Report of the Peer Consultation Meeting On Decabromodiphenyl Ether

April 2 and 3, 2003
University of Cincinnati
Cincinnati, Ohio

Submission by
American Chemistry Council's Brominated Flame Retardant Industry Panel for the Voluntary Children's Chemical Evaluation Program (VCCEP)

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

September 30, 2003

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Executive Summary

A panel of scientists with expertise in toxicity testing, risk assessment, exposure assessment, and children's health met on April 2 and 3, 2003 to conduct a peer consultation of a submission on decabromodiphenyl ether (a.k.a. decabromodiphenyl oxide, DBDPO). The American Chemistry Council's Brominated Flame Retardant Industry Panel (BFRIP) prepared the submission for the Voluntary Children's Chemical Evaluation Program (VCCEP). The purpose of the meeting was to provide a science-based forum to determine whether the existing data are adequate to characterize the risks of DBDPO to children, and, if not, to identify data needs.

DBDPO is used solely as a flame retardant in the hard, dense plastics of consumer electronics products and in the latex back coating of flame retardant upholstery textiles. BFRIP noted that DBDPO saves an estimated 280 lives each year in the U.S. by prevention of fires, and the toxicity of the chemical is low. A developmental toxicity study in rats and a two-year bioassay in rats and mice both identified oral NOAELs (no-observed-adverse-effect-levels) greater than 1,000 mg/kg-day. The bioassay (NTP 1986) showed "some evidence" of carcinogenicity in male and female rats and "equivocal evidence" in male mice. Behavioral effects were reported in an abstract of a neonatal mouse study (Viberg et al. 2001), but insufficient data were available on this study to use it as a basis for risk assessment. Manufacturing facilities using DBDPO have not reported any acute or chronic health problems from occupational exposures, but no epidemiology studies have been conducted.

The panel discussed whether the existing toxicity data are adequate to fully determine DBDPO's hazard potential for children. Some panel members noted that only a few studies were specifically designed to evaluate adverse effects on young animals, and that these studies do not provide all the information that would be obtained from two-generation or developmental neurotoxicity studies. Other members pointed out that information from the many toxicity studies that do exist on the chemical do not indicate cause for concern regarding potential *in utero* or neonatal toxicities, and the existing data are sufficient to evaluate both the potential hazards to children and to the reproductive ability of adults. The panel discussed the Viberg study that reported radioactivity in brains of neonatal mice after a single gavage dose of [^{14}C]DBDPO. Behavioral disturbances were observed as the mice matured. Sufficient details were not available to fully evaluate the study and its findings, but panelists discussed questions about the approach and data analysis. They concluded that the questions could not be answered until more details on the study are published. Other issues raised by individual panel members included thyroid effects, the lack of inhalation studies, the variation of DBDPO test materials used in the toxicity studies, and uncertainties surrounding DBDPO's metabolism and absorption.

The panel also discussed exposure to DBDPO and the exposure assessment. In the U.S., DBDPO has been detected in outdoor and indoor air, and also in dust, sediments, and sewage sludge. Minimal hydrolysis or photolysis is expected, and DBDPO does not show convincing evidence of biodegradation to penta- or tetrabromodiphenyl ethers in the environment or *in vivo.* The sponsor identified and described the major potential exposure situations to workers, non-workers, nursing infants, and children, concluding that nursing infants of mothers in high-exposure jobs in DBDPO manufacturing plants would have the greatest potential for exposure. The sponsor did not estimate exposures *in utero* or to prospective parents because they had

concluded that existing animal toxicology studies showed no evidence of fetal, developmental, or reproductive toxicity.

Panel members discussed DBDPO's potential for debromination in the environment. They noted that, although debromination appears to be possible in some situations, the penta- and tetrabromodiphenyl ethers found in the environment do not appear to originate from DBDPO molecules. They discussed DBDPO binding to sludge and noted that sludge may be applied to farmlands where exposure to humans might occur directly or via food crops. Panel members thought that if bioconcentration in the food chain does occur, it is likely to be minimal. Some members noted that DBDPO in plastic matrices is an additional potential source of human exposure because the chemical might migrate out of plastic into air and might occur in dust from deteriorated plastic matrices. They noted DBDPO has been detected in house dust and airborne urban outdoor particles. Several of the panel members concluded that DBDPO in the indoor or outdoor environment is not a major source of human exposure.

The panel discussed recent studies on DBDPO in dust and breast milk from Europe and the U.S. These study data were not available when the written submission was prepared, and were not yet published at the time of the panel meeting. The sponsor's preliminary calculations of dust exposures from these data indicate that intake would be several orders of magnitude lower than the estimated intake from ingestion. The breast milk data from women in a U.S. city found some samples containing DBDPO. The sponsors noted that the levels of DBDPO found in these samples would not change the breast milk-to-serum ratio used in the submission and concluded their exposure assessment would not be different if these new data had been included.

Several panel members concluded that the combination of the sponsor's written submission and slide presentation provided a sufficient exposure assessment of DBDPO. Some panel members, however, disagreed with the sponsor's decision not to estimate exposures *in utero* and to prospective parents.

The sponsor summarized their risk characterization and data needs assessment. They identified the Reference Dose (RfD) derived by the National Academy of Sciences (NAS) as the most appropriate value to compare with exposure estimates and noted that their upper estimates of exposures to children were substantially below this RfD value. The hazard quotients for all pathway-specific and aggregate exposures are less than one. The sponsor concluded that risk can be adequately characterized with the existing data and no additional toxicity or exposure data are needed.

While most members thought the NAS RfD was appropriate to use, some members questioned whether this RfD is sufficiently conservative for evaluating risks to children. A concern was raised that use of blood serum data from 1988, collected from a limited number of adults, might underestimate current upper exposures to U.S. infants because of possible increases in DBDPO environmental levels during the past several years. Some panelists thought that the upper levels of exposure estimated in the submission were not sufficiently conservative. Other panelists noted, however, that even if such increases have occurred, the hazard quotients would continue to be less than one.

After discussing potential *data gaps* (i.e., areas for which data are not available, or there are significant uncertainties) in the context of the hazard or exposure assessment, panel members then individually identified *data needs* (i.e., data gaps for which additional information is required before potential risks to children can be adequately evaluated). Identification of data needs was done within the context of all other available information (e.g., on exposure, hazard, and risks).

Panel member's opinions on data needs ranged from one member who did not think there are any data needs to others who identified several needs. In the area of exposure, a majority of panel members thought obtaining more human serum data was a priority data need for DBDPO. If additional serum data demonstrate human exposures to be higher than currently estimated, many panel members would consider the possible need for other data and studies; otherwise, most would not. Several members thought additional work to better clarify environmental fate and the potential for debromination was indicated. Several others commented that they thought the sponsor had identified the major exposure routes and the maximum possible exposures, even though there are uncertainties in the data and estimates. In the hazard area, many members thought it was important to review the complete description of the Viberg study when additional data on that study are available. This review would help determine whether further investigations are needed in that area. Some of the panel members concluded that, although additional toxicity studies might provide useful information, further studies probably would not change the hazard assessment or risk characterization of DBDPO significantly. A complete list of all identified data needs, together with the number of panelists identifying each data need, is provided in the report.

Attendees

Sponsor

American Chemistry Council's Brominated Flame Retardant Industry Panel

Presenters

Marcia L. Hardy, D.V.M., Ph.D.
Senior Toxicology Advisor
Albemarle Corporation

Sean M. Hays, M.S., M.S.
Senior Scientist, Human Health Risk Assessment
Exponent, Inc.

Peer Consultation Panel Members

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

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

Kevin M. Crofton, Ph.D. Toxicology
U.S. Environmental Protection Agency (EPA), National Health and Environmental Effects Laboratory

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

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

Robert C. Hale, Ph.D. Marine Science
Virginia Institute of Marine Science

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

Michael Jayjock, Ph.D. Environmental Engineering
Rohm and Haas Company

Sam Kacew, Ph.D. Pharmacology
University of Ottawa

R. Jeffrey Lewis, Ph.D. Epidemiology
ExxonMobil Biomedical Sciences, Inc.

Ruthann Rudel, M.S. Hazardous Materials Management
Silent Spring Institute

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

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

Observers and Other Attendees

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

Background

Toxicology Excellence for Risk Assessment (*TERA*) organized this peer consultation meeting. *TERA* is an independent, non-profit organization with a mission to protect public health through the best use of toxicity and exposure information in the development of human health risk assessments. *TERA* has organized and conducted peer review and consultation meetings for private and public sponsors since 1996 (see http://www.tera.org/peer for information about the program and meeting reports). Under this program, *TERA* has organized this peer consultation for an assessment of decabromodiphenyl ether (a.k.a. decabromodiphenyl oxide; DBDPO) under the Voluntary Children's Chemical Evaluation Program (VCCEP). The assessment was submitted by the American Chemistry Council's (ACC) Brominated Flame Retardant Industry Panel (BFRIP). BFRIP member companies are: Albemarle Corporation, Ameribrom, Great Lakes Chemical Corporation, and Akzo-Nobel (an associate member).

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

The VCCEP pilot program was designed to use a tiered testing approach. For toxicity data, specific types of studies have been assigned to one of three tiers. For exposure data, the depth of exposure information increases with each tier. Tier 1 assessments should use all available data and therefore some of the Tier 1 chemical assessments will include more than what is indicated

for Tier 1. BFRIP volunteered to sponsor a Tier 1 assessment for DBDPO, utilizing the available information and data. If data needs are identified through this process, then BFRIP will choose whether or not to volunteer for any additional testing and for a Tier 2 assessment.

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

The VCCEP Peer Consultation Panel for DBDPO consisted of 13 members independently selected by *TERA*. Each panel member disclosed information regarding potential conflicts of interest and biases for the VCCEP program in general and for DBDPO in particular. *TERA* evaluated these disclosures in selecting the panel members. The disclosures were publicly presented at the beginning of the meeting. The panel members have experience in various disciplines, including toxicity testing, exposure evaluation, risk assessment, and children's health. The panel received a copy of the submission and key references approximately one month before the meeting, so that they had adequate time to review the documents and prepare for the discussions. Panel members bring a range of views and perspectives to the peer consultations, reflecting the interest in VCCEP by a wide range of stakeholders. The panel does not attempt to reach consensus, rather the individual opinions of the members are noted.

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

TERA prepares a report for each meeting that summarizes the sponsor's presentations, the panel discussions, the sponsor comments, and any comments from the public. The meeting report is a summary, not a transcript. Individual opinions of the panel members are noted (although not identified by name), along with areas of agreement and disagreement. Panel members review and comment on the draft report, which is made available to the public when finalized (see http://www.tera.org/peer/VCCEP/welcome.htm) The sponsor is given the opportunity to review the draft report to confirm the accuracy of the sponsor presentations and comments. Changes suggested by the panel members or sponsors are shared with the full panel before the report is finalized. *TERA* staff resolve any differences by carefully reviewing materials from the meeting.

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

Welcome and Introduction

The meeting opened with a welcome by Ms. Jacqueline Patterson of *TERA*. She described the background and purpose of the VCCEP and the agenda for the meeting, noting that copies of panel members' biosketches and conflict of interest (COI) and bias disclosure statements were provided to all attendees. Panel members introduced themselves and noted whether they had additions or changes in their disclosure statements. No panelists had changes or additions, and the panelists had no questions regarding one another's disclosures. See Appendix B for the panel biographical sketches and disclosure statements.

Dr. Michael Dourson, the panel chair, described how the meeting would be conducted. He explained that discussions would be based on the questions found in the charge to the panel (Appendix B). He noted that all panelists would have the opportunity to state their positions on the charge questions, to ask one another clarifying questions, and to further discuss the issues. No attempt would be made to reach a consensus position on the charge questions. The chair reminded the panel that the purpose of the peer consultation is not to critique the submission document, but to answer questions on data adequacy for characterizing risk to children. He noted the panel is free to ask anyone questions during the meeting break times, but any meeting-related information gained from these discussions should be shared with the rest of the panel when the panel reconvenes.

The meeting was open to the public. Observers were invited to submit technical comments in writing before the meeting and to make oral comments during the meeting. Two sets of written comments were received before the meeting, and one set was presented orally during the meeting. Both sets of written comments were distributed to the panel members and sponsors before the meeting, and copies were provided at the meeting for observers. These written comments are found in Appendix C. The summary of the oral comments is provided within the discussions captured below.

The panel members agreed to distinguish between the terms *data gaps* and *data needs*. Data gaps are areas for which data are not available, or there are significant uncertainties. Data needs are data gaps for which additional information is required before potential risks to children can be adequately evaluated. Members will identify data gaps during the hazard, exposure, and risk characterization discussions. At the end of the meeting, after considering the data gaps within the context of all other information (e.g., on exposure, hazard, and risks), the individual panel members will identify those items they personally believe are data needs. Because the purpose of the VCCEP meeting is to obtain a wide range of viewpoints it is to be expected that many data needs may be identified. The peer consultation is not a consensus process and no attempt is made to agree on a common list of data needs. To provide perspective for the reader and an overall sense of concern, the number of panel members who identify each data need is noted in the report.

Hazard Assessment

Sponsor Presentation

On behalf of BFRIP, Dr. Marcia Hardy of Albemarle Corporation presented general background information on DBDPO and the hazard assessment (see Appendix D for a copy of the presentation slides). DBDPO is used solely as a flame retardant in the hard, dense plastics of consumer electronics products (~80% production volume) and in the latex back coating of flame retardant upholstery textiles (~20% volume). In the applications in which DBDPO is used, an estimated 280 lives are saved each year in the U.S. through the prevention of fires (F. Clarke 1997). Children, especially vulnerable in fires, are at high risk of death, injury, or burns.

DBDPO is a large, poorly absorbed molecule with a low order of toxicity. It is not acutely toxic, not irritating or sensitizing to the skin or eyes, and not genotoxic. It has been tested in acute, subchronic, chronic, developmental, pharmacokinetic, and carcinogenicity studies, including NTP bioassays in mice and rats.

DBDPO has a no-adverse-effect-level of at least 1000 mg/kg-day based on repeated dose studies in rats and/or mice (NTP 1986, Hardy et al. 2003). Doses of 2.5 or 5% DBDPO were administered in the diet to rats and mice for two years (NTP 1986). Histopathology showed liver thrombosis and degeneration in male rats, and liver granulomas and thyroid follicular cell hyperplasia in male mice. Rats of both sexes showed some evidence of carcinogenicity based on hepatic neoplastic nodules. Male mice showed equivocal evidence of carcinogenicity based on the combined incidence of hepatic adenomas and carcinomas. A recent developmental toxicity study in rats (Hardy et al. 2002) identified an oral NOEL (no-observed-effect-level) greater than 1,000 mg/kg-day.

Following oral dosing, DBDPO is poorly absorbed and rapidly eliminated in feces. Some metabolism occurs in the gut to conjugates and hydroxy compounds. According to El Dareer et al. (1987), over 98% of ingested DBDPO is excreted as the parent molecule.

The sponsor described a neonatal mouse study (Viberg et al. 2001; Appendix IV of the submission), noting that the published information on this study is limited to a four-page abstract, which includes minimal data and few details[1]. According to the abstract, behavioral effects were observed in pups receiving a single gavage dose of 20 mg/kg laboratory-synthesized DBDPO. The effects were observed when the test material was given on Post Natal Day (PND) 3, but not when it was given on PNDs 10 or 19. The sponsor's opinion was that the total amount of information available on this study -- from the published abstract and from subsequent contacts with the authors -- is not sufficient to draw conclusions regarding potential neurotoxicity or other adverse effects. Further, the sponsor calculated that for mouse pups to obtain an equivalent DBDPO dose from their mothers' milk, the dams would need to ingest DBDPO at a rate of 4,160 mg DBDPO/kg food/day.

[1] As this report identified behavioral effects that had not been investigated or reported in other studies, the sponsors attempted to obtain additional study details from the authors. The authors declined to share more information before publication.

The sponsor noted that a major issue for DBDPO is its potential degradation to less brominated diphenyl ethers. DBDPO comprises about 80% of the polybrominated diphenyl ethers (PBDEs) manufactured, yet tetrabromodiphenyl ether (tetraBDE) and pentabromodiphenyl ether (pentaBDE) are the predominate congeners detected in the environment and biota. A key question is whether these compounds originate from DBDPO. DBDPO strongly partitions to soil and sediment. There is no indication of degradation in sediment based on monitoring data and long-term anaerobic sediment degradation studies. Minimal partitioning to air and water is observed, and minimal hydrolysis or photolysis is expected based on DBDPO's water solubility and structure. A 32-week anaerobic sediment study using [^{14}C]DBDPO found no evidence of degradation (Schaefer and Flaggs 2001). A two-year anaerobic sediment study also found no degradation of DBDPO (de Wit 2000). Sediment monitoring in Europe does not provide evidence that DBDPO is degrading to tetra- and pentaBDE congeners (de Boer et al. 2001). Reconstruction of the PBDEs detected in an industrial region of the Frasier River near Vancouver, British Columbia, showed the pattern more closely approximated the penta- and octaBDE commercial mixtures and supports the position that these congeners did not derive from DBDPO (Rayne and Ikonomou 2002). Photolysis studies sponsored by BFRIP at Purdue University provided no evidence for the production of tetra or pentaBDEs from DBDPO.

Clarifying Questions from Panel

The panel members asked a number of clarifying questions of the sponsor. Some of the questions and responses are noted here, while others are included in the panel discussions below.

The sponsor addressed questions from two panelists regarding DBDPO's physical form and half-life when used in electronics equipment and upholstery textiles. DBDPO is added as a powder to resins and encapsulated within the plastic matrix for electronics equipment. The sponsor's opinion was that migration of DBDPO from the plastic is theoretically possible but expected to be minimal due to DBDPO's physical/chemical properties. The sponsor noted that the latex backing of upholstery textiles could crumble with age, but thought that particles likely would be larger than respirable size and would consist of DBDPO encapsulated in latex.

In response to a question regarding the availability of human data to evaluate toxicity, the sponsor noted that no epidemiology studies have been conducted on DBDPO; however, manufacturing facilities using this chemical have not reported any acute or chronic health problems in exposed workers.

When asked about the basis for the fugacity modeling discussed in the *Environmental Fate and Transport* section of the submission (page 48), the sponsor explained that the methods were developed by the Syracuse Research Corporation and the estimates were based upon DBDPO's chemical structure. A DBDPO release rate of 1000 kg/hr into air, soil, and water was assumed. The sponsor believes the 23% DBDPO assumed to undergo advection is an over-estimate.

