Report of the Peer Consultation Meeting on Pentabromodiphenyl Ether

Submission by Great Lakes Chemical Corporation for the Voluntary Children's Chemical Evaluation Program (VCCEP)

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

June 3 and 4, 2003
University of Cincinnati
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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 June 3 and 4, 2003, to conduct a peer consultation of a submission on pentabromodiphenyl ether (pentaBDE). The Great Lakes Chemical Company (GLCC) 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 pentaBDE to children, and, if not, to identify data needs.

The sponsor provided the panel with brief presentations summarizing the submission's assessments of hazard, exposure, risk, and data needs. The sponsor explained that commercial pentaBDE is a broad mixture of polybrominated diphenyl ether (PBDE) congeners. Its primary use is in flexible polyurethane foam for items such as cushions and bedding materials. The major findings from subchronic and chronic pentaBDE toxicity studies were induction of hepatic enzymes and effects on thyroid homeostasis. No adverse effects on pregnancy or standard developmental endpoints were reported from reproduction and developmental studies, but decreased thyroxine (T_4) levels were noted in both dams and offspring. Some rodent studies observed changes in neurobehavioral parameters, but the reproducibility and biological significance of these findings was unclear. The major source of PBDE exposure for humans of all age groups except infants was from ingestion of food products, especially fish. The primary source of exposure for infants was breast milk. Children one to two years of age had the greatest exposure (mean of 0.0013 mg/kg-day). Total aggregate exposure in this highest exposed age group (assuming all the detected PBDEs were pentaBDE.) was below pentaBDE's estimated toxicity benchmark value for thyroid effects (0.04 mg/kg-day) and below the U.S. EPA RfD of 0.002 mg/kg-day. The estimated toxicity benchmark value for induction of hepatic enzymes was 0.002 mg/kg-day, but the sponsor did not consider this effect to be a valid toxicity endpoint because it occurred in the absence of histopathology.

Discussing the hazard assessment, several panel members identified areas they believed had insufficient information: metabolism, bioaccumulation, fertility, reproduction, *in vivo* genotoxicity, carcinogenicity, and developmental neurotoxicity. Other members said enough is known about pentaBDE toxicity to conclude the existing hazard data are adequate for a Tier 1 screening assessment. Panelists noted the primary mechanism for pentaBDE's toxicity appears to be changes in thyroid homeostasis, possibly resulting from induction of hepatic enzymes. Members discussed the importance of determining whether a thyroid-related mechanism was responsible for all of the observed toxicities, and they suggested ways to explore the relative sensitivity of humans and rodents to chemical-induced thyroid toxicity. Some members suggested the toxicities of pentaBDE and polychlorinated biphenyl compounds (PCBs) might be additive, but most panelists thought more data would be needed to support that conclusion. The panel discussed studies investigating neurobehavioral changes in rodents, noting that different laboratories had generated varying results, both positive and negative. Some members did not think the rodent neurotoxicity studies should be used for human risk assessment because they were inconsistent, used small numbers of animals, and showed results that may not be reproducible. Because most of the toxicity data were generated on commercial product mixtures,

some members were concerned that the exact toxic moieties were unknown; therefore, the observed toxicity endpoints could not be attributed conclusively to any specific chemical.

Regarding the exposure assessment, several panelists voiced concern that recent human sampling of people not occupationally exposed to polybrominated diphenyl ethers found blood levels up to 40 times higher than the high-end exposures estimated in the submission. These findings indicated to some members that the exposure assessment was not sufficiently conservative. Several members wondered whether human pentaBDE concentrations might be approaching levels of toxicity, but not all panelists shared this concern. Some noted that unexplainable data outliers often exist, and accurate bounding estimates should not be expected from screening level exposure assessments. Some panelists observed that levels of environmental pentaBDE were increasing, both from increased production of the chemical and from the decomposition and disposal of products containing the chemical. Because of the environmental increases, these panelists thought human body burdens of pentaBDE were likely to increase in the future. One panel member said the lack of data on half-life and exposure pathways, together with the problems differentiating between the commercial mixture and individual congeners, indicated insufficient information was available to adequately determine the exposure conditions or the populations of concern. Another member said the sponsor did an adequate job identifying exposure pathways, but additional exposure information in several areas would be useful.

