characterized by the standard bioassays, for example neurotoxicity or immunotoxicity. If the database is complete, a value of 1 is appropriate. If only the minimal database is available, then a default of 10 is used. A value of 3 may be used if the database is missing one or two key studies.

The panel agreed that the oral database for C8 is complete. For the purpose of evaluating uncertainty factors, the panel felt that the human occupational studies provided sufficient information on the effects of long-term exposure in humans to function as a chronic bioassay. In addition, the consistency between the monkey and rat subchronic studies provides confidence that non-rodent species respond similarly to rats and that liver is a sensitive target organ in all species. Furthermore, a developmental toxicology study indicated that such effects only occurred at high concentrations, and reproductive effects were monitored in the 2-generation reproductive study.

Therefore, the panel unanimously concluded that a UF$_D$ value of 1 is appropriate with either the rat or monkey toxicology studies selected as the critical study.

Outcome: The summary of the panel's unanimous conclusions regarding individual and composite uncertainty factors is presented in Table 2 below. The composite uncertainty factor is obtained by multiplying the individual factors. (Note, that following EPA convention, an uncertainty factor of 3 actually represents the log of the halfway point between 1 and 10. Therefore multiplying half-log values of 3 results in a full log value of 10, rather than 9 as would be expected for numeric multiplication.)

Table 2. Panel Recommendations of UF Selection for Oral pRfD						
Study	**UF$_H$**	**UF$_A$**	**UF$_L$**	**UF$_D$**	**UF$_S$**	**Composite UF**
All Rat	10	10	1	1	1	100
Monkey	10	10	3	1	3	1000

Oral Reference Dose (RfD)

The final value of the RfD is obtained by dividing the point-of-departure by the composite uncertainty factor. As discussed above, the point-of-departure selected by the panel is the BMDL of 0.42 mg/kg-day estimated from the rat two-generation study (York et al., 2002) and the composite factor is 100. Therefore, the resulting pRfD is 0.42 ÷ 100, or 0.0042 mg/kg-day. Because of the lack of precision inherent in the RfD, only one significant figure is appropriate; therefore, this value is rounded to 0.004 mg/kg-day.

For comparison purposes, the panel considered the pRfD values that would result from choosing alternative NOAELs or BMDLs as the point of departure. This analysis is presented in Table 3 below:

Table 3. Comparison of pRfDs Derived Using Different Studies					
Study	**UF**	**NOAEL**	**RfD**	**BMDL**	**RfD**
Palazzolo et al. (1993)	100	0.47	0.005	0.72	0.007
Riker Laboratories (1983)	100	1.3	0.01	0.73	0.007
York et al. (2002)	100	---	---	0.42	0.004
Thomford et al. (2001)	1000	3-10 (LOAEL)	0.003-0.01	---	---

Based on this review table developed by the panel, the pRfDs that could be derived from the C8 oral database range from 0.003 to 0.01 – at most a factor of 3 separates the different potential pRfDs. Considering that the definition of the RfD states that the RfD incorporates uncertainty spanning an order of magnitude (a 10-fold variation), the panel noted that close agreement of the potential pRfD values provides added confidence in the derived pRfD of 0.004 mg/kg-day.

Noncancer Assessment: Review of the Dermal Studies
(Note: Dr. Seed abstained from voting during this part of the meeting)

The data on C8 by the dermal route of exposure are limited. Other than acute lethality, skin sensitization, and irritation studies, the dermal database consists of only a single 2-week study.

Kennedy et al. 1985

This is a two-week study in male rats in which animals had C8 applied to the skin for 6 hours/day, 5 days/week at doses of 0, 4.2, 42, and 420 mg/kg-day. Although this is a short-term study, it is the only candidate for possible use in determining a reference dose for the dermal route of administration. The primary effects observed were increased liver weight and liver pathology. A panelist noted that the study design prevented animals from ingesting the dermally-applied material. Although the amount of material inhaled was considered to be low, some inhalation almost certainly occurred in the dosed animal because the control animals had detectable C8 blood levels. It was also noted that the consistency of the material applied to the animals varied among the dose groups, depending on the concentration of C8 in the material matrix. In all instances the amount of material on the skin was considerably thicker than a monolayer, and therefore, the applied doses might not reflect accurately the absorbed doses of C8 in this study.

Key Panel Discussion Points: One panelist stated that this study could provide potentially useful information because systemic effects are observed at dose levels below those which cause portal of entry effects (skin irritation). The panel discussed whether it would be appropriate to extrapolate the results of this study to longer durations in order to derive a dermal pRfD. The panel concluded that such extrapolation would not be advisable because of the possibility of unpredictable longer-term dermal effects. One panelist asked if route-to-route extrapolation could be done from the oral studies

to estimate a dermal NOAEL or LOAEL. Other panelists thought this would not be possible due to uncertainties in the C8 toxicokinetics by oral versus dermal exposure routes. For example, enterohepatic circulation is known to occur following oral exposure, but would not occur following dermal exposure. Therefore, the toxicokinetics of C8 is different between the two routes of exposure. Regardless of the route of entry, C8 is not metabolized. Furthermore, no data on the dermal absorption rate were identified. One panelist noted that if the findings from this study were used to determine a reference dose, the resulting value would be higher than the reference dose obtained from the oral studies. Therefore, using oral studies to set the reference dose would be adequately protective, of systemic exposure via the dermal route. Another panelist agreed, stating that no dermal reference dose should be identified at all, and that a specific reference dose for dermal exposure was not needed.

Outcome: The panel agreed unanimously that this study should not be used to determine a dermal pRfD because of uncertainties inherent in the study design as noted in the discussion.

Noncancer Assessment: Review of the Inhalation Studies
(Note: Dr. Seed was absent during this part of the meeting)

The data on C8 by the inhalation route of exposure are limited. Other than acute lethality studies, the inhalation database consists of a 2-week study and a developmental toxicity study.

Kennedy et al. 1986 and Staples et al. 1981

Two inhalation studies were discussed as potential candidates for deriving the pRfC. Kennedy et al. (1986) reported a two-week study in male rats in which animals were exposed head-only 6 hours/day, 5 days/week to C8 air concentrations of 0, 1, 7.6, or 84 mg/m^3. The primary effects observed in this study at the mid-concentration included increased absolute and relative liver weight, supported by clinical chemistry and histopathology findings. The high concentration resulted in severe toxicity, including mortality in one rat. Other findings at the high concentration group were increased lung and testes weight. A concentration-dependent increase in the incidence of nasal and ocular discharge was noted.

A second potential critical study for deriving the pRfC was a developmental toxicity study by Staples et al. (1981). Pregnant rats were exposed whole-body 6 hours/day on gestation days 6 to 15 to C8 air concentrations of 0, 0.14, 1.2, 9.9, and 21.0 mg/m^3.

The panel agreed the Kennedy two-week study provided the highest quality data for possible determination of critical effects and provided a slightly lower NOAEL/LOAEL boundary, even though both studies used similar air concentrations. In addition, the Kennedy et al. (1986) study evaluated a broader array of systemic endpoints, and included a histopathology examination.

In describing their initial review of the study, *TERA* noted that EPA's RfC methodology states that the air concentrations to which animals are exposed are to be converted to "Human Equivalent Concentrations (Conc$_{HEC}$)" by applying dosimetric adjustments (USEPA, 1994). Dosimetric adjustments account for the different structure and surface area of animal respiratory tracts compared with humans. Different dosimetric adjustments are applied depending on where effects are observed. For example, a different dosimetric adjustment will be applied for liver effects than will be applied for lung effects. *TERA* noted that the key piece of data needed to calculate the Conc$_{HEC}$ is a description of the particle size distribution (i.e., the mass median aerodynamic diameter and geometric standard

deviation or GSD). Data available from the published study did not provide complete information about the mass median aerodynamic diameter for the low-concentration group, or GSD for any exposure group. In order to facilitate the discussion of the study, *TERA* presented human equivalent concentrations for liver (extrarespiratory) and lung (pulmonary) effects from this study assuming either a monodisperse particle size distribution or a polydisperse particle size distribution. These results were presented to the panel as shown in Table 4 below.