Public Comments on Hazard Assessment

Ms. Kathleen Lawson, representing The Learning Disabilities Association of America (LDA), read a statement that was excerpted from the organization's written comments found in Appendix C. The panel had no clarifying questions for Ms. Lawson.

Panel Discussion of Hazard Assessment

The panel discussion on hazard assessment was framed by the following charge questions:

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

2. Is the quantitative hazard and dose-response information that is carried forward to the risk characterization the appropriate information to use?

Because the panel discussion did not strictly follow the charge questions, the text below is organized by topic area. The primary topics discussed by the panel included the Viberg abstract, *in utero* and perinatal studies, thyroid effects, inhalation and lung effects, purity of the test material, metabolism, and use of the National Academy of Sciences (NAS) RfD value.

Viberg Abstract[2]

The panel extensively discussed the information provided in the abstract by Viberg et al. (2001). This abstract reports finding radioactivity in brains of neonatal mice after a single gavage dose of [^{14}C]DBDPO in a high-fat emulsion carrier. Behavioral disturbances were observed as the mice matured. The effects were observed when the dose was given on PND 3, but not when it was given on PND 10 or 19. Several panel members expressed concern regarding the lack of details available on this study. Individual panelists said the reported information is inconclusive because of insufficient data on study methods, animals, test materials, litter effects, and statistical treatment of data. They noted the small numbers of animals and litters per dose group, and use of statistical analysis based on pup, rather than the preferred litter, basis.[3] Moreover, no data or information on its variability was provided in the abstract. One panelist thought that Viberg's experimental and statistical procedures, while not reported in the abstract, were almost certainly the same as those previously published by the Ericsson laboratory (e.g., Ericsson et al. 1998; Ericsson 1997).

A panelist stated that the 20% fat emulsion used in the Viberg study was close to the fat percentage found in mouse milk. Mice gavaged with this emulsion on PND 3 or 10 displayed about 0.4% of the administered radioactivity from [^{14}C]DBDPO in their brains 24 hours after

[2] Subsequent to the meeting, this study has been published (Viberg et al 2003)

[3] After the meeting a panelist contacted the investigators and determined they did not control for the selection of animals from each litter for subsequent experiments.

administration.[4] Dosing of the mouse pups was timed to occur during the animals' brain growth spurt. Since the brain growth spurt in mice follows birth, the panelist thought using an emulsion vehicle that may mimic mouse milk was appropriate. A panelist noted that this vehicle, with its possible enhancement of absorption, would not be relevant for humans because in humans the brain growth spurt occurs prenatally. A panelist cautioned that brain growth spurts occur at different times in different parts of the brain. He said that generalizing these events to the entire brain and then comparing their timing among different species is an over-simplification.

In addition to the concerns discussed above, some panel members thought the increased radioactivity detected in the mouse brains seven days after dosing, relative to 24 hours after dosing, might indicate presence of DBDPO metabolites. They suggested that DBDPO might need to be metabolized before it can enter the brain. Another panelist expressed concern that the observation of spontaneous motor activity was done only once for each animal. He said such observations should be done more than once because this parameter can vary greatly in the same animal.

When panel members were queried whether information in the Viberg abstract was sufficient to form the basis for estimating a different RfD, several members stated that it was not, but they suggested it did identify potential uncertainties with the existing RfD. Acknowledging that there are questions on the study protocol, many members thought the study still suggests absorption and metabolism differences may exist between very young mice and slightly older ones.

In Utero and Perinatal Studies

In discussing the available database from the *in utero* and perinatal toxicity studies, a panel member noted that the existing one-generation study (Norris et al. 1975) is unable to provide information on many of the important endpoints that would be obtained from two-generation or developmental neurotoxicity studies. Another member acknowledged the Norris study does not provide all the desired information, but noted that it does evaluate the reproductive ability of adults and includes postnatal exposure up to three weeks. Moreover, no effects were observed on pup weight gain, viability, histopathology of numerous organs, including bone marrow, or any other parameters to indicate cause for concern. In addition, there was no indication of neurotoxicity effects in any of the developmental, reproductive, 90-day, or two-year studies. Other members responded that nothing was seen in the one-generation study because the dose was far below the effect level (the top dose given was 100 mg/kg-day). They emphasized that seeing no effects in tested parameters does not predict a lack of effects in parameters that have not been tested. They added that since the DBDPO studies mainly observed animals as adults, the studies do not predict whether developmental neurotoxicity will occur. The target organs for DBDPO in adults (liver and thyroid) may not be the target organs in children. Other members expressed the view that available DBDPO data on children and on young animals are insufficient for a thorough hazard assessment because the only DBDPO studies on young animals are the one-generation study of Norris et al (1975) and the Viberg abstract, which lacked sufficient experimental detail to allow a proper scientific assessment. The sponsor responded to these

[4] This information was not in the published abstract; it was obtained by a panel member who contacted the investigators directly.

concerns by noting that an additional developmental toxicity study on DBDPO funded by the sponsor recently has been published (Hardy et al. 2002). This study exposed rats on days 0-19 of gestation and found the NOEL to be 1000 mg/kg-day, which is higher than either the Viberg or the Norris et al. (1975) study doses. The sponsor believes the Hardy et al. (2002) study provides a valid, up-to-date investigation of DBDPO's potential to induce developmental effects resulting from *in utero* exposure.

One panelist cited a literature survey by Goldey et al. (1994) indicating that developmental neurotoxicity could not be reliably predicted from other types of studies. This survey found that a lack of effects on birth weights, viability, and other parameters was a valid predictor for lack of neurotoxicity in only 65% of 126 chemicals evaluated. These chemicals represented a broad spectrum of compounds that had been assessed in various reproduction studies. The survey suggests further work on DBDPO should not be excluded, even though no neurotoxicity was observed in the existing studies. A second panelist cited an International Life Sciences Institute report (Middaugh et al 2003) that reviewed developmental endpoints for pharmaceutical agents and concluded that studies other than developmental neurotoxicity studies could determine neurotoxic endpoints. He noted that different data sets often provide different conclusions. Several members thought that the absence of developmental neurotoxicity and two-generation studies were clearly data gaps, but whether they were also data needs would depend upon consideration of other toxicity and exposure data.

The systemic distribution of DBDPO and whether the compound reaches the fetus was discussed. Using data from the rat bioassay (NTP 1986), a panelist compared the distribution of DBDPO in various organs 72 hours following intravenous or oral dosing (see Appendix E for a copy of the panelist's handout). He noted that the oral dose went to the liver and then was excreted unchanged as the parent compound, never reaching the systemic circulation to any great extent. He said these data reinforce his opinion that *in utero* exposure after oral dosing is likely to be minimal because DBDPO does not reach the systemic circulation. The sponsor provided clarification on the liver bromine levels from the reproduction gavage study (Norris et al. 1973), noting that analyses of maternal and fetal livers showed elevated hepatic bromine levels only in maternal livers, regardless of the dosage given to the dams. The sponsor believed these data and the pharmacokinetic studies indicating minimal absorption support a conclusion that DBDPO dosed orally to dams does not reach the fetus. A panelist responded that up-to-date developmental pharmacokinetics studies would be needed to verify that DBDPO does not reach the fetus.

Thyroid Effects

Panelists discussed whether the thyroid hyperplasia occurring in mice in the NTP bioassay (1986) was an indication of thyroid toxicity. Some members noted that this effect was observed in only one sex (males) of one species, and only at a high dose level. Others thought it was unclear whether the effect resulted from DBDPO or from another component of the test material. One member added that thyroid hyperplasia was reported in a 30-day rat feeding study (Norris et al. 1973). When asked if the chemical must be present in the thyroid to cause thyroid effects, he responded that thyroid effects could be secondary to the chemical affecting hepatic enzymes.

Inhalation and Lung Effects

The lack of repeat-dose inhalation toxicity studies troubled one member who described this as a data need (but later concluded it was instead a data gap). Another member was less concerned, stating that DBDPO's large size and insolubility would prevent it from being absorbed to any great extent via the lung. He said DBDPO would be expected to diffuse slowly across the membranes of the respiratory tract with an absorption rate similar to the rate that occurs in the gut following ingestion. He added that any systemic effects following pulmonary or oral administration might be similar because hepatic metabolism from the first-pass effect is not considered a major factor with DBDPO. The sponsor agreed, confirming that no repeat-dose inhalation studies had been conducted because pulmonary absorption was considered unlikely to be a significant route of exposure. The first panelist remained concerned about the lack of longer-term pulmonary studies, noting that once particles reach the alveoli, they may remain there for weeks, possibly triggering macrophage involvement leading to subsequent pathology.

Purity of Test Material

A panelist said she had done rough calculations comparing the NOAELs from studies using test materials containing 77% DBDPO with studies using 95% DBDPO. She wondered whether such comparisons might be helpful in determining whether DBDPO or another test material component caused the effects observed in these studies. Several panelists responded that there are so many variables among these studies (e.g., purity of the dosing material, study duration, testing facilities, experimental procedures, toxicological endpoints) that explaining the differences among them would be extremely difficult. After further discussion, most members concluded it was not possible to determine with any degree of certainty whether DBDPO or other test material components caused the observed effects in any single study. In studies where 95% or greater DBDPO was used, many panelists thought it likely that DBDPO was the cause of the observed effects, but they acknowledged this was not certain.

DBDPO Metabolism

A panel member shared a paper by Morck et al. on DBDPO metabolism. (At the time of the meeting, this paper was in press.[5] With the authors' permission, it was shared with the panel and meeting attendees.) Under the experimental conditions employed, at least 10% of the radiolabeled oral dose given to rats was absorbed, and 65% of the radioactivity was excreted in the feces as metabolites. This percent absorption is greater than the value of 3% or less reported in the literature (El Dareer et al. 1987; NTP 1986) when DBDPO was administered in the diet.[6] Some panelists questioned the relevance of the findings because investigators used special techniques (organic solvents, sonication, and emulsification in a phospholipids vehicle) to

[5] Subsequent to the meeting, this paper has been published (Morck et al 2003)

[6] After the meeting, a panelist commented that a number of papers more recent than 1987 demonstrate a DBDPO uptake of more than 2% following oral administration.

increase absorption. Several members suggested that these techniques might have altered the DBDPO molecule, making the identity of the dosed substance unclear.[7]

A panelist expressed surprise that Morck found so many DBDPO metabolites in the mammalian gut because very little metabolism occurs in the environment and in environmental biota. Others suggested that the sonication might have increased DBDPO's vulnerability to metabolism, but one member thought that was unlikely to have occurred. Alternatively, the metabolites could have resulted from DBDPO being absorbed and then metabolized in the liver or elsewhere with the metabolites excreted back into the gut via the bile. Several panelists noted that Morck found fairly low bioavailability overall, so they thought impact of this paper on DBDPO risk characterization is minor.

Use of the National Academy of Sciences (NAS) RfD Value

The RfD value for DBDPO used in the BFRIP submission was derived by the NAS Subcommittee on Flame Retardant Chemicals (NAS 2000), based upon a two-year bioassay in rats and mice (NTP 1986). The panel discussed the appropriateness of using this RfD for evaluating risk to children. Some questioned whether an RfD based on a chronic bioassay was appropriate for risk characterization, given that the potential endpoints of concern might occur in the prenatal to two-year age range. They thought this issue was especially important because neither a two-generation study nor a developmental neurotoxicity study has been conducted. While the NAS report did not discuss concerns over the lack of these two types of studies, the Viberg abstract was not available at that time. One member noted that the NAS RfD is 4 mg/kg, while the Viberg abstract indicated a possible NOAEL of 2 mg/kg. That these are approximately the same value indicates a gap in hazard identification related to the dose-response of DBDPO. In response, a panel member who was on the NAS Committee noted that NAS did not have any clear markers of toxicity, and the available data indicated exposure was very low. He explained that the NAS Committee considered the RfD valid for children because of the uncertainty factors (UFs) they used in its derivation (UF of 300).

Responding to a question of whether there might be a better way to evaluate children's exposure than using an RfD based on a lifetime study, a member reminded the panel that RfDs are developed using UFs to protect sensitive individuals and to account for gaps in critical studies. RfDs are intended to protect every age group throughout its lifetime. Thus, an RfD developed from a lifetime chronic study should protect children in all developmental life stages, including *in utero.*

The panel discussed how one might derive an RfD specifically for children, using the current data set. Several members suggested evaluating how the validity of the existing NAS RfD would be affected by NOAELs derived from the Viberg abstract and other shorter-term studies that corresponded to the developmental life stages of children. One panelist disagreed with this approach, noting that NAS appropriately calculated their RfD based on an evaluation of the

[7] After the meeting, a panel member obtained additional information from an author of the Morck et al. report suggesting that ultrasonic agitation and the other techniques employed did not cause DBDPO debromination; however, an analysis of the Lutrol dosing mixture to confirm the presence of DBDPO was not conducted.

entire data set of all studies. Another panelist stated that the VCCEP panel's function is to look at all available data and consider if the data in total are adequate to characterize the risks to children. This panel member thought that considering abstracts and brief study reports such as Viberg's is acceptable, but such information should be given less weight than scientifically peer-reviewed and published studies.

Exposure Assessment

Sponsor Presentation

On behalf of BFRIP, Mr. Sean Hays of Exponent, Inc. presented the exposure assessment (see Appendix D for the sponsor's presentation slides). He noted that DBDPO has a low vapor pressure, low solubility, and does not show evidence of biodegradation to penta- or tetrabrominated diphenyl ethers in either the environment or *in vivo.* These physical characteristics suggest that air concentrations are not likely to be high, dissolution into saliva is expected to be limited, and the presence of penta- or tetrabrominated diphenyl ethers in the environment and breast milk is not a result of DBDPO. In the U.S., DBDPO has been detected in sediments, sewage sludge, and outdoor air. [Note: After the meeting, the sponsor noted that one of the presentation slides incorrectly included indoor air data from Sweden as being from the U.S.] Detections of DBDPO in outdoor air occurred near manufacturing plants or urban areas; however, no DBDPO was detected in air in rural or remote areas over a 3-year period. DBDPO was not detected in fish samples. DBDPO was found in chicken fat, but greater than 60% of the detections reported were below the average level in the blanks.

The sponsor noted that two sets of values were used in the calculations of each exposure parameter: (1) median or mean values were used to calculate intakes representing reasonable estimates of exposures to the general U.S. population; and (2) the extreme bound on each parameter was used to calculate an upper estimate of exposures that theoretically might be encountered in the U.S. general population. The parameters for various exposure scenarios are listed in detail in Tables 5-14 through 5-19, and the aggregate exposures are presented in Table 5-20 of the submission document. The sponsor explained that the exposure assessment relied on currently available data (consistent with Tier 1 requirements). The sponsor characterized the exposure assessment as highly conservative and said it used biomonitoring data to reduce uncertainties and account for the wide range of potential exposures.

The sponsor identified and described three major exposure situations:

1. occupational inhalation exposures of nursing mothers and subsequent ingestion of breast milk by their infants;
2. inhalation of indoor residential air, plus oral exposures from infant-specific mouthing of consumer products such as TVs, computer monitors, and upholstery textiles, and dermal exposures from upholstery textiles;
3. all other potential environmental exposures such as inhalation of outdoor air and ingestion from soil, as well as potential exposures from any and all other media or routes of exposure, including food, water, and unidentified exposure pathways.

Because of the sponsor's opinion that there has been no convincing evidence of fetal or developmental toxicity in animals exposed to DBDPO, the sponsor did not evaluate *in utero* exposures. Similarly, the sponsor did not estimate exposures to prospective parents because they concluded that there has been no evidence of reproductive toxicity in animals.

Occupational exposures to nursing mothers were estimated by calculating air-to-serum ratios based on Swedish worker data combined with air concentration estimates from the U.S. The partitioning of DBDPO from serum to breast milk was estimated based on the partitioning of less brominated diphenyl ether compounds. Airborne concentrations of 1 mg/m^3 (realistic exposure; RE) and 5 mg/m^3 (upper exposure; UE) were assumed for the exposure estimates. This UE value is the Workplace Environmental Exposure Limit (WEEL) and is based on nuisance dust levels, because of DBDPO's low toxicity. For the second occupational exposure pathway, DBDPO levels in serum from Swedish workers employed to shred and recycle electronic products containing DBDPO were used, rather than the air-to-serum ratios, but the serum to breast milk partitioning was estimated in the same way as for the first pathway. Both of these breast milk ingestion calculations involved conservative estimates for each step, resulting in compounded conservatism in the final estimated intakes. To estimate children's exposures to DBDPO in the general environment, the sponsor used DBDPO levels measured in the serum of non-occupationally exposed people (Sjödin et al. 2001). These serum data are the only reported serum data for non-occupationally exposed people in the U.S., and were obtained from 12 samples taken in 1988 from adult blood donors. A one-compartment model was used to back-calculate the intake required to achieve the measured serum levels.

Pathway-specific intakes were aggregated for three potential receptors:

- Infant whose mother manufactures DBDPO (includes breast milk ingestion plus all infant-specific direct exposures, plus general environmental exposures)
- Infant whose mother disassembles electronics containing DBDPO (includes breast milk ingestion plus all infant-specific direct exposures, plus general environmental exposures)
- Child over the age of two years, exposed via the general environment

The sponsor concluded that after evaluating all possible routes of exposure to infants and children from the three situations described above, and aggregating exposures for the three receptors described above, calculations indicate that infants of mothers working in jobs with the highest potential exposure in DBDPO manufacturing plants would be predicted to have the highest potential for exposure. This exposure to the infant would occur via breast milk, plus infant-specific direct exposures to DBDPO-containing consumer products (i.e., through mouthing), and general environmental exposures. If nursing mothers were employed in these occupations, the upper estimate of total aggregated daily intake for their infants would be 0.76 mg/kg-day. This is five-fold less than the NAS RfD for DBDPO (4 mg/kg-day). However, no women currently work in these jobs, and all employees performing tasks with the highest potential for exposure to DBDPO are required to wear respirators.

In order to provide a qualitative sense of the potential overestimates in the exposure calculations, the sponsor presented a graph comparing the highest calculated serum values used (manufacturer) to the median serum values measured in the general U.S. population (Sjödin et al. 2001) and Swedish workers (see Table 5-1). The serum levels reported by Sjödin for the U.S.

general population ranged from non-detect to about 34 ng/g lipid and are similar to serum levels reported for Swedish workers (summarized in Table 5-1, page 58 of the sponsor's submission). The highest calculated serum levels (manufacturer) were about 3 to 4 orders of magnitude higher than any measured value for either an exposed worker or the general population. The sponsor stated that this comparison of calculated versus measured values provides persuasive evidence that the exposure calculations used in the upper estimates are highly conservative.