Many panel members disagreed with the assumptions used to determine the uncertainty factors and other toxicity benchmark values in the risk assessment. Some noted the uncertainty factors were not used consistently for each endpoint, and one member thought the uncertainty factors should be up to 30 times greater. Others thought the risk characterization failed to account for potential additive effects of pentaBDE and other chemicals. They also were concerned that the risk characterization did not address the possibility of pentaBDE exposure increasing over time. One panelist stated the exposure uncertainty was so great that it severely limited ability to perform any reasonable risk characterization. Other members, however, thought the overall approach used to calculate the toxicity benchmarks, estimate the benchmark doses, and calculate the hazard indices appeared to be sound. One panelist wondered if aggregation of all potential maximum exposures was appropriate for the U.S. population and questioned whether any relevant population for total aggregate exposure existed in this country. If this population did exist, however, she thought the risk characterization indicated the population might be approaching a range of toxicity. Others added that certain population subgroups, such as pregnant women and people with iodine deficiency, may not be target populations for total aggregate exposures, but they do comprise potentially vulnerable subpopulations that should be considered in the overall risk characterization.

After discussing potential *data gaps* (i.e., areas for which data are not available, or where there are significant uncertainties) in the context of the hazard or exposure assessment, panel members 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). Considering the submission in total, all panelists identified at least two items as data needs, and most members identified several. A majority of the panel members said that obtaining more information on pentaBDE levels in humans and more completely identifying sources of human

exposure were important data needs. Other data needs focused on gaining a greater understanding of pentaBDE's potential toxicity to humans. A complete list of all identified data needs, together with the number of panelists identifying each data need, is provided in the report.

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Participants

Sponsor

Great Lakes Chemical Corporation

Presenters

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Physicians Committee for Responsible Medicine

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U.S. Environmental Protection Agency (EPA), National Health and Environmental Effects Laboratory

George P. Daston, Ph.D. Developmental Biology and Teratology
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Toxicology Excellence for Risk Assessment (*TERA*)
(Panel Chair)

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Harvard University

Observers and Other Attendees

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

Background

This peer consultation meeting has been organized by Toxicology Excellence for Risk Assessment (*TERA)*. *TERA* is an independent, non-profit organization with a mission to protect public health through the best use of toxicity and exposure information in the development of human health risk assessments. *TERA* has organized and conducted peer review and 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 pentabromodiphenyl ether (pentaBDE) as a part of the Voluntary Children's Chemical Evaluation Program (VCCEP). The pentaBDE assessment was submitted by the Great Lakes Chemical Corporation (GLCC).

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

[1] Ms. Rudel was not able to attend the meeting. However, she provided written comments (see Appendix A) that were considered by the panel members in their discussions.

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

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

The VCCEP Peer Consultation Panel for pentaBDE 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 pentaBDE 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 (link to the report from http://www.tera.org/peer/vccep/OctaPenta/OctaPentaWelcome.html). 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 resolves any differences by carefully reviewing materials from the meeting.

The meeting report is organized into sections corresponding to the submission's hazard assessment, exposure assessment, and risk characterization/data needs sections (links to the submission document, appendices, and key references are located at http://www.tera.org/peer/vccep/OctaPenta/OctaPentaWelcome.html). 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 (Appendix C). All the panel members then introduced themselves and noted whether they had additions or changes in their disclosure statements. Four panel members offered additional information. Dr. Kevin Crofton noted that he has received research materials from GLCC for use in his laboratory. Dr. Michael Dourson noted that he had helped prepare and review the existing IRIS files for pentaBDE and for octabromodiphenyl ether (octaBDE) in the mid-1980s while working at EPA. Ms. Nicole Cardello mentioned that she currently is doing contract work for EPA while enrolled as a student at Johns-Hopkins University. Dr. Thomas McDonald noted that, at the request of the author of California Assembly Bill 302, he provided brief testimony before the Committee on Environmental Safety and Toxic Materials on the PBDEs on April 22, 2003. AB302 proposes a phase out of the octaBDE and pentaBDE mixtures of the PBDEs in California in 2008. His testimony provided information on the chemicals but took no position regarding a ban. A panel member asked Dr. McDonald if he would provide a citation to his testimony transcripts for the meeting report.[2] No other panelists had changes or additions.