Table 4. Preliminary $Conc_{HEC}$ Calculations from Kennedy et al. (1986)				
Study Concentration[a]	GSD = 1.3 (Monodisperse)		GSD = 3 (Polydisperse)	
	Liver	Lung	Liver	Lung
1.0	0.6	0.018	0.5	0.09
7.6	4.6	0.14	4.0	0.70
84	67.7	17.7	46.9	7.4
a. All values are presented in units of mg/m^3.				

Key Panel Discussion Points: It was noted that the inhalation database does not meet the minimum database requirements for determining an RfC of one subchronic 90-day study that includes histopathology of the respiratory tract, but that the consent order required a pRfC in order to set air screening levels. One panelist stated that it was not appropriate to extrapolate from oral studies to derive a RfC because of the absence of data on toxicokinetics differences between these routes (e.g., effects of enterohepatic circulation, or absorption).

One panel member indicated that the data needed to calculate the $Conc_{HEC}$ (i.e., the mass median aerodynamic diameter [MMAD] and geometric standard deviation [GSD]), but not reported, in the published study could be made available to *TERA* after the meeting. The panel agreed that these data should be provided to *TERA*, for calculation of the appropriate $Conc_{HEC}$ following the meeting. The panel then discussed whether the lung or the liver was the critical organ, recognizing that the final designation of critical effect could not be made until the correct $Conc_{HEC}$ is calculated. *TERA* raised the question of whether the reported increases in the incidence of nasal and ocular discharge should be considered an adverse effect. It was noted that this effect is not uncommon for the exposure protocol that was used, and the effect was seen in all groups. It was further noted that C8 is not an irritant, and that no nasal histopathology was observed in exposed animals. In selecting critical study concentrations the panel discussed the lung effects at higher doses. One panel member suggested that at the high concentration the overt pulmonary toxicity was observed due to the large particle burden. Uncertainties in interpreting the lung effects were raised by the panel. One panelist noted that the studies were too short to determine what effect chronic exposure would have on the respiratory tract. Another suggested that existing human data associated with the human study reports discussed earlier (pulmonary function testing of workers, etc.) might be useful in determining NOAEL/LOAEL values. After this discussion, the panel considered the study concentration of 7.6 mg/m^3 to be the NOAEL for pulmonary effects, with the LOAEL of 84 mg/m^3.

The panel next discussed the liver effects. It was noted that the observed increases in liver weight were consistent with the effects observed in the oral studies. Another panel member noted the increased alkaline phosphatase (AP) values observed at the higher doses were not necessarily the result of the types of liver effects seen in the oral and dermal studies, since increased AP levels often reflect disorders of biliary flow. One panelist questioned the ability of the study to detect systemic effects given the short exposure period and the kinetics of the compound; however, another panelist replied that the half-life of C8 in rats is 5 to 7 days, and the study design would have allowed achievement of

steady-state concentrations in the blood. The panel considered the study concentration of 1.0 mg/m^3 as the NOAEL for liver effects. However, one reviewer suggested that if the liver effects are found to be the critical effect based on the $Conc_{HEC}$, then benchmark concentration modeling should be conducted before assigning a critical effect level.

The panel considered the appropriate uncertainty factors for a pRfC, noting that the final choice of an appropriate value for some areas of uncertainty may change depending on whether lung or liver effects are found to be critical. (Note to the reader: Essentially the same areas of uncertainty are considered in developing a RfC as for the RfD. For a full explanation of the purpose for each factor, see the earlier discussion.) For the same reasons as discussed for the pRfD, the panel unanimously agreed that a value of 10 was appropriate for UF_H. When considering interspecies extrapolation, it is generally considered that the dosimetric adjustments used to derive the $Conc_{HEC}$ account for the toxicokinetic differences between animals and humans. Therefore, the uncertainty factor only needs to address the toxicodynamic differences. Since there are no data regarding dynamic differences between rats and humans, the panel agreed that the default value of 3 was appropriate for UF_A. Since the Kennedy study identified a NOAEL, the panel unanimously agreed that a value of 1 was appropriate for UF_L.

The panel considered that two of the factors, UF_S and UF_D, were related to the decision of whether lung or liver is the critical effect. If liver effects are determined to be the critical effect, then at least one panelist felt that UF_S, could be addressed with an uncertainty factor of 1 because the oral studies provided enough information to be confident that the liver effects would not progress in severity following a chronic inhalation exposure. However, other panel members stated that there were insufficient data to assess whether liver would continue to be the critical effect or to provide information on how the respiratory tract would respond following longer-term inhalation exposures, and that a value greater than 1 for UF_S was needed. For the UF_S and liver as the critical organ, the panel votes were 1, 3, or 10 with the majority choosing 3. If liver effects are determined to be the critical effect, then panelists were split on the value of the uncertainty factor for UF_D, choosing values of either 3 or 10 with the majority of the panel choosing 3. No unanimous consensus was reached on these two factors; however, a clear majority vote was reached on uncertainty factors of 3 each for UF_S and UF_D in reference to liver as the target organ.

If lung effects are determined to be critical, the panel was divided almost equally on the appropriate value for UF_S with opinions covering the full range of options from 1 to 3 to 10. Note however, that six scientists voted for a factor less than 10 (either 1 or 3) and five scientists voted for a value greater than 1 (3 or 10). Similarly, the panel was divided on the appropriate value for UF_D; panel opinions covered the full range of options from 1 to 3 to 10 with the majority of panelists choosing 3.

As noted above, after each discussion votes were taken on individual factors. These votes are shown in Table 5. Note that one scientist was reviewing the dosimetric adjustment calculations during this discussion and so was unable to vote on these UFs; also note that one more vote at any point in Table 5 would not have changed the final outcome. In addition, the panel did not reach consensus on the confidence in the RfC, with opinions ranging from "none" to "high" with the average being medium-to-low.

Table 5. Tally of Panel Votes for UF_S and UF_D						
	UF_S			UF_D		
Factor	1	3	10	1	3	10
Liver as critical	1	6	1	0	6	2
Lung as critical	3	3	2	1	5	2

Outcome: One panelist reminded the group that the purpose of Kennedy et al., (1986) was to identify the inhalation hazard, not to look closely at NOAEL, LOAEL, etc. A prospective inhalation study designed to look more closely at the NOAEL/LOAEL aspects, to evaluate lesions as a function of exposure time, and to evaluate tissues of the respiratory tract using up-to-date methodology would be valuable and would allow a more focused evaluation of the RfC. Nonetheless, the panel agreed that a pRfC could be developed, but this agreement was not unanimous. The panel also recommended that TERA obtain additional data on the particle size GSD value to determine the $Conc_{HEC}$ corresponding to the NOAEL before determining whether the pulmonary or the hepatic effects are considered critical. If the liver effects are determined to be the critical effect, then BMD modeling should be done. The composite uncertainty factor was expressed as a range of 30 to 3,000. The final pRfC is presented in the Post Meeting Action Items.