The sponsor discussed recently obtained data (not published at the time of the meeting) on DBDPO levels in indoor dust and in breast milk, noting that these data were not available when the submission was being prepared. Two recent studies in Europe (Leonards et al. 2001; Santillo et al. 2001) and one in the U.S. (Rudel et al. submitted manuscript[8]) reported DBDPO concentrations up to 20,000 ng/g dust (the highest concentration was in the contents of a vacuum cleaner bag), although most reported concentrations were below 1,000 ng/g. Using a graph of intake via ingestion versus dust concentration, and comparing this with the RfD, the sponsor demonstrated that dust would not be a meaningful pathway of DBDPO exposure to children. Even at a dust concentration of 10,000,000 ng/g (i.e., 1% DBDPO), the oral intakes would be less than 0.5 mg/kg-day, which is considerably lower than the NAS RfD of 4 mg/kg-day. Preliminary calculations of exposures via inhalation of re-suspended dust indicate that intakes would be even lower, by several orders of magnitude, than intakes via ingestion.

The sponsor presented some preliminary information on a not-yet-published study by Dr. Arnold Schecter and colleagues, in which 24 breast milk samples from women in Texas were analyzed for several PBDEs, including DBDPO. The preliminary, unpublished data showed that DBDPO was one of the least often and lowest detected of the PBDEs, and was detected in less than 30% (7 of 24) of the samples analyzed for DBDPO. A comparison of the measured breast milk concentrations versus the calculated concentrations for the infant whose mother is a manufacturer of DBDPO showed that the calculated estimates were 3 to 4 orders of magnitude higher than the measured values (i.e., calculated values of 2,740–68,500 ng/g lipid versus measured values of 0.92–8.24 ng/g lipid). The sponsor concluded that the new data of measured dust and breast milk values confirm the conservatism of the upper exposure estimates used in the submission.

Panel Discussion of Exposure Assessment

The panel discussion on the Exposure Assessment was framed by these charge questions:

3. Is the fate of decabromodiphenyl ether adequately understood?

4. Based on the information at hand, are the data adequate to characterize exposure to children and prospective parents?

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

[8] This study now has been published (Rudel et al. 2003)

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

5. Are the estimates of exposure calculated appropriately and correctly?

Because the panel discussion did not strictly follow the charge questions, the text below is organized by topic area. The primary topics discussed by the panel responded to these charge questions, including DBDPO's fate in the environment and in products, characterizing exposure to children and prospective parents, and exposure calculations.

Fate of DBDPO in the Environment

One panelist summarized his opinions of DBDPO in the environment stating that limited debromination seems to be occurring. Because DBDPO is resistant to hydrolysis and to microbial aerobic and anaerobic degradation, the debromination mechanism probably is photolysis, but photolytic debromination studies have produced conflicting results. One study (Selstrom et al. 1998) showed reductive debromination could occur with light in organic solvents, but this situation may not be the same as that which occurs in aqueous environments. More environmentally realistic exposure situations are required to determine if DBDPO degrades in the environment via photolyses, and, if so, to what products. The sponsor noted that industry is supporting photolysis debromination research at Purdue University and in Germany. In a study at Purdue University, DBDPO was photolyzed under hydrated conditions and adsorbed onto various substrates (Jafvert and Hua 2001a, 2001b, 2001c). Disappearance of DBDPO was seen, but no PBDEs with fewer than seven bromines were observed. In a study of DBDPO photochemistry at the Fraunhofer-Institut für Toxikologie und Aerosolforschung in Germany, work not yet published indicates substantially decreased ultraviolet light absorption (hence lack of photolysis) in PBDE congeners with fewer than seven bromine atoms.

A panel member stated that once DBDPO is adsorbed to sediments its contact with light and thus its potential for photolytic debromination is questionable. Searches of the environment find mostly DBDPO and the penta- and tetraBDE congeners, but it is not clear that the penta- and tetraBDE result from DBDPO debromination. The sponsor added that environmental monitoring studies do not provide evidence of DBDPO debromination to tetra- and pentaBDEs. If DBDPO were degraded in the environment, it is highly unlikely that the predominant products would be tetra- and pentaBDE. Other chemical structures are more likely to be formed. Thus, the sponsor does not believe the DBDPO is the source of tetra- and pentaBDEs found in the environment.

The panel discussed DBDPO's long-range transport and bioaccumulation potential. One panelist noted that studies using four different computer models show DBDPO does not undergo long-range transport, and that 94% of it adsorbs to sludge. Another member responded that sewage sludge applied to farmlands in the U.S. might result in DBDPO applications of up to eight tons per year. This estimate is based on the concentration of DBDPO detected in U.S. sewage sludge (Hale and La Guardia 2002; Hale et al. 2001). Although some DBDPO has been found in

aquatic organisms, the chemical was not detected in three studies that examined a total of 70 samples of fish from the U.S. and Canada. A Swedish study found DBDPO in falcon eggs (Sellstrom et al. 2001); however, DBDPO shows little bioaccumulation compared to less brominated PBDEs.

The sponsor gave its opinion that DBDPO in the environment is not a major contributor to human exposure, and several panelists agreed.

Fate of DBDPO in Products

The panel discussed the fate of DBDPO used in various product matrices (e.g., plastic components of electronics and textiles used in furniture). Some members noted that since DBDPO does not react with the matrix components, it might migrate out of the product and find its way into dust. Others agreed this was possible, but thought the majority of DBDPO in dust recently reported (Rudel et al. submitted manuscript) came from the breakdown of the product matrix itself and not migration out of the intact product. This indicates the importance of knowing the lifetimes of the products themselves, together with their rates and extents of disintegration. A panelist noted that anything in a plastic matrix may diffuse out and become attached to dust. He noted that there are models (e.g., Arthur D. Little's Migration Estimation Model) to estimate the fraction of additives in polymers that will migrate out of the matrices under various conditions.

Another panel member discussed the fact that although the DBDPO present in products may form brominated dioxins and furans when the products are ignited in fires, plastics themselves produce dioxins and furans when burned – perhaps more than DBDPO does. This panelist believes pyrolysis of DBDPO is not a safety concern, even though it receives considerable attention. The sponsor added that life-cycle studies of electronics products with and without flame-retardants demonstrate that the addition of flame-retardants serves to decrease the amount of polycyclic aromatic hydrocarbons released during fires.

Characterizing Exposure to Children and Prospective Parents

The panel discussed the DBDPO human exposure information, including new data on dust and breast milk that were not available when the written submission was prepared, but were described in the sponsor's slide presentation. One panel member indicated that the combination of the submission and slide presentation nicely synthesized and updated all the exposure data. Although the submission did not provide much discussion of inhalation exposure, the updated slide presentation by the sponsor adequately covered the inhalation route and the recent data on DBDPO in dust. The panelist suggested the exposure data might be expanded further by adding the Consumer Product Safety Commission (CPSC) analyses noted in the written public comments by Ms. Delpire (see Appendix C). The sponsor replied that using the CPSC's calculated values instead of the BFRIP estimates in the submission would have a negligible effect on the total exposure values and would not change the overall conclusions of the exposure assessment.

In response to panelist questions, the sponsor expanded on the new data from Dr. Arnold Schecter and his colleagues on PBDE congeners in breast milk. Although these data have not yet been published, Dr. Schecter had provided the sponsors with some preliminary information to share with the panel. Schecter sent 24 breast milk samples to each of his collaborators (Dr. Jake Ryan and Dr. Olaf Papke) for PBDE analyses; however, only Dr. Papke currently tests for DBDPO. Dr. Ryan did not test for DBDPO because he has not been able to obtain results he felt were reliable; sample concentrations were similar to what was seen in the blanks. Dr. Papke found DBDPO in seven of the 24 samples he analyzed (range: 0.48–8.24 ng/g lipid; mean: 0.92 ng/g lipid; standard deviation: 1.96 ng/g lipid; detection limit 0.24–1.29 ng/g lipid). The sponsors noted that these new breast milk data cannot be used to revise the breast milk-to-serum ratio used in the submission because there were no matched or otherwise similar serum data for comparison. They added that the values measured by Schecter suggest that the calculated intakes in the submission may significantly overestimate actual exposures.

A panelist stated that the submission's discussions on breast milk exposure and on childhood exposures during key development periods were well done, but he questioned the decision not to address the potential for prenatal exposure based on a lack of observed toxicity, noting that other PBDEs have been detected in cord blood. The sponsor explained that the hazard data suggest there is no need to evaluate *in utero* DBDPO exposures in humans because none of the *in utero* exposures in laboratory animals showed reproductive or developmental effects. The guidance for VCCEP submissions (Federal Register, 2000) indicates that toxicity data and the hazard assessment should guide which exposure scenarios are evaluated. The sponsor also noted that even if a mother were exposed at the occupational limit (WEEL of 5 mg/m^3) for 24 hours per day, the exposure would not be expected to exceed 1.4 mg/kg-day (5 mg/m^3 x 20 m^3/day / 70 kg). The result is below the RfD established by NAS. Furthermore, in workplace environments where DBDPO exposure levels might be of concern, the workers are required to wear respirators. Therefore, the sponsor added, even if *in utero* exposures had been included in the exposure assessment calculations, the exposures would have been less than the RfD.

Two panelists thought estimates of fetal exposure could be done by modeling placental transfer, but acknowledged that this exercise might not be useful because there are no toxicity data to which the exposure levels could be compared. Another panelist reiterated that DBDPO kinetic studies looking for bromine in dams and fetuses found elevated bromine in maternal livers but not in fetal livers (Norris et al. 1973), thus indicating that fetuses may not be exposed to DBDPO following maternal exposures.

Other members discussed ways to expand the exposure data on children, taking into consideration that children might absorb DBDPO at higher rates than adults. The sponsor explained that using a higher absorption rate would yield a *lower* intake, because the intakes were back calculated from measured blood levels. One member thought obtaining serum data directly from children would be best, but an acceptable alternative would be to use the EPA Office of Pesticide Programs (OPP) default assumptions and algorithms for comparing children's exposures with adults. Panelists felt that both of these suggestions were possible ways to provide more direct data on children's DBDPO exposures.

Exposure Calculations

Referring back to the sponsor's presentation where the sponsor stated that the comparison of calculated versus measured values provided persuasive evidence that the exposure calculations used in the upper estimates are highly conservative, one panelist disagreed. She said the estimated manufacturer serum levels were not used to estimate risk to children but to calculate exposure to infants from consumption of breast milk. The panelist said this comparison was not appropriate to use as a quantitative check on the conservative nature of the exposure estimate because it does not account for the uncertainties associated with the full calculation.

A panelist asked the sponsor to explain the assumptions leading to the upper estimates of exposure as described in Table 6-1 on page 108 of the submission. (Table 6-1 lists both *reasonable* and *upper* estimates of DBDPO exposures to infants and children). The table includes aggregate estimates for potential breast milk ingestion from mothers exposed to DBDPO in the workplace, other ingestion from infant mouthing of fabric and electronic products that contain DBDPO, and additional, general environmental exposures to DBDPO. In response to this request, the sponsor provided a more detailed explanation of how both intake estimates were calculated from measured serum levels, and how various exposure parameters affect those calculations. He noted that exposure parameters include DBDPO concentration in workplace air, air-to-serum conversion factors, breast milk-to-serum ratios, lipid fraction of breast milk, infant ingestion rates and body weights, and percent DBDPO absorption (see Tables 5-14 through 5-19, pages 90-103 of the submission for a complete list of *reasonable* and *upper* parameter estimates and the source references).

Several panelists also requested additional details regarding the method of back-calculating intakes for general environmental exposures from measured serum levels (Table 5-19, p. 103). The sponsors explained that to calculate the absorbed dose based on the measured levels of DBDPO in the serum of humans, the sponsor assumed (1) that the kinetics of DBDPO can be sufficiently described using first-order kinetics, and (2) that the serum levels of DBDPO are at steady-state. The first assumption is reasonable for most compounds for the purposes of calculating absorbed dose. Further, the studies by Sjödin seem to indicate that DBDPO elimination reasonably approximates first-order kinetics. The second assumption is also reasonable, given the moderate half-life of DBDPO in humans (approximately 7 days). The result of these assumptions is that a one-compartment, steady state model can be used to relate the absorbed dose to its concentration in the body The parameters in a one-compartment steady-state model include (a) the half-life of DBDPO in human serum, (b) the volume of distribution for DBDPO in humans (i.e., the volume of the tissues in the body into which a chemical will distribute), and (c) the absorbed daily dose.

The one-compartment, steady state concentration (*Css*) is given by:

$$Css = \frac{ADD}{Vdist \times k}$$

where:

k is the first-order rate of elimination and equals ln (2)/half-life,
ADD is the absorbed daily dose, and
Vdist is the volume of distribution within the body.

ADD is equal to the product of the measured serum concentration of DBDPO multiplied by the volume of distribution, divided by the half-life (with a constant and some unit conversion factors included). Therefore, for a given serum level of DBDPO, the calculated absorbed dose required to yield that serum level increases as the volume of distribution increases, and decreases as half-life increases. To calculate intake, the absorbed dose is divided by the percent absorption. Therefore, a higher absorption will yield a lower calculated intake for a given absorbed dose.

For each of these parameters, the sponsor used two sets of values in the calculations: (1) median or mean values to calculate intakes representing reasonable estimates of exposures to the general U.S. population, and (2) the high-end value for each parameter to calculate an upper estimate of exposures that theoretically might be encountered in the U.S. general population. For instance, for the upper estimate, the sponsor assumed a volume of distribution of DBDPO in the body of 50%, although it is more likely that the actual volume is closer to 25%, based on studies of the distribution of DBDPO in rats. The measured half-life of DBDPO in humans averages 6.8 days, with a lower bound statistical confidence limit of 3 days. Since half-life is in the denominator in the calculation of absorbed dose, a shorter half-life yields a higher calculated absorbed dose. Then, when calculating intake, a lower percent absorption yields a higher calculated intake. For the upper estimate of absorption, the sponsor used the lower bound on percent absorption of 1 %. The sponsor noted that the result of using conservative assumptions for each parameter is a highly conservative estimate of intake.

Risk Characterization and Data Needs

Sponsor Presentation

On behalf of BFRIP Dr. Marcia Hardy of Albemarle Corporation summarized the risk characterization and data needs assessment, noting that the uses of DBDPO impart minimal potential for exposure to children and that DBDPO is a poorly absorbed molecule with low toxicity (see Appendix D for the sponsor's presentation slides). She emphasized that DBDPO is not acutely toxic or mutagenic, nor is it a developmental or reproductive toxicant. Both the chronic and the developmental studies provide NOAELs greater than 1,000 mg/kg-day. She reviewed the children's exposure pathways described in the preceding section, adding that significant levels in breast milk would not be expected, given DBDPO's physicochemical properties and pharmacokinetics. Additionally, food is unlikely to be a significant exposure route, and DBDPO is not expected to partition into air or to undergo long-range transport.

The sponsor compared the two RfDs available for DBDPO. One is the EPA-derived value of 0.01 mg/kg-day based on the report of Kociba et al. (1975). That study reported a chronic rat NOEL of 1 mg/kg-day, the highest dose tested in this study, which was the best available study at the time EPA developed its RfD. The second RfD was derived by NAS in 2000 (discussed previously in the hazard assessment section). The 4 mg/kg-day NAS RfD is based on the 1986

NTP bioassay reporting a chronic rat NOAEL of 1,120 mg/kg-day. NAS based its RfD on the NTP study instead of the Kociba study because of the purer test material (>96% DBDPO versus 77%), the larger numbers of animals (50 versus 25 rats/sex/dose), the higher dose levels, and the presence of confirming results from a second species (mice). The sponsor noted that studies with the lower purity material, which is no longer in production, showed toxicities not observed with the higher purity material currently produced in the U.S. The sponsor believes the NAS RfD of 4 mg/kg-day is clearly the better value to use for the four reasons listed above.

Upper estimates for children's exposures are substantially below the NAS RfD, and the hazard quotients (HQs) for all estimated pathway-specific and aggregate exposures are less than one. Existing toxicity test data cover VCCEP Tier 1, 2, and 3 hazard endpoints. Although existing data on exposures are sparse, the upper exposures that have been estimated are highly conservative, yet they are still below the NAS RfD. Additionally, the sponsor believes the use of biomonitoring data (i.e., measured serum levels) significantly reduced potential uncertainties in estimating environmental exposures and surmounts the difficulty of identifying what the exposure pathways might be. Recent dust and breast milk measurements support the conservatism of the exposure estimates. The sponsor concluded that no additional toxicity or exposure data are needed.

Panel Discussion of Risk Characterization

The panel discussion on risk characterization and data needs was framed by these charge questions:

6. Does the risk characterization appropriately integrate the exposure and hazard information of decabromodiphenyl ether to characterize risk a) *in utero*, b) to the infant and child, and c) to prospective parents?

7. Based on the information at hand and the panel discussions, are any additional toxicity studies from the next tier needed? If so, explain their value.

8. Based on the information at hand and the panel discussions, are any additional exposure data or analyses from the next tier needed? If so, explain their value.

Because the panel discussion did not strictly follow the charge questions, the text below is organized by topic area. The primary topics discussed by the panel included integration of hazard and exposure data, upper estimates of exposure, toxicity data needs, and exposure data needs.

Integration of Hazard and Exposure Data

Several members stated that the risk characterization appropriately integrated the available hazard and exposure data and included a reasonable assessment of risk for all stages of childhood development. Many agreed that the NAS RfD is an appropriate value to use for infants and

young children, noting that the NAS considered all the relevant information currently available, except for the Viberg abstract. These panel members did not consider the Viberg abstract useful for risk characterization because of its insufficient details. Another panelist suggested adding the recent breast milk and dust data presented during the meeting to the written submission for completeness, but thought these new data had minimal impact on the risk characterization.

Upper Estimates of Exposure

One panelist said data in the recent EU Report (EU 2002) suggest the older (1988) U.S. serum data used to estimate the current general environmental exposures to children (Table 5-19, which were included in the aggregate for each receptor presented in Tables 5-19 and 6-1) might underestimate the true upper exposures to children occurring in the U.S. by as much as four times because of increased environmental levels of DBDPO since 1988. If this were true, the upper estimate would be the same order of magnitude as the NAS RfD. The panelist believed having the upper estimate so close to the RfD was a cause for concern because of the large uncertainties in both of these numbers. Another member responded that making the sponsor's upper exposure values four times greater to account for presumed increases since 1988 was not justified. The increases noted in the EU Report are for exposures in Europe, not in the U.S., and the EU Report assumes DBDPO concentrations increased because the less brominated PBDE levels increased. She said even if these assumptions are true, the resulting upper estimate does not exceed the RfD, and the resulting hazard quotient is still less than one. The sponsor clarified that the aggregate intakes presented in Table 6-1 for each of the three receptors included the estimated intake from general environmental exposures, which relied on serum data from samples taken in 1988 (Table 5-19).

Other panelists questioned whether the upper exposure estimates summarized and aggregated in Table 6-1 were truly upper estimates. These panelists noted that the serum levels used in the calculations not only were taken 15 years ago when environmental levels of DBDPO in the U.S. may have been lower, but also were based on only 12 samples from adults, 7 of which had non-detectable levels. They said that blood concentrations of less brominated PBDEs have increased in recent years in the U.S. as well as in Europe, so DBDPO blood concentrations may have increased in the U.S. also. These members did not think the sponsor's upper exposure estimates in Table 6-1 were sufficiently conservative. In reply, the sponsor pointed out that data from Europe on tetra- and pentaBDE in breast milk (*not* blood serum) was reported to show an increasing trend that peaked in 1997. Time trend data on U.S. blood concentrations of the less brominated PBDEs are not available. The sponsor further noted that assuming DBDPO exposures have increased because the less brominated congeners have increased is not justified because DBDPO has different physicochemical properties (K_{ow}, K_{oc}, water solubility, etc.) from these other PBDE chemicals. The sponsor explained that the estimates for all exposure pathways of the submission employed calculations using extremely conservative assumptions, in addition to using real measurement values to estimate general environmental exposures (Table 5-19) (see the sponsor's explanation in the preceding *Exposure Calculations* section). Some panelists agreed with the sponsor's approach and considered the upper estimates in the table to be sufficiently conservative, but one member said that, even if DBDPO does act differently than the less brominated congeners, the U.S. production of DBDPO is known to be increasing by as much

as 5 % each year. The panelist who originally raised the concern about Table 6-1 reiterated her concern, stating that the driving force for the final exposure estimate continues to be the measured serum values used for the calculation of general environmental exposures (Table 5-19), and the uncertainty in these numbers is large. She voiced concern that there are potentially highly exposed children that may be reaching exposures close to the RfD.

Approaching this issue from a different perspective, one member suggested relating the exposure estimates to the hazard data. This member said the most relevant hazard data are from the one-generation study. Taking the NOAEL from this study and using a Margin of Exposure (MOE) approach shows that the lowest dose producing toxicity is considerably above the aggregate infant exposure estimates. Therefore, this panelist did not think the exposure numbers indicated a potential hazard for children.

Panel Discussion of Data Gaps and Needs

For the Hazard Assessment

Panel members discussed possible toxicity data gaps and needs and expressed a range of opinions regarding whether additional data are needed to characterize the risk to children. They did not limit their discussion to toxicity tests specified in the next VCCEP tier, but took a broader view in identifying information they believed would contribute to characterizing DBDPO's risk to children.

Several panelists noted that although many additional toxicity studies could be done, additional work would not likely change the hazard assessment or risk characterization significantly. Given the lack of toxicity found in the one-generation study and other relevant studies, some members agreed with the sponsor that toxicity studies specific to *in utero* exposures or to the reproductive functioning of prospective parents were not necessary. They mentioned that the study comparing liver bromine content in dams and fetuses found increased bromine levels only in the livers of the dams. Some panel members thought that sufficient toxicology data exist to address all the essential issues, and additional toxicity studies are not justified. They said that although not all of the tests listed in the three tiers have been conducted, the existing data indicate that DBDPO shows no potential to affect fetal or postnatal development at doses likely to be encountered by children or prospective parents. They were satisfied with the NAS RfD value, saying NAS had considered all the available data and applied reasonable conservatism.

Some other panelists disagreed and expressed concern about the lack of data available from the existing toxicity studies conducted on immature animals (e.g., existing reproduction studies essentially are limited to the Norris et al. one-generation study in rats). They also noted that in several cases the actual study reports were not available, so the panel was unable to determine details such as concentrations of test material in various tissues and organs. These panel members cautioned against giving too much credence to reproduction and developmental studies in the database for which only summaries were available. These panelists thought that obtaining the complete study reports was an essential data need that should be addressed before concluding

that additional toxicity studies were not needed. One panelist stated, however, that the existing reproduction studies could not provide sufficient data on immature animals, even if the complete study reports were made available.

Several panelists noted the importance of reviewing the Viberg work when it is published, paying particular attention to the statistics in order to understand the relevance of the reported effects. Others thought that all available toxicity studies evaluating young animals should be reviewed in detail to investigate the kinetics in young versus older animals.

Considering the degree of oral absorption reported by Viberg, a member suggested it would be helpful to determine whether a fatty emulsion, because of its higher absorption potential, is a more appropriate medium than corn oil or lab chow for dosing DBDPO to animals. Other panel members noted that an emulsion vehicle might mimic a DBDPO exposure route for nursing human infants, but neither emulsions, corn oil, or food vehicles would mimic major DBDPO exposure routes for non-nursing children or for adults. Several members thought that using dust as the dosing vehicle, with inhalation rather than oral as the exposure route, would be the most relevant conditions for an animal study intended to mimic the major route of human exposure. They further suggested that inhalation might provide more absorption and address the worst-case occupational exposures occurring in bagging operations in manufacturing plants. The sponsor reiterated that exposure calculations showed dust inhalation was a negligible exposure pathway for DBDPO and that exposure via the respiratory route was not expected to significantly increase the internal dose.

Individual panel members mentioned a number of other areas where further data or analyses would be useful. These included estimating levels of DBDPO in rat milk to confirm the lack of increased bromine in fetal livers and exploring the toxicity of DBDPO's hydroxy and methoxy metabolites. Other members mentioned developmental neurotoxicity, longer-term inhalation studies, measurement of placental transfer, effects on brain development, and more immunotoxicity work as areas where additional information might be useful.

For the Exposure Assessment

The panel also had a range of opinions on potential exposure data gaps and needs. Some panelists thought the sponsor likely had identified the major exposure routes and the maximum possible exposures. They acknowledged that uncertainties exist in DBDPO's exposure assessment, such as clearly defined exposure pathways, environmental concentrations, potential for debromination, and overall fate and transport. However, they suggested that while additional work would provide increased information in these areas, it is difficult to identify situations in which exposure to DBDPO would actually present a hazard; therefore, they did not recommend further exposure work at this time.

Others disagreed. One member noted that, while DBDPO in the environment appears to be innocuous, its persistence would cause increased human exposures with resulting decreased safety margins. He thought that emissions from industries needed to be more thoroughly assessed and also that more work is needed to identify all the consumer products containing

DBDPO. He also questioned where DBDPO goes in the environment, what ultimately happens to it after adsorption to sewage sludge, and what its metabolites are in the gut following ingestion.

Most panel members thought collection of more serum measurements in the U.S. population is a data need. Some panelists thought that breast milk measurements are also needed. One panelist noted that analyzing DBDPO in breast milk is difficult and a more standardized analytical methodology for DBDPO detection is needed. This panelist thought that if further breast milk sampling finds higher DBDPO levels, more work similar to that done by Viberg might be justified.

One member suggested putting all the exposure data needs in a sequential order. She agreed with many others that the biggest source of uncertainty is the human serum data set because the current data are from only a small number of people. She said she would not recommend any other work until more serum samples were obtained and the results of their analyses indicated exposures higher than currently estimated. At present, she sees data gaps in other areas, but not data needs. Another panelist added that constructing a more robust database from additional human serum samples is critical for comparing the bounds of exposures to the bounds of hazards. He supported obtaining and evaluating these data as they come in, noting that work to generate these data is in progress at the Center for Disease Control and Prevention (CDC) and at National Institutes for Occupational Safety and Health (NIOSH). Data also are expected from firefighters who were involved with the World Trade Center cleanup. Many of the other panelists agreed that getting additional exposure data from serum samples is the greatest data need and the highest priority. These panelists disagreed, however, whether pursuing all the other suggestions should be postponed pending additional sampling that shows DBDPO serum levels to be higher than currently estimated.

The panel also discussed whether one result of the VCCEP peer consultation process should be a request to CDC to analyze serum levels of DBDPO via its National Health and Nutrition Evaluation Survey (NHANES) program. Some members thought NHANES data would be of little value because it would not come from subjects exposed to high DBDPO levels or from children. These panelists thought conducting a smaller, more-targeted study would be preferable. After discussion, the panel agreed that it was beyond the scope of the VCCEP Peer Consultation Panel to make requests to CDC.

Individual Panelist Data Needs

Following the above discussions, each panel member in turn identified the items that he or she personally considered *data needs* for DBDPO. The VCCEP peer consultations are intended to obtain a broad range of opinions regarding whether further data collection, analyses, or studies are needed to adequately characterize risks to children. Consensus is not sought, and therefore a listing of individual panel member's identified items is provided below. Similar data needs are grouped, and the number of panel members identifying them (out of the 13 panelists) is indicated. The number of items identified as data needs by individual panelists ranged from none (1 panelist) to six items (1 panelist). Most panelists identified two or fewer items.

The following four items were listed most frequently as data needs:

- Measure DBDPO in human samples (9 panelists in total: 7 for blood serum; 2 for blood serum and breast milk)

  Several members said additional human samples should be obtained and analyzed first; then, depending on the results, the panelists would determine if any further data needs existed.

- Evaluate details of the Viberg study and, if warranted, conduct further studies (8 panelists)

- Obtain greater understanding of environmental fate and transport, including persistence, hydroxylation, and debromination (4 panelists)

- Obtain further information on placental transfer and fetal distribution (2 panelists)

In addition, the following other items were mentioned by single panel members:

- Standardize an assay to measure systemic absorption (1 panelist)

- Measure metabolism occurring in gut (1 panelist)

- Study immunotoxicity potential (1 panelist)

- Review the complete reports of all the existing toxicity studies (1 panelist)

- Estimate administered doses in the toxicity studies on young animals (1 panelist)

- Determine relative absorption kinetics of young versus adult animals (1 panelist)

- Determine environmental emissions from industry (1 panelist)

- Identify all end product uses (1 panelist)

References

Clarke F. 1997. The life safety benefits of brominated flame retardants in the United States. Final Report of the Chemical Manufacturers Association Brominated Flame Retardant Industry Panel. Bemjamin/Clarke Associates.

de Boer J, Aldridge J, Allchin C, Bennett M, Boon JP, Brandsma S, van Hesselingen JM, Law R, Lewis W, Morris S, Tjoen-A-Choy MR, and Zegers B. 2001. Polybrominated diphenyl ethers in the aquatic environment. RIVO Report, C023/01, June.

de Wit C. 2000. Brominated Flame Retardants. Swedish Environmental Protection Agency Report 5065.

El Dareer S, Tillery K, Hill D, and Kalin J. 1987. Disposition of Decabromodiphenyl ether in rats dosed intravenously or by feeding. J Toxicol Environ Health, 22: 405-415.

EU. 2002. European Union Risk Assessment Report Bis(pentabromophenyl) ether. Volume 17. Luxembourg: Office for Official Publications of the European Communities.

Eriksson P. 1997. Developmental neurotoxicity of environmental agents in the neonate. Neurotoxicology, 18(3): 719-26.

Eriksson P, Jakobsson E, and Fredriksson A. 1998. Developmental neurotoxicity of brominated flame-retardants, polybrominated diphenyl ethers and tetrabromo-bis-phenol A. Organohalogen Compounds, 35: 375-377.

Goldey E, Tilson H, and Crofton K. 1995. Implications of the use of neonatal birth weight, growth, viability and survival data for predicting developmental neurotoxicity: a survey of the literature. Neurotoxicol Teratol, 17(3): 313-332.

Hale R and La Guardia M. 2002. Have risks associated with the presence of synthetic organic contaminants in land-applied sewage sludges been adequately assessed? New Solutions: A Journal of Environmental and Occupational Health Policy, 12(4): 371-386.

Hale R, La Guardia M, Harvey E, and Mainor M. 2001. Brominated diphenyl ethers in land-applied sewage sludges in the U.S. Second International Workshop on Brominated Flame Retardants, May 14–16, Stockholm University, Sweden, pp 149–152. This study was also published as Hale, R.C., M.J. LaGuardia, E. Harvey, M.O. Gaylor, T.M. Mainor and W.H. Duff. 2001. Flame retardants: Persistent pollutants in land-applied sludges. Nature 412:141-2.

Hardy M, Schroeder R, Biesemeier J, and Manor O. 2002. Prenatal oral (gavage) developmental toxicity study of decabromodiphenyl oxide in rats. Int J Toxicol, 21: 83-91.

Jafvert C and Hua I. 2001a. Photochemical Reactions of Decabromodiphenyl Oxide and 2,2',4,4'-Tetrabromodiphenyl Oxide. Final Report. School of Civil Engineering, Purdue University, West Lafayette, IN.

Jafvert C and Hua I. 2001b. Letter to Wendy Sherman, American Chemical Council Brominated Flame Retardant Industry Panel, October 20, 2001.

Jafvert C and Hua I. 2001c. Photochemical Reactions of Decabromodiphenyl Oxide and 2,2',4,4'-Tetrabromodiphenyl Oxide. Submitted to American Chemical Council Brominated Flame Retardant Industry Panel, October 20, 2001.

Kociba R, Frauson L, Humiston C, Norris J, Wade C, Lisowe R, Quast J, Jersey G and Jewett G. 1975. Results of a two-year dietary feeding study with decabromodiphenyl oxide (DBDPO) in rats. Combustion Toxicology 2, pp 267-285.

Leonards PEG, Santillo D, Brigden K, van der Veen I, Hesselingen JV, de Boer J andJohnston P. 2001. Brominated flame retardants in office dust samples. Poster presentation, Second International Workshop on Brominated Flame Retardants, May 14-16, Stockholm University, Sweden, pp 299-305.

Middaugh LD, Dow-Edwards D, Li AA, Sandler JD, Seed J, Sheets LP, Shuey DL, Slikker W Jr, Weisenburger WP, Wise LD, Selwyn MR for International Life Sciences Institute (ILSI) 2003 Neurobehavioral Assessment: A Survey of Use and Value in Safety Assessment Studies Toxicol Sci 1,2,3. On-line Aug 12
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=search&DB=PubMed

Morck A and Klasson Wehler E. 2001. Metabolism of Decabromodiphenyl ether (BDE-209) in the rat. BFR 2001 Stockholm. The Second International Workshop on Brominated Flame Retardants. May 14-16, 2001. Stockholm University, Sweden.

Morck A, Hakk H, Orn U, Klasson Wehler E. 2003 Decabromodiphenyl ether in the rat: absorption, distribution, metabolism, and excretion. Drug Metab Dispos 31: pp. 900-907

NAS. 2000. Toxicological Risks of Selected Flame-Retardant Chemicals. National Academy Press. Washington, DC. Available at: http://www.nap.edu

NTP. 1986. Toxicology and carcinogenesis studies of Decabromodiphenyl oxide (CAS No. 1163-19-5) in F344/N Rats and B6C3F1 Mice (feed studies). National Toxicology Program Technical Report Series No. 398. U.S. Department of Health and Human Services. Public Health Service. National Institutes of Health. Research Triangle Park, NC.

Norris J, Ehrmantraut J, Gibbons C, Kociba R, Schwetz B, Rose J, Humiston C, Jewett G, Crummett W, Gehring P, Tirsell J, and Brosier J. 1973. Toxicological and environmental factors involved in the selection of Decabromodiphenyl oxide as a fire retardant chemical. Applied Polymer Symposia. No. 22. Polymeric Materials for Unusual Service Conditions. pp 195-219.

Norris J, Kociba R, Schwetz B, Rose J, Humiston C, Jewett G, Gehring P, and Mailhes J. 1975. Toxicology of Octabromobiphenyl and Decabromodiphenyl oxide. Environ Health Perspect, 11: 153-161.

Rayne S and Ikonomou MG. 2002. Reconstructing source polybrominated diphenyl ether congener patterns from semi permeable membrane devices in the Fraser River, British Columbia, Canada: comparison to commercial mixtures. Environ Toxicol Chem, 21: 2292-2300.

Rudel R, Camann D, Spengler JD, Barr D, and Brody JG. 2003. Household exposure to phthalates, pesticides, alkylphenols, PBDEs, and other endocrine active compounds. SOT 2003 Abstract # 896

Rudel R, Camann D, Spengler JD, Barr D, and Brody JG. 2003. Phthalates, Alkylphenols, Pesticides, Polybrominated Diphenyl Ethers, and Other Endocrine-Disrupting Compounds in Indoor Air and Dust Environ. Sci. Technol., ASAP Web Release Date: September 13

Santillo D, Johnston P and Brigden K. 2001. The presence of brominated flame retardants and organotin compounds in dusts collected from Parliament buildings from eight countries. Greenpeace Research Laboratories Technical Note 03/2001.

Schaefer EC and Flaggs RS. 2001. Potential for biotransformation of radiolabelled decabromodiphenyl oxide (DBDPO) in anaerobic sediment. Wildlife International Ltd., Project Number 439E-104, Wildlife International Ltd., Maryland, United States.

Schecter A. 2003. Personal communication of unpublished data. [Subsequent to the VCCEP meeting, this study has been published in Environmental Health Perspectives (online 7 August 2003) as Schecter A, Pavuk M, Papke O, Ryan JR, Birnbaum L, and Rosen R. Polybrominated Diphenyl Ethers (PBDEs) in U.S. Mothers' Milk.]

Sellstrom et al. 2001. Higher brominated PBDEs found in eggs of Peregrine Falcons breeding in Sweden. Proceedings, BFR 2001. The Second International Workshop on Brominated Flame Retardants. Stockholm. pp 159-162.

Sjödin A, Patterson D, and Bergman A. 2001. Brominated flame retardants in serum from U.S. blood donors. Environ Sci Tech, 35: 3803-3833.

U.S. EPA. 2000. Voluntary Children's Chemical Evaluation Program. Fed Regist, FRL-6758-5. 65 FR 81700. December 15, 2000. Available at: http://www.epa.gov/oppt/chemrtk/ts00274d.htm

Viberg H, Fredriksson A, Jakobsson E, Orn U, and Eriksson P. 2001. Brominated flame retardant: uptake, retention, and developmental neurotoxic effects of Decabromodiphenyl ether (PBDE 209) in the neonatal mouse. BFR 2001 Stockholm. The Second International Workshop on Brominated Flame Retardants. May 14-16, 2001. Stockholm University, Sweden. pp 279-282.