Cancer Assessment
(Note: Dr. Seed abstained from voting during this part of the meeting)

U.S. EPA's 1999 Guidelines for Carcinogen Risk Assessment were used to frame the discussion of C8 carcinogenic potential. TERA opened the discussion with a short introduction to these guidelines, highlighting the recent focus on evaluation of the mode of action data in developing a weight of evidence characterization, and in deciding the most appropriate dose-response approach, linear or margin of exposure (MOE). It was noted that the EPA's 1999 guidelines would be used as the basis for the deliberations of the panel.

Cancer Hazard Identification and Mode of Action

The panel discussed the evidence for C8 carcinogenicity in humans and agreed that the human carcinogenicity evidence is inconclusive. Although four prostate tumors were reported in retired workers, three of these four cases now are known to have had minimal or no C8 exposure. (See Human Studies section for more detailed discussion.)

The panel noted that two animal carcinogenicity studies had been conducted. The first study (Riker Laboratories, 1983) reported treatment-related increases in Leydig cell adenomas and mammary gland fibroadenomas. The second study (Biegel et al., 2001) reported treatment-related increases in tumors in the liver, Leydig cells, and pancreas. Panelists noted that the tumors identified in the Biegel et al. (2001) study correspond to the triad of tumors associated with some chemicals that cause peroxisome proliferation. Other panelists agreed and suggested that a further examination of the data may indicate that this triad of tumors can be best addressed using a MOE approach. The panel also noted that the mammary fibroadenomas may require the default linear model because, following U.S. EPA cancer guidelines, no actual mode of action data for C8 and this tumor type are available to warrant moving from the default assumption. Each of the four types of tumors found in the two C8 animal

carcinogenicity studies was then discussed in detail with regard to the weight of the evidence for the mode of action, and the evidence supporting a linear or MOE dose-response assessment approach. Listed below are the outcomes and discussions for each tumor type.

Liver tumors

Key Panel Discussion Points: The discussion on liver tumors focused on the role of peroxisome proliferation as the mode of action for the observed liver tumors. In relating this liver tumor effect to humans, one panelist said humans are much less sensitive to peroxisome proliferation than rats. Another panelist noted that IARC's approach for clofibrate and other non-genotoxic peroxisome proliferation chemicals was to assume that the mode of action was not relevant to humans if no evidence of peroxisome proliferation was observed in humans. Another panelist said that although rats may be more sensitive than humans from a toxicodynamic standpoint (due to interspecies differences in receptors), humans may be more sensitive from a toxicokinetic standpoint, since they clear C8 more slowly than rats. As a result, the panel member suggested that these two considerations would tend to decrease overall differences in species sensitivity. On the other hand, a panel member noted that no increased incidence of tumors have been found in people taking clofibrate, a known peroxisome proliferator, which suggests that humans are much less sensitive to peroxisome proliferation than rats and they may have no response at all. Based on these data, the panel member suggested that the lack of tumor development in humans exposed to C8 should not be discounted. The panel discussed differences in results between the two cancer studies. One panelist noted the studies have differences in their internal delivered doses because of differences in the animal diets. This could explain the difference noted in toxic effects.

Outcome: The majority of the panel agreed that the data indicate peroxisome proliferation is the mode of action for the liver tumors, and that although the liver tumor response is not likely to be quantitatively similar between rats and humans, the use of the liver tumor response data for human health risk assessment cannot be totally discounted. However, other scientists indicated that based on the lack of peroxisome proliferation in the non-human primate studies, the rodent liver tumors are not relevant at all to humans.

Leydig Cell Tumors

Key Panel Discussion Points: In reviewing the summary tables prepared for the meeting, one panelist noted that Leydig cell hyperplasia should be evaluated. In response, the hyperplasia data from Biegel et al. (2001) was reviewed by the panel. The panel developed Table 6 to facilitate the comparison on hyperplasia and tumorigenic outcomes.

Table 6. Summary of Beigel et al., 2001 Leydig Cell Data		
	Pair fed controls	300 ppm
Liver carcinomas/adenomas	3/79	10/76*
Leydig ademonas	2/78	8/76*
Pancreatic carcinomas/adenomas	1/79	8/76*
Leydig cell hyperplasia	26/78	35/76

The panel noted that no significant increase in Leydig cell hyperplasia was apparent from these data; however, due to different survival times between the two groups (C8 treated animals survived longer) a false positive effect could have occurred because older animals would have more time to develop naturally occurring tumors. It was noted that a more formal analysis would be needed to determine whether the incidence of Leydig cell tumors would still be increased after adjusting for differences in survival, but the formal statistical analysis was too complex to complete during the meeting.

The panel discussed the role of peroxisome proliferation as the mode of action of Leydig cell tumors. Specifically, the panel discussed a workshop publication **(**Clegg et al. 1997**)** that evaluated the seven known modes of action for Leydig cell tumors. Most of the modes of action involve altered hormonal response in response to peroxisome proliferation, including increased estradiol via hepatic aromatase and binding to the TGF α receptor or elevations in leutinizing hormone to compensate for the testes becoming less responsive to this hormone. One panelist emphasized that the monkey study (Thomford et al., 2001) showed no effects in the testes, even though the animals were dosed at C8 levels high enough to cause major weight loss and mortality. This panelist suggested that this indicates the Leydig cell effects seen in rats are unlikely to occur in primates. This panel member also noted that no increased estradiol was noted in the monkeys.

One panelist observed that Leydig cell tumors were a classic response to peroxisome proliferation but the available studies do not provide positive evidence, such as increased estradiol levels, that peroxisome proliferation is the operative mode of action. The panelists agreed that while data gaps exist, a peroxisome proliferation mode of action was a reasonable assumption. One panelist stated that whatever the MOA was, it was not genotoxicity.

The panel agreed unanimously that for Leydig cell tumors:

- All 7 possible mechanisms for Leydig cell tumors are non-linear; therefore a non-linear dose-response approach is reasonable;
- Humans have a low incidence of these tumors;
- The monkey study did not demonstrate Leydig cell pathology or increased estradiol;
- Leydig cell tumors are a known tumor type for other peroxisome proliferators;
- Humans do not develop Leydig cell tumors following exposure to other known peroxisome proliferators such as clofibrate;
- Regardless of the actual mode of action, it is likely to be non-genotoxic.

Outcome: The panel agreed that based on the absence of genotoxicity, the Leydig cell tumors were likely to be caused by a non-genotoxic mechanism. The panel further agreed that if sufficient evidence were available to show increased estradiol levels (i.e., secondary to peroxisome proliferation) as the mechanism for the observed tumors, then the mechanism would be non-genotoxic and would not be quantitatively similar or possibly not relevant at all to humans. However, without this evidence this effect can not be totally discounted.

Pancreatic tumors

Key Panel Discussion Points: Since the tumor results from the Beigel et al., (2001) were not provided in the summary table distributed to the panel prior to the meeting, the pancreatic tumor data from this study were presented as a table at the meeting (see Table 7 below):

Table 7 Biegel Study: Pancreas Tumors			
	Control	pair-fed control	300 ppm
Hyperplasia	14/80 (18%)	8/79 (10%)	30/48* (40%)
Adenomas	0/80	1/79	7/76*
Carcinomas	0/80	0/79	1/76

One panelist described an analysis that had been done to compare the two cancer studies with regard to the pancreatic tumors. This panelist noted that although the first study (Riker Laboratories, 1983) did not report pancreatic tumors or hyperplasia, the second study (Biegel et al., 2001) did. However, this panel member also noted that the studies were not inconsistent because of the different definitions of adenoma versus hyperplasia based on pancreatic cell size used by the respective investigators. Also, the criteria for separating hyperplasia from adenomas is based on lesion size. Both studies were qualitatively similar with a number of larger lesions (adenomas) found in the Biegel study. Another scientist commented, when the two studies were recently compared by a group of pathologists using current criteria, there was a consistency in a pancreatic response; however, there was not an increased number of adenomas found in the earlier study. Instead, an increase in hyperplastic nodules of the acinar pancreas was found, which is consistent with the Beigel study. However, even though the dietary dose was the same (300 ppm), the Riker Laboratories study rats did not develop these hyperplasias into adenomas to the extent that occurred in the Beigel study.

With regard to the potential mode of action, one panelist suggested that the persistent increase seen in cholecystokinin and increased bile acids may be involved in the MOA, but the evidence in rats, monkeys and humans does not support this hypothesis. When a panelist asked if a strong case could be made that the pancreatic tumors resulted from peroxisome proliferation, several panelists responded no. Another added that while some peroxisome proliferation agents cause the triad of tumors seen with C8, not all do. Another panelist added that no pancreatic, liver, or testes hyperplasia was noted in monkeys at the time of sacrifice.

Outcome: The panel agreed that the evidence was not sufficient to demonstrate the MOA for pancreatic tumors, but enhanced cell proliferation (hyperplasia) was likely to be involved. The MOA appears to be non-genotoxic based on the results of genotoxicity bioassays.

Mammary Fibroadenomas

Key Panel Discussion Points: The panel considered whether the fibroadenomas observed in the Riker Laboratories study were a real treatment-related effect, or an artifact of classification, since other mammary tumor types observed in this study showed no clear relationship with dose. Table 8 below shows the data for several types of mammary tumors from this study:

Table 8. Riker Study: Mammary Tumors			
	Control	30 PPM	300 PPM
Adenomas	7%	0	0
Adenocarcinomas	15%	31%	11%
Carcinomas	2%	0	0
Fibroadenomas	22%	42%	48%*

One panelist suggested that even though fibroadenomas were statistically significant, when all mammary tumor types are combined, they are not likely to be significant. It was noted by the panel that the individual incidence data from the study would need to be examined to determine the combined incidence of all mammary tumor types, rather than adding the percentages from each category. The panel discussed the histological basis for reporting separately fibroadenomas versus other types of mammary adenomas. A panelist suggested that since fibroadenomas do not progress to the other types it is correct to report them separately. Another said that the National Toxicology Program (NTP) reports fibroadenomas combined with adenomas.

The panel also discussed potential modes of action for mammary tumors. Increased estradiol was proposed as a possible MOA for the induction of hyperplasia and tumor formation, but the panel did not believe the data were sufficient to demonstrate this proposed mode of action. A panelist asked if a linear assessment could be done to help decide the importance of the effect. Another responded that the data were not adequately fit by any of the acceptable dose-response models, so a quantitative dose-response assessment was not reported for this data set.

Outcome: The panel agreed the data are not adequate to demonstrate a MOA; however based on the negative genotoxicity assays, C8 is unlikely to be genotoxic. Several panelists were not convinced the data demonstrated any real tumorigenic effect.

Cancer Dose-Response Assessment

After evaluating the relevance of each tumor type to humans, and the potential mode of action, the panel members were asked to recommend a dose-response approach for each tumor type. In all cases the panel agreed unanimously unless noted otherwise. For the liver tumors, the panel agreed that the MOE approach was most appropriate. For the remaining tumor types, the panel agreed that both linear and MOE approaches were appropriate, since the mode of action was not considered to have been adequately demonstrated for any of these three tumor types. All panel members agreed with these conclusions, except for the Leydig cell tumors, where one panel member argued that only an MOE approach should be used.

For the liver tumors, the MOE approach was selected. Since the MOE analysis often uses the benchmark response for a precursor as the basis of deriving a point of departure, the panel judged the pRfD for liver effects as sufficiently protective of potential liver carcinogenicity.

For Leydig cell tumors, benchmark dose modeling was conducted to identify a point of departure for the linear and MOE assessments. The Point of Departure (POD) for Leydig cell was chosen by the panel from the BMD modeling output. The BMDL of 0.32 mg/kg-day was selected as the most appropriate basis for deriving the assessment.

The panel discussed the appropriate factors to apply to the BMR for completing the MOE assessment. The panel noted that EPA's 1999 guidelines have only recently begun to be applied, and that formal guidance or examples of the interpretation and default values to use in deriving the MOE are lacking. In discussing the important considerations for the MOE, the panel decided that the critical factors to be considered were for "Nature of Effect", Intrahuman sensitivity" and "Animal to Human Extrapolation". A summary of the factors chosen is shown in Table 9.

For the Leydig cell tumors, a factor of 3 for nature of effect was selected as the most appropriate value, since the observed effect was for benign tumors. A factor of 10 was selected for Intrahuman sensitivity. A factor of 3 was used for Animal to Human Extrapolation, since dosimetric adjustments were applied to the dose data used for the BMD modeling. This composite factor of 100 was further supported since these types of tumors, although common in rats, are found rarely in people. In addition, the mode of action is likely via peroxisome proliferation which is quantitatively much less important in humans. The panel agreed that the composite MOE of 100 was appropriate.

For the linear dose-response assessment for Leydig cell tumors the BMDL of 0.32 mg/kg-day was used to calculate an oral cancer slope factor as follows:

Slope factor $= $ risk/dose $= 0.1/0.32 = 0.31$ per mg/kg-day

(Note: risk is numerically expressed as 0.1 because the BMDL is the point that represents a 10% increased in tumor incidence in accordance with EPA guidance.) BMD modeling failed for the tumor data for pancreatic tumors and mammary gland fibroadenomas. Therefore, the panel determined that the data for these two tumor types were not adequate to conduct a quantitative dose-response assessment.

Table 9.
Factors Used to Describe Various Areas in the
Development of MOEs for Cancer Endpoints.

Tumor	Model	Nature Of Effect	Intra Human	Animal to Human	Steepness of Slope	Total Exposure	MOE
Liver	MOE	1	10	10	NR	NR	100
Leydig	both	3	10	3	NR	NR	100
Pancreas	both	NA (cannot be modeled)					
Mammary	both	NA (cannot be modeled)					

NR = Not Relevant based on panel judgment; NA = Not Applicable

The panel also voted on confidence ratings for the cancer assessment. *TERA* noted that according to EPA guidance "high confidence" suggests that the assessment is unlikely to change with the availability of new data, while "low confidence" indicates that the assessment is likely to change with new data. Based on these criteria the panel voted on their confidence in the cancer assessment using either the pRfD for liver toxicity to adequately account for the liver cancer risk or using the assessment based on Leydig cell tumors. The panel voted as follows:

> Liver pRfD = high (7 votes); medium-high (2 votes)
> Leydig tumors = low (7 votes); low-medium (2 votes)

Therefore, the panel agreed that the oral pRfD for liver toxicity would be the basis for determining water and soil screening levels (which are based primarily on oral exposure) for the following reasons:

- high confidence in the pRfD (i.e., not likely to change in the future due to additional data collection);
- the pRfD would be protective against the quantitatively less sensitive and questionable relevance peroxisome proliferation-related liver cancer in humans;
- low confidence in the Leydig tumor analysis and questionable relevance to humans;
- limitations in study design, data quality, and data interpretation rendered difficult the determination of whether the reported increased incidence of pancreatic tumors or mammary tumors were related to C8 treatment, and did not allow the modeling of a point of departure that could serve as the quantitative basis for risk value development.