Viberg H, Fredriksson A, Jakobsson E, Orn U, and Eriksson P. 2003 Neurobehavioural Derangements in Adult Mice Receiving Decabrominated Diphenyl Ether (PBDE 209) During a Defined Period of Neonatal Brain Development. Toxicol Sci. 2003 On-line Aug 12 http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=search&DB=PubMed

Appendix A – List of Attendees
Appendix B – Decabromodiphenyl Ether Meeting Materials
Appendix C – Premeeting Observer Comments
Appendix D – Sponsor Presentation Slides
Appendix E – Panelist Handout Comparing DBDPO in Various Organs (NTP, 1986)

Appendix A
List of Attendees

Ms. Mary Albert
Health Canada

Mr. John A. Biesemeier
Great Lakes Chemical Corporation

Mr. Robert Campbell
Great Lakes Chemical Corp.

Ms. Colleen Cushing
Exponent

Ms. Lynne Delpire
U.S. EPA

Mr. Nathan Dodder
Indiana University

Mr. James E. Downes
Solutia Inc.

Mr. Chuck Elkins
Chuck Elkins & Associates

Mr. Kenneth Moss
USEPA – OPPT

Mr. Jonathan Raff
Indiana University

Ms. Lee Salamone
American Chemistry Council

Dr. Chad B. Sandusky
PCRM

Dr. Lingyan Zhu
School of Public and Environmental Affairs
Indiana University, Bloomington

Dr. Colette Hodes
U.S. EPA - OPPT/RAD/ECAB

Ms. Eunha Hoh
Indiana University

Dr. Frederick Johannsen
Solutia Inc.

Dr. Mike Kaplan
DuPont - Haskell Laboratory

Dr. Karen Kohrman
Procter and Gamble Co.

Ms. Kathleen Lawson
Learning Disabilities Association of America

Ms. Regina McCartney
Syracuse Research Corp.

Appendix B

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

Meeting Materials

April 2-3, 2003

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

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Introduction

This peer consultation meeting has been organized by Toxicology Excellence for Risk Assessment (*TERA*). *TERA* is an independent non-profit organization with a mission to protect public health through the best use of toxicity and exposure information in the development of human health risk assessments. *TERA* has organized and conducted peer review and consultation meetings for private and public sponsors since 1996 (see http://www.tera.org/peer for information about the program and reports from meetings). As a part of this program, *TERA* is organizing peer consultation panel meetings for assessments developed under the Voluntary Children's Chemical Evaluation Program (VCCEP). This panel meeting will review an assessment on Decabromodiphenyl Ether, prepared by the Brominated Flame Retardant Industry Panel (BFRIP).

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

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

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

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

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

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

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

Decabromodiphenyl Ether Peer Consultation Panel

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

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

Additional *ad hoc* experts are invited by *TERA* to participate in panel meetings on a case-by-case basis to provide additional expertise relevant to a specific chemical or issue. Nominations were solicited from interested parties for *ad hoc* panelists for the decabromodiphenyl ether panel, with the nomination period closing in November 2002. *TERA* independently selected four additional *ad hoc* scientists for the decabromodiphenyl ether panel. *Ad hoc* panelists have the same status and responsibilities as the core group panelists.

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

Conduct of the Peer Consultation

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

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

Public Observation and Comments

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

Meeting Report

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

Agenda for the VCCEP Peer Consultation for Decabromodiphenyl Ether

April 2-3, 2003
University of Cincinnati, Kingsgate Conference Center, Salon AB

Wednesday April 2, 2003

8:00 **Registration and Check In**

8:30 **Meeting Convenes**[9]

Welcome: Ms. Jacqueline Patterson, *TERA*
Introductions and Disclosures, Panel
Meeting Process: Dr. Michael Dourson, Chair

9:00 **Sponsor Introduction and Presentation on Hazard Assessment**
Presenter: Dr. Marcia Hardy, Albemarle Corporation/Brominated Flame Retardants Industry Panel (BFRIP)

Clarifying Questions from Panel

Public Comments on Hazard Assessment
Clarifying Questions from Panel and Sponsors

Panel Discussion on Hazard Assessment
Discussion of Panel Charge Questions regarding Hazard Assessment

12:30 **Lunch**

1:30 **Sponsor Presentation on Exposure Assessment**
Presenter: Mr. Sean Hays, Exponent
Clarifying Questions from Panel

Public Comments on Exposure Assessment
Clarifying Questions from Panel and Sponsors

Panel Discussion on Exposure Assessment
Discussion of Panel Charge questions regarding Exposure Assessment

5:00 **Adjourn**

[9] The Chair will call a break each morning and afternoon.

Thursday April 3, 2003

8:00 **Registration**

8:30 **Meeting Re-convenes**
Sponsor Presentation on Risk Characterization and Data Needs
Presenter: Dr. Marcia Hardy, Albemarle Corporation/BFRIP

Clarifying Questions from Panel

Public Comments on Risk Characterization and Data Needs
Clarifying Questions from Panel and Sponsors

Panel Discussion on Risk Characterization
Discussion of Panel Charge questions regarding Risk Characterization

12:15 **Lunch**

1:15 **Panel Discussion on Data Needs**
Discussion of Panel Charge questions regarding Data Needs

Closing Remarks and Evaluation of Meeting

4:30 **Adjourn**

Decabromodiphenyl Ether Panel Charge

Introduction

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

To help the Panel discuss the sponsor's submission and address whether a chemical has been adequately characterized, *TERA* has prepared these charge questions. The questions are consistent with the directions for VCCEP submissions given in the December 26, 2000, Federal Register: http://www.epa.gov/oppt/chemrtk/ts00274d.htm. These questions will form the basis for the Panel discussions. Panel members will be queried regarding their opinions on these questions and the conclusions.

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

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

Questions Regarding the Hazard Assessment and Dose Response

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

2. Is the quantitative hazard and dose-response information that is carried forward to the risk characterization the appropriate information to use?

Questions Regarding the Exposure Assessment

3. Is the fate of decabromodiphenyl ether adequately understood?

4. Based on the information at hand, are the data adequate to characterize exposure to children and prospective parents?

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

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

5. Are the estimates of exposure calculated appropriately and correctly?

Questions Regarding the Risk Characterization

6. Does the Risk Characterization appropriately integrate the exposure and hazard information of decabromodiphenyl ether to characterize risk a) *in utero*, b) to the infant and child, and c) to prospective parents?

Questions Regarding the Data Needs Assessment

7. Based on the information at hand and panel discussions,

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

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

Panel Biographical Sketches and Conflict of Interest and Bias Information

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

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

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

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

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

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

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

A brief biographical sketch of each panel member is provided below, together with a disclosure statement describing any potential conflict of interest or bias issues. The disclosure statements do not address funding provided by organizations unrelated to VCCEP or this chemical and sponsor. For the core panelists, the disclosure statements cover the chemicals and sponsors in

the entire VCCEP pilot program. For the *ad hoc* panelists, the disclosures are specific to Decabromodiphenyl Ether and its Sponsor, the Brominated Flame Retardant Industry Panel (BFRIP).

Dr. John Balbus

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

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

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

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

DISCLOSURE:

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

Ms. Nicole Cardello

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

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

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

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

DISCLOSURE:

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

Dr. Kevin M. Crofton

Dr. Kevin Crofton is a Neurotoxicologist with the Neurobehavioral Toxicology Branch of the National Health and Environmental Effects Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina. His primary research interest is the effects of thyrotoxic chemicals on the ontogeny of the nervous system. He is a member of the EPA Intra-Agency Workgroup on PBDEs (polybrominated diphenyl ethers) and is conducting research on the toxicology of these chemicals.

Dr. Crofton received his Ph.D. in Toxicology from the University of North Carolina, Chapel Hill. He has been a toxicologist at EPA since 1986; and during his tenure at EPA has received numerous awards, including Scientific and Technological Achievement Awards and a Bronze Medal for Commendable Service. In addition, he has also served as an Adjunct Assistant Professor in the Department of Toxicology at North Carolina State University since 1993. Dr. Crofton's professional activities include membership in numerous scientific societies and participation on many professional review boards.

Dr. Crofton is currently on the Editorial Boards of several scientific journals, including NeuroToxicology, Neurotoxicology and Teratology, and Toxicological Sciences; and serves as an ad hoc reviewer for many other scientific journals related to toxicology, pharmacology and neuroscience. He has presented invited lectures for a variety of government agencies in Europe, Canada, and the U.S., for professional societies, and universities. Many of these lectures have addressed developmental exposure and toxicity. In addition, he has authored or coauthored at least nine book chapters or reviews and over 80 additional publications on the subject of neurotoxicology.

DISCLOSURE:

Dr. Crofton has been selected as an *ad hoc* member for the VCCEP panel on decabromodiphenyl ether. He is employed by the U.S. EPA, working at the Office of Research and Development, National Health and Environmental Effects Laboratory, Neurotoxicology Division. EPA has taken public positions on the selection criteria used for the VCCEP pilot chemicals and on the toxicology tests included in the VCCEP Tiers. Dr. Crofton recently published papers on the effects of PBDEs on thyroid hormones.

Dr. George Daston

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

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

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

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

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

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

DISCLOSURE:

Dr. Daston is a VCCEP Core Panel member. He is employed by the Procter & Gamble Company (P&G). P&G uses thousands of chemicals, which it purchases individually, or in

mixtures. It is possible that some VCCEP pilot chemicals are included in these purchases. P&G purchases chemicals from numerous suppliers, including companies that are sponsors of the VCCEP pilot chemicals.

Dr. Michael L. Dourson

Dr. Michael Dourson directs Toxicology Excellence for Risk Assessment (*TERA*), a nonprofit corporation dedicated to the best use of toxicity data for estimating risk assessment values. *TERA*'s projects include the development of complex risk assessments, such as soluble nickel salts; research into improvements of risk methods, such as differential sensitivity of children and adults to chemical toxicity, organizing peer review and consultation meetings for risk assessment topics and documents; and education and outreach on risk assessment values through lectures and data bases, including the International Toxicity Estimates for Risk (*ITER*).

Before founding *TERA* in 1996, Dr. Dourson held leadership roles in the U.S. Environmental Protection Agency for fifteen years; as chair of EPA's Reference Dose (RfD) Work Group, charter member of the EPA's Risk Assessment Forum and chief of the group that helped create the Integrated Risk Information System (IRIS) in 1986. Dr. Dourson received his Ph.D. in Toxicology from the University of Cincinnati and a B.A. in biology from Wittenberg University. Dr. Dourson's research interests include investigating methods to extrapolate toxicity data garnered on experimental animals or healthy adults to the appropriate sensitive human population. Topic such as adversity of effect, and characterization of risk are also of interest.

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

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

DISCLOSURE:

Dr. Dourson is a VCCEP Core Panel member. He is Director of the non-profit organization Toxicology Excellence for Risk Assessment (*TERA*). Previously, he was employed by the U.S.

EPA. *TERA* has performed work for organizations associated with VCCEP. These include the U.S. EPA, the American Chemistry Council, and some companies that are sponsors of VCCEP chemicals. TERA has worked on the following chemicals included in the VCCEP pilot program: acetone, decabromodiphenyl ether, methyl ethyl ketone, and toluene. For decabromodiphenyl ether, *TERA* staff drafted text on the toxicity assessment under contract to the National Academy of Sciences (NAS). After review and revisions by the NAS Subcommittee on Flame-Retardant Chemicals, this text was incorporated into NAS's 2000 publication *"Toxicological Risks of Selected Flame-Retardant Chemicals."*

Dr. Robert C. Hale

Dr. Robert Hale is a professor in the Department of Environmental & Aquatic Animal Health of the Virginia Institute of Marine Science (VIMS) at the College of William & Mary. His current research areas encompass the analysis, distribution and environmental chemistry of synthetic organic chemicals, including flame retardants and PCBs; and he has authored or coauthored numerous publications and given invited presentations on these subjects. He is conducting primary research into the sources, analysis, fate, transport and bioavailability of PBDEs in the environment. His knowledge of PBDE behavior and presence in the environment and organisms relates to the potential exposure of target human populations to these chemicals via the food chain and other pathways.

Dr. Hale received his Ph.D. in Marine Science from the College of William and Mary. He has received numerous academic honors and awards, as have many of the students that he has mentored. Prior to joining the College of William and Mary in 1987, Dr. Hale worked as an environmental chemist in the Environmental and Health Sciences Laboratory at Mobil Corporation.

Since 1987, Dr. Hale has served in numerous governance positions for VIMS, including the Faculty Council and the Academic Council. In addition, he has served as the Chair of the Chemistry Group Subfaculty. Dr. Hale has also served on a number of review panels, program reviews, and national or international research programs. He is also a manuscript reviewer for multiple scientific journals, books, and proposals. Dr. Hale has provided information on the presence of PBDEs in fish and the aquatic environment as a potential pathway to humans at the U.S. EPA Region 9 Roundtable on Brominated Flame Retardants in Electronics.

DISCLOSURE:

Dr. Hale has been selected as an *ad hoc* member for the VCCEP panel on decabromodiphenyl ether. He is employed at the College of William & Mary in the Department of Environmental & Aquatic Animal Health of the Virginia Institute of Marine Science (VIMS). In 1999 Dr. Hale received analytical standards from the Brominated Flame Retardant Industry Panel (BFRIP) to improve his ability to quantify PBDE congeners in environmental matrices. He has published numerous papers and contributed to book chapters dealing with PBDEs in the environment.

Dr. Elaine Cohen Hubal

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

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

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

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

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

DISCLOSURE:

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

Dr. Michael Jayjock

Dr. Michael Jayjock is a Senior Research and Environmental Health and Safety Fellow and Manager for Risk Assessment at the Rohm and Haas Company; and he has been working with this company for 33 years. In his current position, he is responsible for the determination of human health risk from exposure to Rohm and Haas products, reactants, and intermediates. Dr. Jayjock was a member of the National Research Council's Subcommittee on Flame Retardant Chemicals, and, in this capacity, he participated in the review of decabromodiphenyl oxide (aka, decabromodiphenyl ether).

Dr. Jayjock received both his Ph.D. in Environmental Engineering and his M.S. in Environmental Science and Occupational Health from Drexel University. He is also certified in the Comprehensive Practice of Industrial Hygiene by the American Board of Industrial Hygiene.

Dr. Jayjock's professional activities include membership in numerous scientific societies and participation on many professional review boards. He is a former member and current consultant to the U.S. EPA's Science Advisory Board, Integrated Human Exposure Committee; and is a member of and serves on several committees of the National Research Council - National Academy of Sciences. In addition, he is a Member of the Peer Review Panel for the science program at the National Exposure Assessment Laboratory of the EPA. He has authored or coauthored numerous publications and given invited presentations on risk assessment, occupational exposure, industrial hygiene, and modeling.

Dr. Jayjock also serves as a Guest Lecturer for universities and professional organizations. He is a Guest Lecturer at the University of Pennsylvania Medical School, Residency Program for Occupational Medicine; and he is also an Instructor for a Professional Development Course on risk assessment for the American Industrial Hygiene Conference and Exposition. Previously, he served as Course Director and Instructor for Risk Assessment and Intermediate Exposure Modeling at the University of North Carolina Education Research Center, Summer Institute.

DISCLOSURE:

Dr. Jayjock has been selected as an *ad hoc* member for the VCCEP panel on decabromodiphenyl ether. He is active on several working groups of the American Chemistry Council (ACC), but not on the Brominated Flame Retardant Industry Panel (BFRIP) that is sponsoring decabromodiphenyl ether. As a member of the National Research Council's Subcommittee on Flame Retardant Chemicals, Dr. Jayjock participated in the review of decabromodiphenyl oxide (aka, decabromodiphenyl ether).

Dr. Sam Kacew

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

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

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

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

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

DISCLOSURE:

Dr. Kacew is a VCCEP Core Panel member. He is a Professor in the Department of Cellular & Molecular Medicine in the Faculty of Medicine at the University of Ottawa in Canada. Several years ago, in 1993 and 1995, he received honoraria from two VCCEP sponsors, Mobil Oil and Dow, for talks he delivered at their facilities. As a member of the National Research Council's Subcommittee on Flame Retardant Chemicals, Dr. Kacew participated in the review of decabromodiphenyl oxide (aka, decabromodiphenyl ether).

Dr. R. Jeffrey Lewis

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

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

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

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

DISCLOSURE:

Dr. Lewis is a VCCEP Core Panel member. He is employed by ExxonMobil Biomedical Sciences, Inc. and is Adjunct Assistant Professor of Occupational Health at the University of Texas Health Science Center, School of Public Health. Exxon Mobil is sponsoring the VCCEP pilot chemicals benzene, methyl ethyl ketone, m-xylene, o-xylene, and toluene. Dr. Lewis, therefore, has a conflict of interest with these chemicals and will recuse himself from participating in the Peer Consultation Meetings for these chemicals. Dr. Lewis is active on several committees, work groups, and task forces associated with the American Chemistry Council, but not on the Brominated Flame Retardant Industry Panel (BFRIP) that is sponsoring decabromodiphenyl ether.

Ms. Ruthann Rudel

Ms. Ruthann Rudel is a Senior Scientist responsible for toxicology and environmental risk assessment for the Silent Spring Institute. She manages the toxicology and environmental exposure components of the multi-disciplinary Cape Cod Breast Cancer and Environment Study. For this study, Ms. Rudel designs and manages investigations of the hypothesis that exposure to endocrine disruptors might play a role in breast cancer etiology. Her work includes designing and managing field sampling programs and developing exposure variables, as well as managing work with study collaborators with at Tufts Medical School, Harvard University School of Public Health, and other institutions. She has considerable experience in risk assessment of chemicals such as the PBDEs.

Prior to joining the Silent Spring Institute, Ms. Rudel worked as an environmental toxicologist for Gradient Corporation. As such, she evaluated the health effects of exposure to hazardous chemicals in the environment in order to provide a sound basis for environmental management decisions. She reviewed international properties contaminated with pesticides and chlorinated solvents, and evaluated blood biomarkers and exposure from inhalation, soil and dust ingestion and bioconcentration, and fish ingestion. In addition, Ms. Rudel also worked as an Editor for World Information Systems where she researched, wrote and edited a national weekly newsletter entitled, *Hazardous Materials Intelligence Report*.

Ms. Rudel received her M.S. in Hazardous Materials Management from Tufts University and has completed graduate coursework at the Harvard Extension School and the New England Epidemiology Institute. She also received a B.A. in Chemistry with High Honors in Neuroscience from Oberlin College.