Screening Levels
(Note: Dr. Seed was absent during this part of the meeting)

The consent order required that screening levels be developed for drinking water, soil, and air. The panel followed the guidance provided by U.S. EPA's "Risk Assessment Guidance for Superfund" as further explained by both Region 3 and Region 9 risk-based concentration guidance. In cases where a conflict occurred between the guidance documents, Region 9 guidance was followed because it is more conservative, i.e. more health protective. For drinking water and soil, only ingestion and dermal absorption were considered as routes of exposure. EPA guidance indicates volatilization from water or soil should only be evaluated for chemicals with Henry's law constants greater than 10^{-5} and molecular weights less than 200. Since C8's Henry's Law constant is 10^{-11} and its molecular weight is 431, volatilization was not evaluated.

As discussed above, the panel concluded that since both liver and Leydig cell tumors were potentially formed via nonlinear modes of action, and further since greater confidence was placed in the quantitative assessment based on the liver endpoint, the pRfD and pRfC for liver toxicity would be protective of potential cancer effects of C8. The panel considered that the linear extrapolation for Leydig cell tumors was too uncertain to be used with confidence and that the MOE approach based on the Leydig cell tumors gave essentially the same numerical value as that for the liver endpoint, but with less confidence. Thus, the pRfD and pRfC for liver toxicity, and "noncancer" equations were used for calculating screening levels. Screening levels are calculated following the premise that if lifetime exposure is equal to or less than the pRfD or pRfC, then no risk of deleterious effects is expected. Mathematically, this concept can be expressed by the following standard equation; the ratio of the measured or estimated exposure to the RfD is called the Hazard Quotient.

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If Exposure ÷ RfD = 1 or less, then no risk of deleterious effects is presumed.

Using this concept, it is possible to estimate the concentration in media that results in a lifetime exposure equal to the pRfD or pRfC. These equations, from EPA Region 9's guidance on deriving risk based concentrations, are listed below:

Air Screening Level : $[\ ]$ ug/m^3 = $\dfrac{\text{THQ x RfDi x BW x AT x 1000}}{\text{EF x ED x air IR}}$

$\qquad$ Note: RfDi (mg/kg-day) =   RfC x $\dfrac{20\text{m}^3/\text{d (IR)}}{70 \text{ kg (BW)}}$

Soil Screening Level: $[\ ]$ mg/kg = $\dfrac{\text{THQ x AT x BW}}{\text{EF x ED x [soil IR / RfD x } 10^{-6} + \text{ SA x AF x ABS / RfD x } 10^{-6}]}$

Water Screening Level: $[\ ]$ ug/L = $\dfrac{\text{THQ x AT x BW x 1000}}{\text{EF x ED x [water IR / RfD]}}$

Where:

THQ	=	Target Hazard Quotient, assumed to be 1
RfDi	=	The RfC expressed in terms of dose, mg/kg-day
RfD	=	The oral reference dose estimated by the panel, 0.004 mg/kg-day
RfC	=	The inhalation reference concentration estimated by the panel, see below
BW	=	Body weight, assumed to be 70 kg for adults and 15 kg for children
AT	=	Averaging time, 10950 days, the exposure duration expressed in days
EF	=	Exposure Frequency, 350 days/year, the average number of days each year people are exposed
ED	=	Exposure duration, 30 years, the average number of years people are exposed
IR	=	Inhalation rate for air screening levels, 20 m^3/day; Ingestion rate for soil and, Water screening levels, 200 mg/day soil ingested based on child exposure and, 2 L/day water ingested based on adult exposure
SA	=	Surface area of exposed skin, 2800 cm^2/day
AF	=	Adherence factor, 0.2 mg/cm^2, the amount of soil that adheres to skin
ABS	=	Skin absorption factor, specific factor not available for C8, assumed to be 0.1 for semi-volatile chemical per EPA guidance

The panel unanimously agreed that the equations, assumptions, and default exposure parameters described above were the appropriate choices for calculating screening levels for air, soil, and water. The following values are the screening levels estimated by the equations.

For air: 0.1–6.0 micrograms per cubic meter of air ($\mu g/m^3$) ambient air. Note that the panel considered this range to be interim until the additional work discussed for the RfC is completed. This range incorporates the range of possible NOAEL$_{HEC}$s estimated by *TERA* prior to the meeting as well as the range of composite uncertainty factors recommended by the panel. The final pRfC is discussed in the following section Post Meeting Action Items.

For soil: 244 miligrams per kilogram of soil (mg/kg) residential soil, rounded to 240 mg/kg.

For water: 146 micrograms per liter of water ($\mu g/L$), rounded to 150 $\mu g/L$.

2.3 POST MEETING ACTION ITEMS

The following activities were conducted after the CATT Toxicologists meeting.

Derivation of the pRfC for C8

The CATT panel could not develop a final recommendation on the pRfC or the air screening level during the May 6 and May 7, 2002 meeting. This was due to a lack of data necessary for these calculations. At the meeting, the panel chose the key study for risk factor derivation as the 2-week inhalation study by Kennedy et al. (1986) and voted upon the uncertainty factors. They directed the author, panel member Kennedy (DuPont), to (1) retrieve the standard deviation data for the absolute and relative liver weight data sets; and (2) to measure the particle size distribution in the exposure chamber and determine the corresponding standard deviation; and (3) to provide these data to DEP and to *TERA*. The panel directed *TERA* to utilize these data to develop the pRfC based on the most sensitive organ (liver or lung) and the air screening level based on USEPA Region 9 standard formulas.

During the meeting, the CATT panel agreed that the Kennedy et al. (1986) study was the most appropriate basis for deriving the pRfC, with the developmental study by Staples et al. (1981) providing support for the selected critical effect levels. The CATT panel identified a NOAEL for increased liver weight at the lowest study concentration of 1.0 mg/m^3, with a LOAEL of 7.6 mg/m^3. The NOAEL for lung effects was identified by the CATT panel as 7.6 mg/m^3, with a LOAEL was 84 mg/m^3.

In order to derive an pRfC, the reported study concentrations were converted to human equivalent concentrations (Conc$_{HEC}$), according to current U.S. EPA RfC methodology (USEPA, 1994). The calculation of the Conc$_{HEC}$ requires two steps. First, the study concentration is adjusted from the exposure duration used in the experiment to an equivalent continuous exposure concentration (Conc$_{ADJ}$). Animals in this study were dosed for 6 hours per day, for five days, then not dosed for two days, and dosed again for five days and sacrificed at the end of the 12th day; hence, continuous exposure duration adjustment was made as follows:

$$\text{Study concentration x (6 hours/24 hours) x (10 days/12 days)} = \text{Conc}_{ADJ}$$

Second, the duration-adjusted concentrations (Conc$_{ADJ}$) were converted to human equivalent concentrations (Conc$_{HEC}$) to account for differences in the respiratory tract anatomy and physiology for the test species versus humans. This conversion is made as follows:

$$\text{Conc}_{ADJ} \text{ x RDDR} = \text{Conc}_{HEC}$$

The RDDR is the Regional Dose Deposition Ratio calculated using U.S. EPA's RDDR software program (USEPA, 1994). The RDDR depends on the characteristics of the particle size distribution (e.g., mass median aerodynamic diameter, and geometric standard deviation), the test species and body weight, and the region of the respiratory tract (or extrarespiratory tissue target if applicable) affected by exposure. Appropriate particle size characteristics to use as inputs into the RDDR software were obtained from a recent communication from DuPont (see attached). For the Kennedy et al. (1986) study, the test sex and species was male rats. Since body weight data were provided in the study, these data were used directly in the RDDR program. The mean body weight data on day 5 of exposure was used for this calculation, rather than the study-day 10 body weight data. The day 5 body weights were

used because there was evidence of changes in body weight over the 12-day study period, and therefore, this value was judged as the best estimate of the mean body weight over the period of exposure.

The CATT panel considered two potential critical effects for deriving the pRfC; increased liver weight and overt toxicity secondary to pulmonary toxicity. The RDDR for extrarespiratory tissues was the most appropriate value to use in calculating human equivalent concentrations for assessing the liver effects. The RDDR program calculates values for a variety of different regions of the respiratory tract. The CATT panel agreed that the overt toxicity of C8 was likely due to particle overload, as supported by pulmonary edema in the acute study reported in the same paper (Kennedy et al., 1986). Therefore, the RDDR for the pulmonary region was selected as most appropriate respiratory tract region for calculating the human equivalent concentrations. The calculation of the human equivalent concentrations used in the dose-response assessment is summarized in Table 10.

Table 10. Calculation of Human Equivalent Concentrations for Kennedy et al. (1986)					
		Extrarespiratory		Pulmonary	
Study Concentration[a]	$Conc_{ADJ}$	$RDDR^b$	$Conc_{HEC}$	RDDR	$Conc_{HEC}$
1.0	0.21	2.956	0.62	0.513	0.11
7.6	1.6	2.954	4.7	0.512	0.81
84	17	2.973	52	0.521	9.1
a. All concentrations reported in the table are in units of mg/m^3.					
b. The RDDR values are taken from the EPA RDDR Program Output provided in the attachment					

Benchmark Concentration Modeling

The CATT panel further recommended that benchmark concentration (BMC) modeling be performed for the increased liver weight endpoint from the Kennedy et al. (1986) study. The published version of the study did not provide standard deviations to accompany the group mean data, and therefore, BMC modeling could not be performed at the time of the CATT panel meeting. Subsequent to the meeting, the individual liver weight data for this study were obtained from DuPont (see attached). The individual animal data were used to calculate group mean and standard deviations. These data were then employed for the BMC analyses.

The modeling was conducted according to draft EPA guidelines (U.S. EPA, 2000) using Benchmark Dose Software (BMDS version 1.3.1), available from the U.S. EPA website (U.S. EPA, 2002). The endpoints of interest with respect to C8 liver toxicity were continuous rather than quantal (e.g., incidence data) in nature. Therefore the absolute and relative liver weight data sets were modeled using the linear, Hill, power, and polynomial models. An acceptable fit to the data was defined as a goodness-of-fit p-value greater than or equal to 0.1, or a perfect fit when there were no degrees of freedom for a formal statistical test of fit. Choice of 0.1 is consistent with current U.S. EPA guidance for BMD modeling (U.S. EPA, 2000). Goodness-of-fit statistics are not designed to compare different models, particularly if the different models have different numbers of parameters. Within a family of models, adding parameters generally improves the fit. BMDS reports the Akaike Information Criterion (AIC) to aid in comparing the fit of different models. When comparing the fit of two or more

models to a single data set, the model with the lesser AIC was considered to provide a superior fit. The benchmark response (BMR) level used for this analysis was set at a standard deviation (SD) value of 1.0. This value was chosen based on EPA draft guidelines for BMC analysis (U.S. EPA, 2000), in the absence of a clear biological rationale for selecting an alternative response level.

The following guidance was followed with regard to the choice of the Benchmark Concentration Lower Limit (BMCL) to use as a point of departure for calculation of the pRfC. This guidance is consistent with recommendations in U.S. EPA's BMC guidance (2000). For each endpoint, the following procedure is recommended:

  1. Models with an unacceptable fit are excluded.

  2. If the BMCL values for the remaining models for a given endpoint are within a factor of 3, no model dependence is assumed, and the models are considered indistinguishable in the context of the precision of the methods. The models are then ranked according to the AIC, and the model with the lowest AIC is chosen as the basis for the BMCL.

  3. If the BMCL values are not within a factor of 3, some model dependence is assumed, and the lowest BMCL is selected as a reasonable conservative estimate, unless it is an outlier compared to the results from all of the other models. Note that when outliers are removed, the remaining BMCLs may then be within a factor of 3, and so the criteria given in item 2 would be applied.

  4. The BMCL values from all modeled endpoints are compared, along with any NOAELs or LOAELs from data sets that were not amenable to modeling, and the lowest NOAEL or BMCL is chosen.

The BMC results are summarized in Table 11 and the individual BMDS model run output is provided in the attachments.

For modeling of the absolute liver weight data set, a constant variance model was appropriate (see test 2 in the BMDS output). The power and polynomial models both defaulted to a linear model. None of these linear models fit the data well. The Hill model provided an excellent fit to the data, as indicated by visual inspection of the fit and the comparison of the maximum likelihood estimates for the fitted model to the optimum model (shown as model A1 in the BMDS output). The linear models failed to provide an adequate fit to the full data set, since they did not accommodate the plateau of the concentration-response curve between the mid- and high-concentrations. BMC modeling was redone using a truncated data set (high concentration group removed) to optimize the fits of these models. Removing the high concentration resulted in good fits for the linear models (the power and polynomial models again defaulted to linear) as indicated by the AIC and goodness-of-fit p-values. The Hill model could not be run with the truncated data set since at least four concentration groups are required to provide a model fit.

Adequate fits to the data were achieved when the high concentration data were removed. An argument could be made for using these results as the best estimate for the data set, since an adequate fit was achieved with fewer parameters than for the Hill model using the full data set. However, the BMCL estimate for the full data set was on the border of 3-fold lower than for the truncated data set, which would suggest that the lower BMCL should be selected. Furthermore, comparison of the chi square residuals in the range of the NOAEL concentration suggests that the Hill model provided a better fit of the data in the low concentration region than the linear models using the truncated data. Finally, since

there was no biological rationale for removing the high concentration data from the modeling, an adequate model fit for the full data set is preferred over the model fit for the truncated data set. Based on these considerations, the BMC of 0.78 mg/m^3 and corresponding BMCL of 0.33 mg/m^3 are considered the best estimates for the absolute liver weight data set.

The relative liver weight data displayed a similar plateau between the mid- and high-concentration groups. The linear, power, and polynomial models all failed to provide an adequate fit. As for the absolute liver weight data, the Hill model provided an excellent fit to the data, but in this case failed to calculate a BMCL. In the absence of an adequate BMCL estimate for any of the models using the full data set, the data were remodeled with the high concentration group data removed. The power and polynomial models were nearly linear, as indicated by the parameter estimates in the BMDS output. The linear, power, and polynomial models all provided a similar, and very good visual fit to the data. The goodness-of-fit statistic for the linear model was 0.9. Although BMDS did not calculate the goodness-of-fit p-values for the power and polynomial models, inspection of the maximum likelihood estimates for these fitted models as compared to the optimum model (model A1 in the BMDS output) confirmed the good fit. The linear model provided a similar BMC and BMCL estimate as the power and polynomial models, but required less parameters to do so (i.e., as reflected in the lower AIC). Therefore, the BMC of 1.3 mg/m^3 and the corresponding BMCL of 0.94 mg/m^3 are considered the best estimates for the data set for relative liver weight.

At the time of the meeting the CATT panel did not provide a recommendation on whether absolute or relative liver weight should be considered more appropriate as the critical effect. Both of these measures were significantly increased beginning in the 7.6 mg/m^3 study concentration group. One would not expect a difference in the sensitivity of these two measures in this case, because there was no change in body weight (the basis for calculating relative liver weight) at the NOAEL. Therefore, both absolute and relative liver weight changes are considered to be an adequate basis for the critical effect. Based on this consideration, the lower of the BMCL estimates for the absolute and relative liver weight changes is the most appropriate basis for deriving the pRfC. The BMC of 0.78 mg/m^3 with the corresponding BMCL of 0.33 mg/m^3 for increased absolute liver weight are the best estimates from the BMC modeling results. The BMCL of 0.33 mg/m^3 is the most appropriate choice as the critical effect level for derivation of the pRfC, because the BMCL is lower than either the NOAEL of 0.61 mg/m^3 for liver effects or the NOAEL of 0.81 mg/m^3 for pulmonary effects in this study.