Ms. Rudel's professional activities include membership in numerous scientific societies and participation as a reviewer for journals and on peer review panels. Ms. Rudel is a member of the Society of Toxicology, Society for Risk Analysis, and the International Society for Exposure Analysis. She is an ad hoc manuscript reviewer for four scientific journals on toxicology, environmental health, and environmental science. She has participated as a reviewer for various government, non-profit, and academic organizations. She also has numerous publications and presentations in the areas of exposure assessment, geographic information systems (GIS), and endocrine disruptors.

DISCLOSURE:

Ms. Rudel has been selected as an *ad hoc* member for the VCCEP panel on decabromodiphenyl ether. She is employed by the Silent Spring Institute, a scientific research organization concerned with public health and the potential environmental effects of persistent chemicals. Ms. Rudel recently submitted a manuscript measuring household exposures to PBDEs.

Dr. Jennifer Seed

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

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

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

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

DISCLOSURE:

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

Dr. Kimberly M. Thompson

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

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

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

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

DISCLOSURE:

Dr. Thompson is a VCCEP Core Panel member. She is Associate Professor of Risk Analysis and Decision Science and Director of the Kids Risk Project at Harvard University in the School of Public Health. She received funding from EPA in 2000 to chair a workshop and prepare a publication discussing changes in children's exposure as a function of age. Dr. Thompson's

research program benefits from unrestricted grants made to Harvard University by the American Chemistry Council and Synthetic Organic Chemicals Manufacturers Association. Both of these organizations are sponsors of VCCEP chemicals.

Sponsor Presenter BioSketches

Dr. Marcia L. Hardy

D.V.M., Ph.D. (Toxicology)
Albemarle Corporation

Dr. Marcia Hardy is currently a Senior Toxicology Advisor with Albemarle Corporation where she works on toxicology and environmental issues relating to brominated flame retardants. Prior to joining Albemarle, she practiced equine medicine and instructed veterinary students in pharmacology and toxicology.

Dr. Hardy has worked almost exclusively with brominated flame retardants for the last dozen years. She served as Chair of the American Chemistry Council's Brominated Flame Retardant Industry Panel (BFRIP) for 5 years. She represented industry on the European Union risk assessments of Decabromodiphenyl Oxide (DBDPO), Octabromodiphenyl Oxide (OBDPO) and Hexabromocyclododecane (HBCD). In that capacity, she attended technical meetings of the member countries to discuss the risk assessments, provided written comments on the assessments, and oversaw and submitted toxicology tests. Dr. Hardy has testified before the U.S. Consumer Product Commission and the U.S. National Academy of Sciences on the toxicology of DBDPO and HBCD. She worked on the task groups assessing polybrominated diphenyl ethers, and tetrabromobisphenol A and its derivatives under the World Health Organization's Environmental Health Criteria document series. She served as the lead negotiator for industry in developing the Voluntary Industry Commitment on Selected Brominated Flame Retardants with the Organization for Economic Cooperation and Development (OECD), Paris. This was the first voluntary commitment entered into by OECD with industry. She participated in developing a voluntary product stewardship program on DBDPO and OBDPO with the U.S. Environmental Protection Agency. She has presented papers on the toxicology and regulatory issues affecting various brominated flame retardants at meetings and symposiums around the U.S., Europe, and Asia. She serves as the sponsor's representative on numerous studies ranging from acute and repeated dose toxicity in mammals and aquatic species, physical/chemical properties, pharamacokinetics, developmental, and carcinogenicity tests.

Dr. Hardy received her Ph.D. in Veterinary Medical Sciences (Toxicology Option) from Louisiana State University in 1986. Her research centered on the comparative toxicology and metabolism of two methylated aniline isomers in two species, the rodent and the canine. She received her Doctor of Veterinary Medicine degree from the Louisiana State University School of Veterinary Medicine (LSU-SVM) in 1977. Dr. Hardy was a member of the original class of 36 students accepted to the LSU-SVM. Dr. Hardy is a member of the Society of Toxicology, the Society of Environmental Toxicology and Chemistry, and the Louisiana Veterinary Medical Association, and is a licensed veterinarian in Louisiana and is certified by U.S.D.A.

Mr. Sean M. Hays

Senior Scientist
Exponent, Inc.

Sean Hays is a senior scientist with the human health risk assessment practice within Exponent, an engineering and scientific consulting firm. Mr. Hays is a toxicologist and chemical engineer with eight years of consulting experience in pharmacokinetic modeling, exposure assessment, conducting toxicology studies, and developing strategies to establish environmental and occupational exposure limits. Mr. Hays has been involved in developing physiologically based pharmacokinetic (PBPK) models for a range of chemicals, including volatile organic solvents, lead, dioxin, chromium, benzo[a]pyrene, and glycol ethers. He has designed animal and applied human studies to develop the data necessary to answer difficult questions concerning the regulation of chemical exposure in environmental and occupational settings. He has expertise in conducting exposure assessments for environmental, occupational, and product use scenarios and has extensive experience in interpreting biomarker data to assess exposure to compounds. Mr. Hays has performed exposure assessments and risk assessments for children exposed to a range of compounds; including children's exposures to decabromodiphenyl ether in the environment, copper-chromated-arsenic (CCA) exposures from playground structures, and children's exposures to natural rubber latex on playground surfacing material. Mr. Hays has published peer-reviewed manuscripts on matters that include the use of PBPK modeling to set regulatory criteria, dioxin exposures and risks, Cr(VI) kinetics, and exposures related to dioxin contamination of breast milk.

Mr. Hays received a B.S. in Biomedical Engineering from Texas A&M University in College Station (1989), an M.S. in Physiology from the University of Vermont in Burlington (1992), and an M.S. in Chemical Engineering from Colorado State University in Fort Collins (1997). Mr. Hays is a member of the International Society of Exposure Analysis and the Society for Risk Analysis.

Appendix C
Pre-meeting Observer Comments

VCCEP Peer Consultation Policy and Procedures for Observers

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

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

Written Comments

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

Oral Comments

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

Meeting Report

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

Ms. Lynne Delpire
U.S. EPA

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C., 20460
OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

March 21, 2003

Ms. Jacqueline Patterson
Toxicology Excellence for Risk Assessment
1757 Chase Avenue
Cincinnati OH 45223

Dear Ms. Patterson:

Enclosed are my comments on the Voluntary Children's Chemical Evaluation Program data submission for decabromodiphenyl ether. I look forward to attending the Peer Consultation Meeting on April 2-3, 2003, as an observer.

Sincerely yours,

/s/

Lynn A. Delpire, Chemist
Exposure Assessment Branch (7406M)

Comments on Consumer Exposure Assessment

The VCCEP data submission for DBDPO could have been improved by including a discussion of recent analyses of house dust or residential indoor air for DBDPO. For example, in a recent, small study in Germany, Knoth et al. 2002 reported that BDE-209 (DBDPO) was the "dominating" PBDE congener in 22 of 24 samples of dust from vacuum cleaner bags from private households. Knoth et al. 2002 believe that "PBDE leak from consumer products treated with this flame retardant and may reach via the pathway house dust, waste water, sewage sludge and its land-application the food chain to humans."

The VCCEP data submission for DBDPO could have been improved by including a discussion of a risk assessment for residential upholstered furniture (Babich and Thomas 2001) written by the staff of the U.S. Consumer Product Safety Commission. The CPSC risk assessment makes use of new data that were not available for the NAS report. These new data include DBDPO migration studies on upholstery fabric samples (Bhooshan and Cobb 2000, as cited in Babich and Thomas 2001) and DBDPO percutaneous absorption data (Hughes 2000, as cited in Babich and Thomas 2001). The availability of migration and percutaneous absorption data improve the risk assessment for DBDPO.

The CPSC risk assessment included more consumer exposure scenarios than did the NAS report. CPSC's consumer exposure and risk assessment evaluated several dermal, oral, and inhalation exposure scenarios and combined them into cases. In the basic case, saline was used to model spills on residential upholstered furniture and aqueous cleaner was used to model spot cleaning of residential upholstered furniture. Oral exposure was estimated for children who chew or suck on upholstery. Direct exposure from cleaning residential upholstered furniture was estimated for adults. The acidic spill case was the same as the basic case, except that citric acid was used to model spills on residential upholstered furniture, because some beverages and foods are acidic. The non-aqueous cleaner case was the same as the basic case, except that a non-aqueous cleaner was used for the cleaning scenario. The aged fabric case was the same as the basic case, except that migration rates from residential upholstered furniture were adjusted for artificially aged or worn fabric.

In the studies of flame retardant migration from upholstery fabric samples, isotonic saline was used as a surrogate for perspiration and neutral spilled liquids or foods. A 5% citric acid solution was used as a surrogate for acidic beverages or foods. A typical water-based consumer upholstery cleaner was used in cleaning tests. Methyl chloroform was used as a surrogate for dry cleaning solvents in cleaning tests. Migration of DBDPO from upholstery fabric samples was not detectable with saline, citric acid, or aqueous cleaner. Detectable migration of DBDPO from upholstery fabric samples occurred with methyl chloroform.

In both adults and children, dermal exposure was the primary route of exposure to DBDPO; the contribution from inhalation of particles was negligible.

Table III-3 in Babich and Thomas 2001 shows the average daily dose and hazard index calculated for the various DBDPO exposure scenarios.

Table III-3. Aggregate non-cancer risks (liver effects) from exposure to decabromodiphenyl oxide (DBDPO).

Case, route, scenario	Adults		Children	
	ADD [a]	HI	ADD	HI{ TC \l4 "}
Basic case [b]	$2.6x10^{-4}$	0.008	$3.8x10^{-4}$	0.008
Dermal [c]	$2.5x10^{-4}$	0.008	$2.4x10^{-4}$	0.008
Passive, normal use	$8.6x10^{-5}$	0.003	$8.3x10^{-5}$	0.003
Passive, spill	$3.4x10^{-5}$	0.001	$3.3x10^{-5}$	0.001
Passive, cleaning	$1.3x10^{-4}$	0.004	$1.2x10^{-4}$	0.004
Active, spill	$5.7x10^{-9}$	$1.8x10^{-7}$	$1.0x10^{-8}$	$3.2x10^{-7}$
Active, spot cleaning	$2.1x10^{-8}$	$6.6x10^{-7}$	0	0
Oral	0	0	$1.1x10^{-4}$	$3.6x10^{-5}$
Inhalation	$1.1x10^{-5}$	$3.5x10^{-6}$	$2.7x10^{-5}$	$8.6x10^{-6}$
Vapor phase	$9.9x10^{-6}$	$3.1x10^{-6}$	$2.4x10^{-5}$	$7.6x10^{-6}$
Particles	$1.3x10^{-6}$	$4.2x10^{-7}$	$3.3x10^{-6}$	$1.0x10^{-6}$
Acidic spill [c]	$2.6x10^{-4}$	0.008	$3.8x10^{-4}$	0.008
Non-aqueous cleaner	$2.2x10^{-3}$	0.07	$2.2x10^{-3}$	0.07
Aged fabric	$4.2x10^{-4}$	0.01		

[a] ADD, average daily dose, mg/kg-d; HI, hazard index.

[b] Cases and scenarios are described in the Introduction. The basic case combines all scenarios, except full cleaning. Uses saline to model spills and aqueous cleaner to model spot cleaning scenario. Oral exposure applies only to children. Direct exposure from spot cleaning applies only to adults.

[c] Migration into saline, citric acid, and aqueous cleaner was below the detection limit. One-half the detection limit was used to calculate dermal exposure in these cases.

Source: Babich and Thomas (2001).

References

Babich M and Thomas T. 2001. CPSC Staff Exposure and Risk Assessment of Flame Retardant Chemicals in Residential Upholstered Furniture. U.S. Consumer Product Safety Commission, Bethesda, MD 20814. April 4, 2001. Available at http://www.cpsc.gov/library/foia/foia02/brief/briefing.html, pages 658 through 765 of 922 pages in Small Open Flame Ignition of Upholstered Furniture (4014), Options to Address Small Open Flame Ignition of Upholstered Furniture; October 30, 2001, Over 900 pages (PARTS 10, 11, and 12).

Bhooshan B and Cobb D. 2000. Migration of flame retardant chemicals from upholstery fabrics. U.S. Consumer Product Safety Commission, Washington, DC 20207. June 2, 2000. Cited in Babich and Thomas 2001. Available at http://www.cpsc.gov/library/foia/foia02/brief/briefing.html, pages 610 through 638 of 922 pages in Small Open Flame Ignition of Upholstered Furniture (4014), Options to Address Small Open Flame Ignition of Upholstered Furniture; October 30, 2001, Over 900 pages (PART 10).

Hughes M. 2000. *In vitro* dermal absorption rate testing of flame retardant chemicals. National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711. July 25, 2000. Cited in Babich and Thomas 2001.

Knoth W, Mann W, Meyer R, Nebhuth J. 2002. Polybrominated Diphenylether in House Dust. Organohalogen Compounds, 58, 213-216.

Ms. Barbara McElgunn
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Submission on risks to neurodevelopment from BDEs and the need for mitigating action. VCCEP Decabromodiphenyl Ether PC Meeting, April 2-3, 2003

The Learning Disabilities Association of America (LDA) was organized in 1964 by parents of children with learning disabilities. The national volunteer organization has approximately 40,000 members organized into roughly 400 state and local affiliates in 43 states, including Puerto Rico. LDA was instrumental in the passage of the Individuals with Disabilities Education Act, the Americans with Disabilities Act, and obtaining funding for the early reading research project at the National Institute for Child Health and Human Development.

LDA Mission statement: LDA is a non-profit organization of volunteers including individuals with learning disabilities, their families and professionals. LDA is dedicated to *identifying causes and promoting prevention of learning disabilities* and to enhancing the quality of life for all individuals with learning disabilities and their families by encouraging effective identification and intervention, fostering research, and protecting their rights under the law. LDA seeks to accomplish this through awareness, advocacy, empowerment, education, service and collaborative efforts.

Learning disabilities and related attention deficit disorders affect an estimated 10-15% of children. The consequences of these and other neurological, developmental and behavioural disorders are lifelong, often serious for both the child and his/her family, and costly for society. The role of toxic chemicals in the etiologies of these disorders has been largely ignored, though the evidence from both experimental animal and clinical research from the few neurotoxic chemicals that have been studied to date is compelling.There is evidence the prevalence of ADHD[10], learning disabilities[11] and autism[12] are increasing in recent years.

LDA has been aware for some time of the warnings from scientists about rising levels of the high-volume industrial chemicals - polybrominated diphenylethers (PBDEs) everywhere in the

[10] Rowland AS, Umbach DM, Stalone L, Naftel AJ, et al. Prevalence of medication treatment for attention-deficit hyperactivity disorder among elementary school children in Johnson county, North Carolina. American Journal of Public Heath 2002, 92 (2) 231-4.
[11] Center for Learning Disabilities. Students with learning disabilities: A national review. Annual Report to Congress, 2001.
[12] Byrd RS. Report to California legislature re jump in autism rates, 2002.

North American environment, in the food chain, and in breast milk. PBDE levels in trout from the Great Lakes rose from non-detectable in 1975 to 60ng/gm in 1990 to 200 ng/gm in the year 2000[13], and varying levels of PBDEs have been found in most commercial foods[14]. These chemicals have been found to be persistent, bioaccumulative, highly lipophilic, and have been shown to disrupt thyroid systems and be developmentally neurotoxic in experimental studies. The levels of these compounds in human tissue, such as breast milk, have been rising exponentially over the years of their use, especially in North America, a recent study by Petras et al. showing that California women have levels 3-10 times higher than measurements from Europe obtained during the same period[15]. Their structure-activity relationships with PCBs, known developmental neurotoxicants is another cause for concern to our organization.

The levels of PBDEs in North Americans appear to be doubling every two to five years. A study of PBDE levels in maternal and cord blood found relatively high levels -15- 580 ng/g lipid in maternal serum and 14- 460 ng/g in fetal samples[16] - far exceeding levels that moved Sweden to ban PBDEs in that country to protect neurodevelopment. The levels of 200 nanograms of PBDEs per gram of fat (ng/g) in breast milk from women in Austin and Denver were so high that the German scientist sent samples to colleagues in Germany and Sweden to have them analyzed independently. The highest concentrations can be compared to the maternal milk PCB concentrations reported by Jacobson and Jacobson as being associated with a 6.2 point loss in full-scale IQ scores and strong effects related to memory and attention in the most highly exposed group (1.25 µg/g or greater), and poorer word comprehension and overall reading comprehension and several other intellectual deficits, in the two groups with highest exposure (1.00 µg/g or greater). These PCB concentrations were only slightly higher than those found in the general population.

A study by Ericksson et al.[17] linked exposure to tetraBDE and pentaBDE, the most common forms of PBDEs in found in human samples, to permanent behavioral aberrations after a single dose on postnatal days 3, 10, or 19. These single exposures during brain development produced dose-related changes in spontaneous behavior in 2-4 month animals, increasing with age. In addition, neonatal exposure to PBDE 99 (pentaBDE) also affected learning and memory functions in these animals as adults. This study was replicated by Viberg et al. finding that mice at 6 months of age in both the low and high-dose groups treated on postnatal day 3 exhibited behavioral changes relative to controls.

Both tetra and commercial penta BDEs have been found to be able to disrupt the normal functioning of thyroid hormones critical for brain development. Learning and behavioral effects have been noted from alterations in thyroid in experimental animal studies, and from clinical

[13] Environment Canada (2002) S&E Bulletin, June, Ottawa.
[14] Alaee M, Bunce N, Ikonomou, M, etal. Determination of the impact of polybrominated Dephenyl Ethers in the Canadian environment and health of Canadians. TSRI report, 2002.
[15] Petras et al. High body burdens of 2,2',4,4'-tetrabromo diphenyl ether (BDE-47) in California women. Envrironmental Health Perspectives, doi: 10. 1289/ehp.6220
[16] Mazdai etal. Polybrominated diphenyl ethers in maternal and fetal blood samples. Environmental Health Perspectives, doi:10. 1289/ehp.6146.
[17] Eriksson P, Jacobsson W, & Fredrikssoni, A. (2001) Brominaaterd Flame Retardants: A novel class of developmental toxicants in our environment? Environmental Health Perspectives, 109 (9)

studies of the effects of thyroid hormone deficiency before birth, or beyond[18]. Thyroid hormone is critical to the expression of many vital processes necessary for normal brain development[19]. It has been known for some time that exposure to PCB mixtures disrupts thyroid function, and longitudinal studies of children exposed to PCBs as fetuses have found an association with reading deficits, lower IQ, and attention at age eleven from exposures that were just at the high end of the range found in the general population[20]. Many other chemicals and compounds have anti-thyroid actions, but these have not been studied for their possible links to neurodevelopmental effects.

Despite their close relationships with PCBs, no NOEL for developmental neurotoxicity has been established for PBDEs. LDA has urged that developmental neurotoxicity data to protect brain development should be required for priority chemicals for two decades. PBDEs are to be evaluated under the Voluntary Children's Chemical Evaluation Program (VCCEP). However we are very concerned about several aspects of this program: The slow pace of first tier toxicity data collection; the fact that DNT testing is included only in the third and last tier of testing; and only if negotiated and triggered by the other two tiers.

An economic analysis by Muir et al. (2002) makes this point: "This analysis suggests that a business-as-usual scenario, where environmental concentrations of BFRs, such as PBDEs, are allowed to continue their increasing upward trend, especially in human mothers' milk, has the potential for very large human health and economic costs and consequences. These costs dwarf any defensible estimate of the benefits of continuing to use BFRs. This result, together with our most basic scientific understanding of the physico-chemical properties of these compounds, strongly supports the idea that we do not need these compounds free in the environment, and calls for precautionary action to eliminate the problem."

The European Union has moved to ban penta-BDE and octa-BDEs in July 2003,and deca-BDE in January 2006.

In conclusion our association recommends

That urgent precautionary action be taken to mitigate exposures to the public from the penta , octa and deca BDEs, as in the European Union.

That USEPA issue a Test Rule to establish a NOEL for developmental neurotoxicity for the PBDEs.

That risk assessments include the cumulative neurotoxic and endocrine effects of environmental exposures from various PBDE congeners and PCBs with a similar mode of action.

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[18] Haddow JE, Palomani GE, Allan, W, et al. (1999) Maternal thyroid deficiency during pregnancy and subsequent neurophysiological development of the child. New England Journal of Medicine, 341 (8) 549-555.

[19] Porterfield, SP. Thyroidal dysfunction and environmental chemicals – Potential impact on brain development. Environmental Health Perspectives 108, (Suppl. 3), 433-437, 2000.

[20]. Jacobson J.L, Jacobson SW. Intellectual impairment in chi;dren exposed to polychlorinated biphenlys in utero. New England J. Med., 335, (11) 783-789, 1996

That thyroid function with associated neurodevelopmental studies in rodents be carried out, and these studies should include the use of lower does levels as well as iodine-deficient animals to better assess the risks to sensitive human populations,.

Submittted by

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Winston H. Hickox, ***Agency Secretary*** **Gray Davis,** ***Governor***

March 26, 2003

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Comments on the American Chemistry Council's data summary of decabromodiphenyl ether (DecaBDE), submitted for the Voluntary Children's Chemical Evaluation Program's (VCCEP) Peer Consultation Meeting

The authors of the VCCEP document have compiled and summarized a wealth of data on decabromodiphenyl ether (DecaBDE), and they should be complemented for that effort. Although I did not review the details of exposure assessment presented in the submission, tissue concentration data indicate that tissue levels of the DecaBDE in humans are lower than levels of the lower molecular weight PBDEs. Likewise, the toxicity of the DecaBDE is lower than the lower molecular weight PBDEs. The purpose of these comments is to list potential health concerns and associated datagaps related to DecaBDE for the Committee's consideration. These include:

1. Debromination of DecaBDE in the environment
2. Environmental conversion to polybrominated dibenzodioxins and furans
3. Limited data on neurodevelopmental toxicity

The primary concerns over the use of DecaBDE rest not in the parent compound but in its environmental transformation products. Specifically, there is concern that DecaBDE debrominates in the environment to less brominated congeners, which are bioaccumulative and more bioactive than DecaBDE itself. Presently it is unclear what proportion of the polybrominated diphenylethers (PBDEs) measured in human tissues and wildlife comes from use of the PentaBDE and OctaBDE formulations (which contain bioaccumulative congeners) and what fraction comes from DecaBDE that has been debrominated by sunlight, biota or other processes.

Tissue concentrations of PBDEs (primarily tetra- to hepta-PBDE congeners) in many individuals in the United States (U.S.) are increasing over time and are now approaching concentrations equivalent to those associated with adverse health effects in studies conducted in rodents. In two populations of California women (Petreas et al., 2003) and one population of Indiana women (Mazdai et al., 2003), roughly 5 % of individuals had PBDE concentrations > 400 ng/g lipid. If these populations are representative of the U.S. population, then roughly 15 million U.S. citizens have body burdens > 400 ng/g lipid. Comparing these PBDE levels in humans to PBDE dose levels shown to induce adverse effects in rodents, it is apparent that the "margin of exposure" for the PBDEs is small. Specifically, several studies in mice have shown that a PBDE dose of approximately 1 mg/kg induces neurodevelopmental deficits and thyroid hormone disruption in mice (Eriksson *et al.*, 2001; Branchi *et al.*, 2002; Fowles *et al.*, 1994). Assuming a rodent body fat content of 10 to 20 %, this dose level would be expected to result in rodent body burdens of just 10 to 20-fold higher than those currently attained in humans (i.e., 400 ng/g lipid). Additionally, a radiolabeled pentaBDE congener administered to mice at a dose associated with adverse neurodevelopmental effects (Eriksson *et al.*, 2002) resulted in PBDE concentrations in mouse brain tissue that are comparable, after adjusting for tissue fat content, to PBDE concentrations currently attained in humans. Given this low margin of exposure for the PBDEs, it is important to assess the extent to which the use of the DecaBDE contributes to the human body burden.

An additional concern over the use of DecaBDE is the evidence indicating that when PBDE-containing products are burned or heated, other toxic compounds are formed, namely brominated dibenzofurans and dibenzodioxins (discussed below).

Specific comments:

Section 3. The issue of fire safety is important, but the discussion misses the point. The issue is not whether products that burn slowly prevent deaths from fires compared to products that burn rapidly. I do not know of anyone who would argue that we do not need flame resistant products. The issue that should be discussed in the document is how society can be produce products that meet strict flame retardancy standards, while at that same time reduce unintended consequences, such as detriments to human health and the environment.

Section 4.1.11 (Developmental Neurotoxicity). The document is overly dismissive of the findings of Per Eriksson's group in Sweden (described on pages 40-41). Behavioral changes in adulthood were observed from a single 20 mg/kg dose of DecaBDE to neonatal mice. If this finding is true (and currently no other data are available to contradict the finding), then it represents the most sensitive toxicological endpoint for DecaBDE itself. It may indicate that the immature gut is capable of higher rates of absorption than adults. The document correctly notes on page 41 that this fact might be mitigated by the different patterns of brain growth between rodents and humans, such that in humans fetal exposures may be more important. Exposures during the fetal period would result from ingestion by the mother whose rate of oral absorption of the DecaBDE is thought to be low. The VCCEP review committee may want to discuss whether further research in this area would be valuable. Further testing of this potentially sensitive endpoint, including possible additive effects with other PBDE congeners, appears warranted.

Environmental debromination

The environmental fate of DecaBDE and especially its propensity to debrominate is a critical datagap and needs more study. The primary question is: Do a portion of the lower molecular weight PBDEs found in human tissues stem from the use of DecaBDE?

Sellstrom et al. (1998) reported the debromination of DecaBDE on silica support by natural sunlight (page 45). This is an important finding since DecaBDE is usually found associated with particulate matter (page 54), including dusts. DecaBDE that is associated with particulate matter in the air (or dusts exposed to sunlight) would be analogous to the DecaBDE on silica support, thus providing a "real world" opportunity for environmental debromination. Therefore, I disagree with the assertion made on page 54 that "Photolysis is not expected, because of DBPDOs negligible vapor pressure . . ." Another example: What about DecaBDE used as backcoatings on textiles such as draperies, which are exposed to sunlight for years?

Studies of aerobic biodegradation appear to be limited (page 46), as no direct measurements were made for lower molecular weight PBDE congeners.

Debromination during warming and recycling: There is some evidence that PBDEs in plastics debrominate when they are recycled (i.e., extruded and reformed) (Riess *et al.*, 2000). As shown in Figure 1 from Riess et al. (2000) shown below, heating during the remolding process converts octaBDE to lower molecular weight congeners. It is not stated whether a similar finding was made for DecaBDE. Follow-up questions include: does the warming of DecaBDE-treated television casing, for example, over the 10+ years of service induce debromination? Has anybody looked for evidence of debromination in used DecaBDE-treated plastic?

Figure 1. Debromination during the recycling of plastics from TV and computer casings (Riess et al., 2000).
("Sample 1" is used PBDE-treated high-impact polystyrene; "Sample 1R" is the same plastic after recycling).

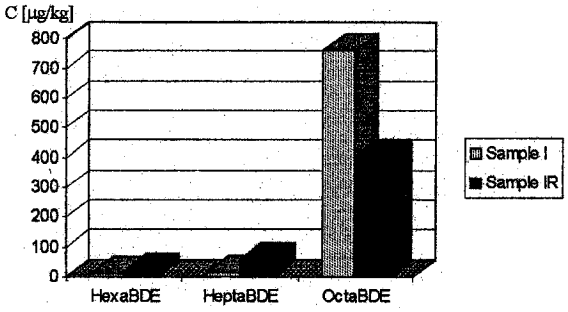


Fig. 5. Influence of material recycling on the PBDE concentrations.

The citation for Jaffvert and Hua (2001) (page 55), a study that the document relies heavily regarding the debromination issue, is not in the reference list and could not be located on Medline. Also, the Sellstrom et al. (1998) citation does not appear in the reference list.

Conversion of PBDEs to brominated or mixed halogenated dioxins and dibenzofurans

There are data to indicate that PBDEs are converted to brominated dioxins and dibenzofurans during fire tests and fire accident studies (IPCS, 1994). Combustion tests conducted by Motorola Corporation indicated "substantial" brominated dioxin/furan formation (Schiefers, 2002), and dioxin/furan formation was cited as the primary reason that Motorola is examining alternative flame retardant materials. Brominated dioxin and furan formation was also cited as a concern by Intel representatives as a reason for evaluating alternatives to the PBDEs and other brominated flame retardants (Clemmons and Brady, 2002). Brominated and mixed halogen (chlorinated and brominated) dibenzodioxins and dibenzofurans have been measured in municipal waste incinerators. It has been suggested that products containing brominated flame retardants are the source of bromine in these reactions (reviewed in Weber and Greim, 1997). However, if incinerators are operating properly, formation of dioxins are not expected (Sakai *et al.*, 2001). It should also be noted that there is uncertainty regarding the stability of brominated dioxins in the environment. They are quite persistent once they enter the body, with half-lives on the order of a year (Weber and Griem, 1997). It is unknown whether exposures to brominated or mixed halogenated dioxins and furans as a result of use of PBDEs are significant enough to warrant concern.

Polybrominated dibenzodioxins and dibenzofurans (PBBD/F) were measured in used PBDE-treated plastics (3.1 ppm total PBBD/F: Sakai et al., 2001; and Riess et al., 2000 see table below).

Concentrations (mg/kg) of biologically active brominated dibenzodioxins and furans (BDD/F) in PBDE-containing Computer and TV Casings (Riess et al., 2000)

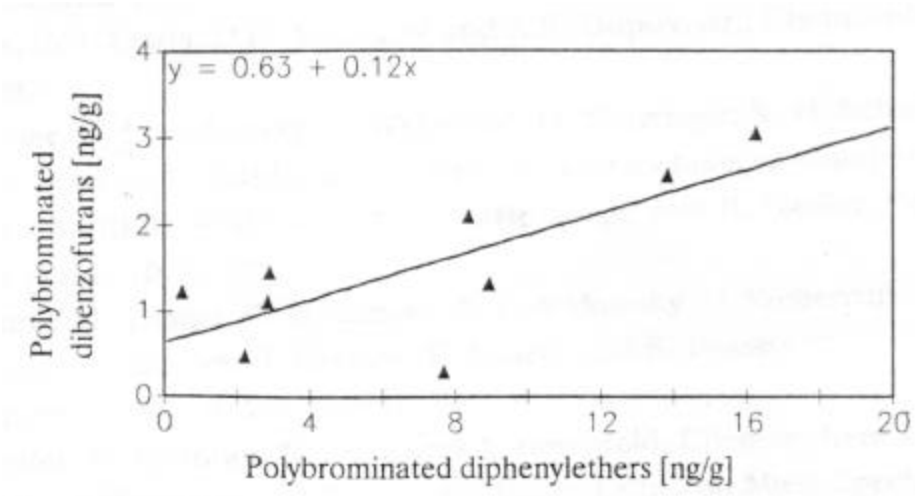
Compound	High-impact polystyrene		Acrylonitrile butadiene styrene	
	Used*	Recycled†	Used	Recycled
2,3,7,8-BDD	<0.01	<0.02	<0.05	<0.02
1,2,3,7,8-BDD	<0.03	<0.03	5.71	12.98
2,3,7,8-BDF	0.41	0.43	<0.01	<3.04
2,3,4,7,8-BDF	5.45	4.05	28.26	86.16
Sum of above	5.90	4.53	34.04	99.23

* "Used" means the plastic from electronic equipment has been discarded for recycling, presumably at the end of the product's lifespan.

† "Recycled" means the product has been heated and remolded into new, usable plastic.

Analysis of sewage sludge in Germany (Hagenmaier *et al.*, 1992) indicated that concentrations of PBDEs (only tri to hepta congeners were measured) were correlated with polybrominated dibenzofuran (PBBF) concentrations, suggesting environmental conversion of the PBDEs to PBBFs (Figure 2). PBDE levels in U.S. sludge are 10- to 100-fold higher than European samples (Hale *et al.*, 2001). Currently, PBBF concentrations in U.S. sewage sludge samples are not known. Sewage sludge is routinely added to food crops as fertilizer and may represent a pathway of human exposure.

Figure 2. PBDEs (tri to hepta) and Polybrominated Dibenzofurans (PBBF) in German Sewage Sludge (Hagenmaier et al., 1992)



References

Branchi I, Alleva E, Costa LG (2002). Effects of perinatal exposure to a polybrominated diphenyl ether (PBDE 99) on mouse neurobehavioural development. *Neurotoxicology* **23**(3):375-84.

Clemmons G, Brady T (2002). "Going bromine free." Intel Corporation. Presentation to the EFC Brominated Flame Retardants and Electronics Conference and Roundtable, U.S. Environmental Protection Agency, San Francisco, September 24, 2002. Located at: http://www.greenstart.org/efc9/bfrs/ppt/GBFRF.ppt.

Eriksson P, Jakobsson E, Fredriksson A (2001). Brominated flame retardants: a novel class of developmental neurotoxicants in our environment? *Environ Health Perspect* **109**(9):903-8.

Eriksson P, Viberg H, Jakobsson E, Orn U, Fredriksson A (2002). A brominated flame retardant, 2,2',4,4',5-pentabromodiphenyl ether: uptake, retention, and induction of neurobehavioral alterations in mice during a critical phase of neonatal brain development. *Toxicol Sci* **67**(1):98-103.

Fowles JR, Fairbrother A, Baecher-Steppan L, Kerkvliet NI (1994). Immunologic and endocrine effects of the flame-retardant pentabromodiphenyl ether (DE-71) in C57BL/6J mice. *Toxicology* **86**(1-2):49-61.

Hagenmaier H, She J, Benz T, Dawidowsky N, Dusterhoft L, Lindig C (1992). Analysis of sewage sludge for polyhalogenated dibenzo-p-dioxins, dibenzofurans and diphenylethers. *Chemosphere* **25**(7-10):1457-62.

Hale RC, La Guardia MJ, Harvey EP, Gaylor MO, Mainor TM, Duff WH (2001). Flame retardants. Persistent pollutants in land-applied sludges. *Nature* **412**(6843):140-1.

IPCS (1994). *Environmental Health Criteria 162. Brominated Diphenyl Ethers*. International Programme on Chemical Safety World Health Organization, Geneva.

Riess M, Ernst T, Popp R, Muller B, Thoma H, Vierle O *et al*. (2000). Analysis of flame retarded polymers and recycling materials. *Chemosphere* **40**(9-11):937-41.

Sakai S, Watanabe J, Honda Y, Takatsuki H, Aoki I, Futamatsu M *et al*. (2001). Combustion of brominated flame retardants and behavior of its byproducts. *Chemosphere* **42**(5-7):519-31.

Schiefers S (2002). "Bromine Free Alternatives in Electronic Products", Motorola Corporation. Presentation to the EFC Brominated Flame Retardants and Electronics Conference and Roundtable, U.S. Environmental Protection Agency, San Francisco, September 24, 2002. Located at: http://www.greenstart.org/efc9/bfrs/ppt/BFAEP.ppt.

Sellstrom U, Soderstrom, G., de Wit C, Tysklind M (1998). Photolytic debromination of decabromodiphenyl ether (DeBDE). *Organohalogen Compounds* **35**:447-50.

Weber LW, Greim H (1997). The toxicity of brominated and mixed-halogenated dibenzo-p-dioxins and dibenzofurans: an overview. *J Toxicol Environ Health* **50**(3):195-215.

Thank you for the opportunity to provide comments towards the VCCEP process.

Sincerely,

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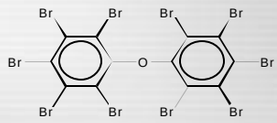
Appendix D

Sponsor Presentation Slides

DBDPO VCCEP: Introduction and Hazard Assessment



M. L. Hardy, DVM, PhD
Albemarle Corporation

April, 2003

DBDPO VCCEP Sponsor

- American Chemistry Council's Brominated Flame Retardant Industry Panel (BFRIP)
  - Albemarle Corporation
  - Ameribrom (subsidiary of DSBG)
  - Great Lakes Chemical Corporation
  - Akzo-Nobel (associate member)
- Organized in 1980s
  - Conduct research
  - Serve as an information source
  - Interact with regulatory agencies and organizations

Decabromodiphenyl Oxide (DBDPO)

- Sole use: flame retardant
  - Highly effective at low load levels
    - ~12% in V-0 TV cabinets
    - ~5 mg/cm2 in back coat of upholstery textiles
  - Acts in gas phase of fire
  - Manufactured at 2 locations in U.S., used at ~75
- Applications
  - Electrical & electronic equipment (~80% volume)
    - TV cabinets, CPU housings, wire & cable
  - Upholstery textiles (~20% volume)
    - Upholstered furniture, auto upholstery
- Volume - 2nd largest volume BFR
  - Largest volume "PBDE" (~82% global PBDE volume)

Fire Risk in the U.S.

- Someone dies in a fire about every 2 hrs
- Most deaths, 85%, occur in the home
  - 3,420 people died in fires in the home in 2000
- At high risk of death, injury or burns
  - Children 5 and under
  - Adults 65 and older
  - Low income
  - 16,975 people injured in fires in the home in 2000

Lives Saved in the U.S.