Selection of uncertainty factors

As described in the technical meeting notes, the CATT panel unanimously agreed on the choice of 3 for extrapolation from an animal study (UF$_A$), a factor of 10 to account for variability in human sensitivity (UF$_H$), and a factor of 1 for extrapolation from study NOAEL or BMDL (UF$_L$). The CATT panel considered the selection of U.S. EPA's other two factors, for extrapolation from a study of less-than-lifetime duration (UF$_S$) and for database insufficiencies (UF$_D$), to be dependent on whether liver or lung was ultimately selected as the critical effect. The panel was not unanimous in selection of the UF$_S$ or UF$_D$ for either organ, but a clear majority vote was obtained for these UFs regarding liver toxicity.

Based on the liver as a critical effect, panel members recommended values of either 1 (one vote), 3 (six votes) or 10 (1 vote) for UF_S, and values of 3 (six votes) or 10 (two votes) for UF_D. Therefore, based on the liver as the critical effect, the composite UF would range from 100 to 1000, depending on the selection of the values for UF_S and UF_D. The majority vote of the CATT panel (Table 5) supported a factor of 3 for UF_S and 3 for UF_D. Based on these values, a composite UF of 300 for liver effects was calculated.

Based on the lung as the critical effect, panel members recommended values of either 1(three votes), 3 (three votes) or 10 (two votes) for UF_S, and values of 1 (one vote), 3 (five votes), and 10 (two votes) for UF_D. Therefore, with the lung as the critical effect the composite UF would range from 30 to 3000. The majority of the CATT panel supported a value of 3 for UF_D based on lung effects. A clear majority vote was not determined for any one value for the UF_S; however, six votes were cast for a value lower than 10 and five votes were cast for a value higher than one; thus the median value of 3 would be a reasonable choice. Therefore, values of 3 for both UF_D and UF_S for lung effects would also result in a composite UF of 300.

However, it is important to note that the panel could not arrive at a consensus on the overall magnitudes of UF_S and UF_D, because of the numerous uncertainties with the inhalation database. The resulting range in the uncertainty factor was generally considered reasonable by the panel, with values falling within this range being indistinguishable from each other.

Calculation of the pRfC

Liver toxicity was identified as the critical effect because it was more sensitive to C8 than the lung (i.e., liver toxicity had a lower NOAEL or BMCL than lung), the composite UF ranged from 100 to 1000 and was 300 based on the majority vote.

The pRfC is calculated as follows:

pRfC (mg/m^3) = critical effect level / composite UF

pRfC range = 0.33 / 1000 = 0.00033 mg/m^3 (or rounded to 0.3 μg/m^3)
to
= 0.33 / 100 = 0.0033 mg/m^3 (or rounded 3.3 μg/m^3)

pRfC (majority vote) = 0.33 / 300 = 0.0011 mg/m^3 (or rounded to 1 μg/m^3)

Therefore, the recommended pRfC based on the majority vote for a composite UF of 300 is 1 microgram per cubic meter of air (μg/m^3) with a range from 0.3 μg/m^3 to 3.3 μg/m^3.

Table 11. Benchmark Dose Modeling Results for C8[a]				
Model/Data Set	AIC	P-value	BMC[b]	BMCL
Absolute Liver Weight –All Data Modeled				
Linear	62.58[c]	<0.001[d]	31	19
Hill	48.67	1.0[e]	**0.78**	**0.33**
Power	62.58[c]	<0.001	31	19
Polynomial	62.58[c]	<0.001	31	19
Absolute Liver Weight - High Concentration not Modeled				
Linear	38.22[c]	0.72	1.6	1.1
Power	38.22[c]	0.29[d]	1.6	1.1
Polynomial	38.22[c]	0.72	1.6	1.1
Hill	Insufficient Number of data points to run model			
Relative Liver Weight – All Data Modeled				
Linear	-167.65[c]	<0.001	21	15
Hill	-184.29	1.0[e]	1.1	Failed
Power	-167.65[c]	<0.001	21	15
Polynomial	-167.65[c]	<0.001	21	15
Relative Liver Weight - High Concentration not Modeled				
Linear	-137.04[c]	0.90	**1.3**	**0.94**
Power	-135.05[c]	Failed	1.5	0.94
Polynomial	-135.05[c]	1.0[e]	1.5	0.94
Hill	Insufficient Number of data points to run model			

[a] Modeling was performed based on absolute and relative liver weight results reported in Kennedy et al. (1986).

[b] BMC and BMCL are based on benchmark response of 1SD. Results are presented in units of mg/m^3. BMC and BMCL estimates in bold type are the estimates judged to be the best estimates for each endpoint. "Failed" indicates that BMDS was unable to produce the estimate or the information required to be able to present a value.

[c] Corrected from erroneous BMDS output. Errors were identified in the degrees of freedom (DF) provided in the output for the fitted model in several cases. For these cases, the AIC was calculated independently using the log likelihoods provided in the output and the correct number of DF. Similarly, the goodness-of-fit p-values were corrected by calculating manually the chi square p-value using the appropriate number of DF.

[d] This model provided an identical fit to the linear and polynomial models. The reported P-value reflects a difference in the maximum likelihood estimate for the comparison model (Model A1 in the BMDS output) across the three models. This difference the maximum likelihood estimate should be the same for all three models, since this estimate is model independent.

[e] A fit that maximizes the likelihood is assigned a p-value of 1.0, even if there were no degrees of freedom for a formal statistical test. The maximized likelihood is given by model A1 for constant variance models and model A2 for non-constant variance models. Models A1 and A2 are independent of the model chosen to fit the data (e.g., power, polynomial, Hill model) and provide the best match possible to the mean and standard deviation for each dose level.

Calculation of an Air Screening Level

As described in the technical meeting notes, U.S. EPA Region 9 methodology was judged by the CATT panel to be an appropriate basis for deriving the air screening level. The following standard formula was used to calculate the air screening level:

$$\text{Air Screening Level } (\mu g/m^3) = \frac{THQ \times RfDi \times BW \times AT \times 1000}{EF \times ED \times \text{air } IR}$$

$$\text{Note:} \quad RfDi \text{ (mg/kg-day)} = RfC \times \frac{20m^3/d \text{ (IR)}}{70 \text{ kg (BW)}}$$

Where:

THQ	=	Target Hazard Quotient, assumed to be 1
RfDi	=	The RfC expressed in terms of dose, mg/kg-day
RfC	=	The inhalation reference concentration (mg/m^3)
BW	=	Body weight, assumed to be 70 kg for adults
AT	=	Averaging time, 10,950 days, the exposure duration expressed in days
EF	=	Exposure Frequency, 350 days/year, the average number of days each year people are exposed
ED	=	Exposure duration, 30 years, the average number of years people are exposed
IR	=	Inhalation rate for air screening levels, 20 m^3/day

Using this equation, the air screening level ranges from 0.3 $\mu g/m^3$ to 10 $\mu g/m^3$. Using a reasonable median value, the air screening level would be 1.1 $\mu g/m^3$ (or rounded to 1 $\mu g/m^3$).

2.4 SUMMARY OF FINDINGS

The key studies, critical effects and levels, uncertainty factors, and provisional risk factors developed by the CATT toxicologists are summarized in Table 12.

Table 12. Summary of RfD and RfC Values for C8 Determined by the CATT Toxicologists									
Reference	Critical Effect	Critical Effect Level[a]	UF$_A$	UF$_H$	UF$_L$	UF$_S$	UF$_D$	Composite UF[b]	RfD/RfC
Oral Studies									
Palazzolo et al. (1993)[c] 90-day rat study	Increased relative liver weight with histopathology in male rats	0.47 (NOAEL in males) 0.72 (BMDL)	10	10	1	1	1	100	0.005 0.007
York et al. (2002) Two-Generation rat study	Increased liver weight in male rats, supported by histopathology at higher doses (histopathology was not examined at the lowest dose, but incidence of hypertrophy was 100% at next highest dose).	0.42 (BMDL in males)[d]	10	10	1	1	1	100	0.004
RikerLaboratories (1983) Two-year rat study	Hepatic megalocytosis in male rats.	0.73 (BMDL in males)	10	10	1	1	1	100	0.007
Thomford et al. (2001)[e]26-week cynomolgus monkey study	Decreased thyroid hormone levels in male cynomolgus monkeys, and supported by a NOAEL at the same dose for clinical signs of toxicity in the co-critical rhesus monkey study (Goldenthal et al., 1978b)	3 - 10 (LOAEL in males)	10	10	3	3	1	1000	0.003 - 0.01

Inhalation Studies									
Kennedy et al. (1986)[f] Two-week rat study	Increased liver weight supported by histopathology and clinical chemistry in male rats	0.61(NOAEL - HEC$_{ER}$males) 0.33 (BMCL, BMC 0.78 absolute liver weight) 0.94(BMCL, BMC 1.3 relative liver weight)	3	10	1	3	3	300	1
Dermal Studies									
Kennedy et al. (1985)[f] Two-week rat study	Increased liver weight in male rats	4.2[g] (LOAEL in males)							Data Inadequate

a. Oral and Dermal effect levels and RfDs are presented in units of mg/kg-day, while the inhalation critical effect level and RfC is presented in units of mg/m^3

b. Areas of uncertainty addressed by uncertainty factors are: animal to human extrapolation (A); intrahuman variability and protection of sensitive subpopulations (H); extrapolation from a LOAEL to a NOAEL(L); extrapolation from a subchronic to chronic exposure (S); and lack of a complete database (D)

c. The subchronic study by Goldenthal et al. (1978a) could serve as a supporting study for liver effects in rats.

d. BMDL is the 95% lower confidence limit on the dose corresponding to a response level of 10% or an increase of 1SD in the continuous endpoint being assessed. Only modeling results that provided the lowest value and provided an adequate fit to the data are provided.

e. The subchronic study in rhesus monkeys by Goldenthal et al. (1978b) is a co-critical study for clinical signs of toxicity in monkeys.

f. These studies are not adequate for derivation of an IRIS quality RfD/RfC of even low confidence. The values shown could be used to derive a provisional value. Derivation of the RfC or RfD via route-to-route extrapolation is not supported by the available toxicokinetic data. Consensus on the values for UF$_s$ and UF$_D$ was not reached by the panel; however, a majority vote was obtained for a value of 3 for both these UFs in reference to liver as the target organ. See text of this report for ranges of UFs and SLs based on the range distribution of the votes for UFs.

g. 4.2 mg/kg-day reflects the study dose of 20 mg/kg adjusted for discontinuous exposure.

I agree that the notes as presented accurately reflect the panel's discussion and conclusions during the May 6-7, 2002 C8 Assessment of Toxicity Toxicologists Panel Meeting, and that the post meeting actions taken to develop the pRfC and Air Screening Level are in accordance with the instructions provided to *TERA* by the panel. (Original signatures are on file at DEP.)

_____   _____
John Cicmanec, D.V.M., M.S., ACLAM, USEPA ORD   Date

_____   _____
Joan Dollarhide, M.S., M.T.S.C., J.D., *TERA*   Date

_____   _____
Michael Dourson, Ph.D., D.A.B.T., *TERA*   Date

_____   _____
Gerald Kennedy, DuPont   Date

_____   _____
Andrew Maier, Ph.D., C.I.H., *TERA*   Date

_____   _____
Samuel Rotenberg, Ph.D., USEPA Region 3   Date

_____   _____
Jennifer Seed, Ph.D., USEPA Headquarters OPPT   Date

_____   _____
Dee Ann Staats, Ph.D., DEP (Chairperson)   Date

_____   _____
John Wheeler, Ph.D., D.A.B.T., ATSDR   Date

_____   _____
John Whysner, M.D., Ph.D., D.A.B.T.   Date

3. 0 COMPARISON OF SCREENING LEVELS TO SITE-RELATED DATA

After the SLs for air, water, and soil were determined, DEP compared these SLs to the site-related data that has been collected to date. These comparisons are summarized below. The work of the CATT was only one facet of an investigation that continues beyond the issuance of this report. The GIST is expected to issue a report of the groundwater and surface water data in early 2003. The air modeling effort continues and is currently focusing on determining the results of the air emissions reduction efforts by DuPont required in the consent order as a 50% reduction in overall emissions (both air and water) by the end of 2003. Upgrades were completed in June 2002 which included the installation of a new scrubber and increased height of the primary C8 emissions stack.

Water

To date, of the 188 samples collected from private wells, cisterns, and springs, 50 were used for drinking water and none exceeded the 150 ppb health protective water SL for C8. Also to date, nine public water supply facilities in West Virginia have been analyzed for C8, including Belleville Locks and Dam, Blennerhassett Island, General Electric, Lubeck Public Service District (PSD), Mason County PSD, Parkersburg PSD, Racine Locks and Dam, New Haven Water Department, and Ravenswood. None of the drinking water from these facilities contained concentrations of C8 that exceeded the 150 ppb water SL. In fact, the concentrations of C8 in public water supplies were all below 2 ppb, below 15 ppb in private non-drinking water, and below 3 ppb in private drinking water wells in West Virginia. Samples were collected from Ohio public and private water supplies. Although C8 levels in some Ohio private water supplies were higher than those detected in West Virginia, none of these samples contained C8 concentrations above the water SL. These data have been provided to Ohio EPA and DEP will continue to share information with throughout the remainder of this investigation. The DEP notes that the water SL is higher than DuPont's internal community exposure guidelines for drinking water of 1 or 3 ppb; however, these guidelines were developed in the early 1990s and based solely on a two-week inhalation study from 1986. Since then significant additional toxicological data have been collected and the CATT water SL is based on a comprehensive examination of all available information. Sampling of the Ohio River has begun; preliminary analytical results are expected from the laboratory in September 2002. To date, no analysis has been performed to measure C8 in soils in West Virginia on private property; therefore, no comparison can be made to the soil SL.

Air

Mathematical computer models that incorporate weather conditions, chemical characteristics, and facility measurements were utilized by DEP to simulate the ambient air concentrations of C8. Based on actual emissions data from the DuPont WW facility for the year 2000, the DEP modeling efforts predicted a maximum C8 concentration in air of approximately 2.7 $\mu g/m^3$ at the facility fence line along the Ohio River. The maximum modeled C8 air concentration in the West Virginia residential area adjacent to the facility was approximately 0.2 $\mu g/m^3$ annual average. Predicted C8 air concentrations across the Ohio River from the WW facility in Ohio residential areas were greater than those predicted in residential areas in West Virginia. These data have been provided to Ohio EPA and DEP will continue to share information with Ohio EPA throughout the remainder of this investigation. Results of similar subsequent air modeling efforts conducted by DuPont are consistent with those of the DEP. Air modeling information can be obtained from the DEP Division of Air Quality.

The DEP's Divisions of Water Resources and Air Quality are currently reviewing all relevant air and water data to determine DuPont's compliance with the November 2001 consent order between DEP and DuPont.