- Due to the use of BFRs (Clarke 1997)
  - TV cabinets, electrical insulation, draperies
  - Mainly attributable to DBDPO
- Estimated lives saved (minimum) = 280/year
- Additional 140 – 220 lives saved/year
  - By using FR-upholstery textiles throughout the U.S.
- Based on 3,420 fire deaths in 2000
  - If use non-FR TV cabinets, electrical insulation, draperies
    - Increase fire deaths by 8%
  - If use FR-upholstery textiles throughout the U.S.
    - Decrease fire deaths by 4 - 6%

DBDPO Toxicology

- High molecular weight solid (959.21)
- Negligible solubility
  - Water < 0.1 ug/L
  - Organic solvents
    - Acetone = 0.05%
    - Benzene = 0.48%
- Range of toxicology tests in mammals
  - Acute
    - Not acutely toxic, irritating to skin or eyes, sensitizing
  - Genetic tox
    - Negative Ames, Chrom Abb, Mouse lymphoma, Chromatid Exchange, Bone Marrow Cytogenetics
  - Repeated dose, developmental, carcinogenicity, PK

DBDPO Repeated Dose Studies

- NOAEL ≥ 1,000 mg/kg/d (NTP 1986)
  - 14 Day rat, mouse
  - 90 Day rat, mouse
- NOEL > 1,000 mg/kg/d (Hardy et al. 2002)
  - Developmental, rat, D 0-19 gestation
- Lifetime (2 year) rat, mouse (NTP 1986)
  - Well tolerated at 2,550 or 7,780 mg/kg/d
  - No effects on body weight or mortality
  - Minimal effects on histopathology
    - Liver (thrombosis & degeneration –high dose male rats, granulomas – low dose male mice, hypertrophy – male mice)
    - Thyroid (follicular cell hyperplasia – male mice)

Carcinogenicity

- 2 Year study in rats, mice (NTP 1986)
  - 2.5 and 5% of the diet
- Some evidence of carcinogenicity - male & female rats at 1,120 & 2,550 mg/kg/d, respectively
  - "neoplastic nodules" in liver
- Equivocal evidence – male mice at 3,200 mg/kg/d
  - Combined incidence of hepatic adenomas or carcinomas
  - Within historical range
  - Influenced by early deaths in control males
- No evidence – female mice at 7,780 mg/kg/d

Pharmacokinetics

- Minimal toxicity likely related to PK (NTP 1986; El Dareer et al. 1987)
- Poorly absorbed < 0.3 – 2% of oral dose
- Rapidly eliminated in feces
  - > 99% in 72 hrs
  - t½ < 24 hrs
- Some evidence of metabolism (NTP 1986, Morck & Klasson-Wehler 2001)
  - Mainly in gut
  - No evidence of production of lower brominated diphenyl ethers

Neonatal Mouse Study

- Briefly reported in 4 page abstract
  - No data included
  - No additional details from contacts with authors
  - Novel experimental design
- Effect on habituation in adult mice
  - Single dose, 20 mg/kg lab-synthesized DBDPO, via gavage to pups on PND 3
  - No effect on PND 10 or 19
- Pups of this age would be exposed via lactation
  - Dose to dam to generate equivalent doses in milk
  - 416 or 4,160 mg/kg food/day

Major Issue

- Not related to DBDPO's toxicology
- Regards potential for metabolism or degradation of DBDPO to lower brominated diphenyl ethers
  - < 7 bromines
- Speculation
  - DBDPO ❍ 80% "PBDEs" manufactured
  - Tetra/PentaBDE congeners
    - Predominate PBDEs detected in environment & biota
    - Derived from DBDPO?
      - Reductive debromination?

DBDPO Environmental Degradation

- Expected to partition to soil and sediment
  - No indication of degradation in sediment
    - Monitoring data
      - Mersey River estuary & other European sediments
    - 32-wk and 2-year anaerobic sediment degradation studies
- Minimal partitioning expected to air and water
  - Neither hydrolysis nor photolysis expected
    - Water solubility, structure
    - Laboratory photolysis results
- Tetra/Penta congeners found in the environment not derived from DBDPO (Rayne & Ikonomou 2002)

DBDPO *In vivo* Metabolism

- **Poor bioavailability argues against significant production of metabolites x gut**
  - Oral absorption in rats 0.3 – 2% (NTP 1986)
  - Oral absorption in fish ~0.005%, BCF < 50 in fish (Kierkegaard et al. 1997, CITI 1992)
- **Metabolism by biological systems**
  - Appears to occur in gut
  - Products not lower brominated DPEs
  - ≥ 98% expected to be excreted as parent at environmental exposure levels
- **Metabolites**
  - Rapid elimination of ^{14}C-activity indicates no apparent accumulation
  - Long term studies at high doses not indicative of toxicity

Conclusion

- DBDPO used solely as a flame retardant
  - Hard, dense plastics in consumer electronics
  - Latex back coating of FR-upholstery textiles
  - Uses impart minimal potential for exposures to children
  - Uses enhance fire safety
    - Fire is a special risk for children
- Large poorly absorbed molecule that induces little toxicity
  - Poor bioavailability
  - NOAEL repeated dose $\gtrsim$ 1,000 mg/kg/d

Assessing Children's Exposure to Decabromodiphenyl Oxide (DBDPO)

Sean Hays
Exponent®
Boulder, CO

April 2003
On behalf of: BFRIP

Overall Characterization of Exposure Assessment

- Few data on DBDPO in environmental media, food, water, and air
- Slightly more data on levels of DBDPO in humans
- Largely relied on biomonitoring levels (in adults) to estimate exposures to children (breast milk, background exposures)
- Can be characterized as a highly conservative exposure assessment

Approach for Exposure Assessment

- Relied on currently available data (consistent with Tier 1 requirements)
- Used overly conservative approaches and made conservative numerical assumptions if data were unavailable
- Quantified all reasonable pathways, even if exposure was expected to be minimal
- Used biomonitoring data, when available, to reduce uncertainties and account for wide range of potential exposures

Physical Characteristics

Characteristic	Implication
• Low vapor pressure	• Air concentrations not likely to be high
• Low water solubility	• Limited dissolution into saliva
• No evidence of biodegradation to lower brominated PBDPOs	• Presence of lower brominated PBDPOs in environment is not a result of DBDPO
• *In vivo* metabolism does not produce lower brominated PBDPOs	• The presence of lower brominated PBDPOs measured in breast milk is not a result of DBDPO exposure

Environmental Data in the U.S.

- Sediment and sewage sludge
  - Some detected concentrations
- Air (outdoors)
  - Detected near manufacturing plant and in urban area
  - Undetected in rural or remote areas (over 3-year period)
  - Detected in dust and smoke after World Trade Center collapse
- Air (indoors)
  - Some detections in offices with computers
  - Some detections in indoor dust
- Food
  - Undetected in fish
  - Detected in chicken fat, but >60% of detections were below average levels in blanks

Pathways Evaluated

- Occupational inhalation exposures to lactating mother and subsequent ingestion of breast milk by infant
  - Manufacture of DBDPO
  - Disassembly of electronics
- Residential exposures from consumer products
  - Electronic products such as TVs and computer monitors (ingestion & inhalation of particulates)
  - Upholstery textiles (ingestion & dermal)
- Other potential environmental exposures, such as soil ingestion or inhalation of DBDPO in ambient air (all routes of exposure)

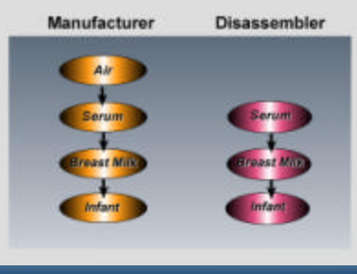
Exposures Excluded from Further Consideration

- No evidence of fetal or developmental toxicity, so *in utero* exposures were not evaluated
- No evidence of reproductive toxicity, so exposures to prospective parents were not evaluated

Approach: Occupational Exposures to Breast-Feeding Mother

- No breast milk concentrations of DBDPO reported at time of assessment
- Manufacture of DBDPO
  - Calculated air-to-serum ratio based on Swedish worker data, combined with air concentration estimates from the U.S.
  - Estimated partitioning from serum to breast milk based on partitioning of lower brominated compounds
  - Airborne concentrations up to 5 mg/m^3 (nuisance dust levels)
- Disassembly of electronics
  - Used serum levels from Swedish workers

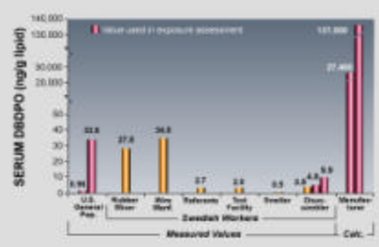
Compounded Conservatism in Estimating Breast Milk Ingestion Intakes



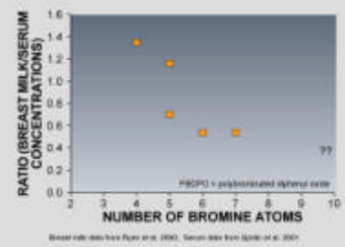
Approach: General Environmental Exposures

- Used measured levels of DBDPO in serum of non-occupationally exposed people
- Half-life of DBDPO (3–7 days in humans)
- Bioavailability: 1–2%
- DBDPO partitions into lipid stores
- Used one-compartment model to back-calculate intake required to achieve serum levels

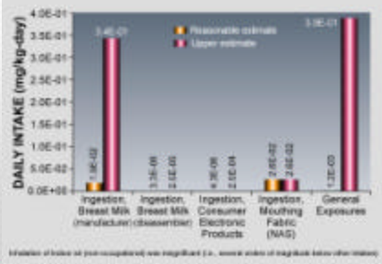
Comparison of Serum Levels Used in Exposure Assessment



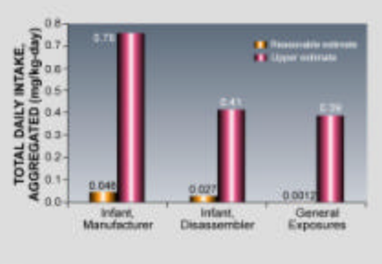
Breast Milk-to-Serum Ratios of PBDPOs as a Function of Bromination



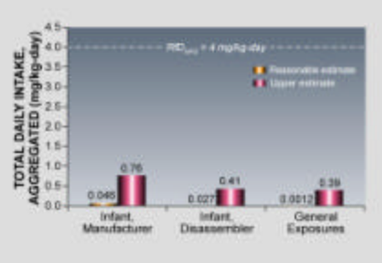
Daily Intakes by Exposure Pathway



Total Aggregated Daily Intake for Each Receptor



Total Aggregated Daily Intake for Each Receptor

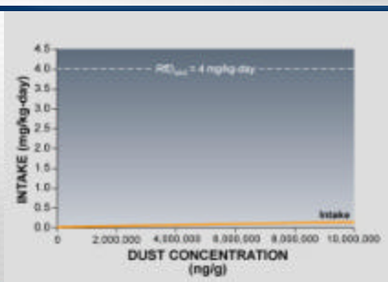


New Data and a Reality Check

DBDPO in Household Dusts

- Recently conducted studies in Europe and US
  - Knoth et al. (2002): dust from vacuum cleaner bags from households in Germany
  - Santillo et al. (2001): dust from European Parliament buildings
  - Rudel et al. (in preparation): dust from households in Cape Cod, MA
- DBDPO concentrations ranged up to 20,000 ng/g dust, most were below 1,000 ng/g dust.
- Could this be an exposure route of potential concern?

Intake of DBDPO vs. Dust Concentration



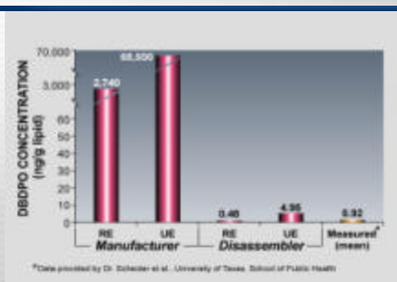
Measured Levels of DBDPO in Human Breast Milk

- Recently completed study by Arnold Schecter, Jake Ryan, and Olaf Papke (has not been submitted for publication yet)
- Collected 48 breast milk samples from women in Texas, and analyzed for wide range of PBDPOs
- DBDPO detected in 7 samples
  - Range: 0.48–8.24 ng/g lipid
  - Mean: 0.92 ng/g lipid
  - Standard deviation: 1.96 ng/g lipid
- DBDPO was one of the least often and lowest detected of the PBDPOs

Measured Levels of DBDPO in Human Breast Milk

- There appears to be no correlation between DBDPO (209) and
  - Any other congeners
  - Age of mother
  - Weeks of nursing
  - Percent lipid of breast milk

Breast Milk Concentrations: Calculated vs. Measured

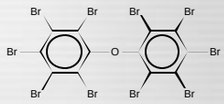


*Data provided by Dr. Schecter et al., University of Texas School of Public Health

Conclusions

- Lack of data was overcome by using biomonitoring data and what we thought were highly conservative assumptions
- New data confirms we were highly conservative

DBDPO VCCEP: Risk and Data Needs Assessments



M. L. Hardy, DVM, PhD
Albemarle Corporation
April, 2003

DBDPO Applications

- DBDPO used solely as a flame retardant
- Not sold directly to the public
- Used in
  - Hard dense plastics in consumer electronics
  - Latex back coating of FR-upholstery textiles
- Uses impart minimal potential for exposure to children

Decabromodiphenyl oxide (DBDPO)

- Large poorly absorbed molecule
  - Molecular wt
    - 959.21
  - Poor bioavailability
    - < 0.30 - 2% oral dose absorbed from GI tract
  - Rapid elimination
    - > 99% eliminated in 72 hrs
- Induces little toxicity
  - NOAEL $_{\text{repeated dose}} \geq$ 1,000 mg/kg/d
  - Not acutely toxic or mutagenic
  - Not developmental or reproductive toxicant

Children's Exposure Pathways to DBDPO

- Secondary to parents' industrial manufacture or use
  - Maximum exposure to parent anticipated
    - Manufacturers' bagging and formulators' mixing operations
    - Inhalation
  - Child's exposure
    - *In utero*, breast milk
- Through consumer electronics or upholstery
  - Dermal contact with upholstery fabric
  - Respiratory exposure from upholstery, electronic equipment
  - Oral contact with upholstery, electronic equipment
- From general environment - food, water, dust, soil

Exposure via Breast Milk

- Significant levels in breast milk not expected
- Poor absorption from gut, rapid elimination in feces
  - Limit amount available for diffusion into breast milk
- Poor and/or slow diffusion into breast milk
  - Due to DBDPO's P/C properties
  - Limit amount reaching breast milk
- Factors affecting xenobiotics' levels in breast milk
  - Protein binding, ion trapping, lipid partitioning
  - Not relevant to DBDPO

Exposure via Food

- Food unlikely to be significant exposure route
- Properties limiting DBDPO's bioavailability will limit amounts in foods derived
  - Fish, poultry, meat, dairy products
  - Limited sampling of U.S. fish and poultry supportive
- Leafy vegetables or root crops
  - Uptake by plants not anticipated
    - DBDPO's P/C properties, data on related molecules
  - Atmospheric deposition
    - DBDPO not expected to partition to air or to undergo long range transport

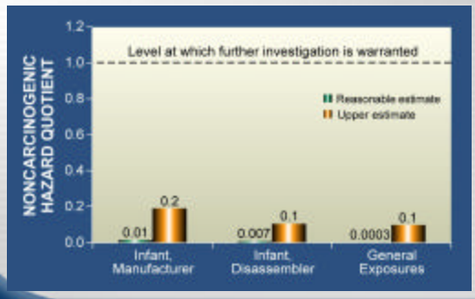
Reference Dose

- IRIS Database (EPA 1999)
  - RfD = 0.01 mg/kg/d
  - Based on Kociba et al. 1975 using 77% DBDPO mixture
    - 2-yr rat NOEL = 1 mg/kg/d, highest dose tested
  - Derived in 1984-85
- NAS 2001
  - RfD = 4 mg/kg/d
  - Based on NTP 1986 using 96-99% DBDPO
    - 2-yr rat NOAEL = 1,120 mg/kg/d
  - Derived RfD using NTP 1986
    - Test article composition, larger # of animals (50 vs. 25 rats/sex/dose), higher dose levels, second species included
    - Uncertainty factors = 300 (10 x 10 x 3)

Risk

- RfD_{NAS} = 4 mg/kg/d
- Children's exposure estimates (mg/kg/d)
  - Pathway specific
    - Reasonable exposure estimate: 0.0000008 – 0.005
    - Upper exposure estimate: 0.000006 – 0.1
  - Aggregate
    - Reasonable exposure estimate: 0.0003 – 0.01
    - Upper exposure estimate: 0.1 – 0.2
- Hazard quotient for all estimated exposures < 1
- Conservative, worst-case estimates of exposure indicate no adverse health effects expected

Hazard Quotient



Risk vs. Benefits of Using DBDPO

- **RISK**
  - All estimated exposures
  - Conservative worst-case exposure scenarios
  - Hazard quotients < 1, indicating no expected adverse health effects
- **BENEFITS**
  - Substantial health and safety benefits
    - Estimated to save at least 280 lives per year in U.S. and prevent 1000's of injuries
  - Fire safety benefits especially relevant to VCCEP
    - Children are at high risk of death or injury from fires
    - Child's risk 2x national average
    - Each year 600 children die & 47,000 injured in fires

Data Needs

- Existing test data
  - Covers Tier I, II and III hazard endpoints
  - NAS concluded re DBDPO in upholstery textiles
    - no additional information needed to assess risk to consumer
  - BFRIP concurs and extends to use in electronics
- Exposure
  - Existing data on exposure sparse
  - Estimated exposures highly conservative
    - overestimates actual exposures
    - < lifetime daily dose causing no harm (RfD)
  - Additional data to refine exposures considered unnecessary due to highly conservative estimates & lack of hazard

Appendix E

Panelist Handout Comparing DBDPO in Various Organs (NTP, 1986)

NTP 1986

Deca
IV (Appendix O, p. 238)

72 hours after 1.07 mg/kg

Feces + Gut	74%
Tail (injection site)	10%
Muscle	13%
Skin	7%
Urine	trace
Spleen	trace
Brain	trace

majority of radioactivity in feces was metabolites

~7% appears in bile at 4 hours, with ~2% per hour afterwards

Deca
Feeding (Appendix O, p 233)

72 hours after 277 or 48,000 ppm

Feces + Gut	~ 85%
Liver	0.1%
Muscle	0.2%
Skin	0.3%
Urine	—
Spleen	—
Brain	0.001%