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

[2] After the meeting, Dr. McDonald indicated to *TERA* that a transcript is not available, but he provided the following additional information for the record. "In my statements, which were limited by the Chair to one minute, I made it clear that I was there to provide scientific information to the committee and did not have a position on the proposed legislation. I noted that PBDE levels have been increasing over the past decade in fish, marine mammals, and humans, and levels in U.S. citizens were the highest measured in the world. I briefly discussed the toxicity concerns for the PBDEs (endocrine disruption and neurodevelopmental effects)."

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. Three sets of written comments were received. These were distributed to the panel members and sponsor prior to the meeting, and copies were provided at the meeting for observers. These written comments are found in Appendix D.

[A peer consultation meeting on octabromodiphenyl ether (octaBDE) immediately followed the pentaBDE meeting. The octaBDE submission was prepared and sponsored by the same company as pentaBDE and followed the same format. Links to a copy of the octaBDE meeting report, appendices, and key references list can be found at http://www.tera.org/peer/vccep/OctaPenta/OctaPentaWelcome.html]

This report on pentaBDE is organized into four sections: overview, hazard assessment, exposure assessment, and risk characterization and data needs.

Overview

Sponsor Presentation

Mr. Robert Campbell of GLCC presented general background information on all the flame retardant chemicals in order to put the information on pentaBDE in context (see Appendix E for the presentation slides). He noted that pentaBDE and the other polybrominated diphenyl ethers (PBDEs) contain an oxygen bridge that allows bending and rotation, making them unlike the coplanar polychlorinated biphenyls (PCBs) to which they are often compared. The PBDEs are efficient in preventing materials from igniting. As a class, brominated flame retardants comprise about 25% of the volume of all flame-retardants produced. Among the PBDEs, (a sub-class of brominated flame retardants), decabromodiphenyl ether has the highest production, with pentaBDE second, and octaBDE third. Current pentaBDE production in the U.S. occurs at a single plant in Arkansas. Its primary use in the U.S. (>98%) is in flexible polyurethane foam (FPUF) for items such as cushions and bedding materials. About 2-5% FPUF content is pentaBDE, with denser materials using less of the chemical. The European Union will ban pentaBDE in July 2004, after using it for over 30 years in a variety of materials including polyurethane foams, hydraulic fluids, roofing shakes, and oil well products.

The sponsor described potential pathways of pentaBDE exposure. He compared theoretical daily intakes by age group to toxicity benchmarks, noting that intakes of age groups from less than one year through adult were below the U.S. EPA reference dose (RfD) and toxicity endpoints.

Clarifying Questions from Panel

The panelists asked several questions including whether the volume of pentaBDE produced was previously greater, if the composition of the commercial product has changed, and what regions of the country use the most pentaBDE material. The sponsor replied that the volume of pentaBDE produced in the U.S. today is higher than in the past. The commercial product made by GLCC has had no dramatic changes in composition over the years. It always has been a broad mixture of congeners. Because FPUF is bulky with high shipping costs, it is not transported long distances. It is produced in regions of the U.S. where furniture is made.

Hazard Assessment

Sponsor Presentation

Dr. Tessa Serex of GLCC briefly summarized the hazard assessment data, which are presented more fully in the sponsor's submitted assessment (links to the submitted assessment, appendices, and key references list are at http://www.tera.org/peer/vccep/OctaPenta/OctaPentaWelcome.html). She noted that most of these data were generated on various pentaBDE product formulations, rather than on the pentabromodiphenyl ether congeners themselves (see Appendix E for the presentation slides). Toxicokinetic data show absorption varies widely among animal species, distribution within the body is mainly to the liver and adipose tissue, and the major elimination pathway is via the feces. Once absorbed systemically, the lower brominated diphenyl ethers are eliminated faster than the higher brominated compounds (e.g., tetraBDE has a shorter half-life than pentaBDE or hexaBDE).

Subchronic and chronic pentaBDE studies show induction of hepatic enzymes involved in xenobiotic metabolism (a phenobarbital-like effect which is not necessarily adverse) and effects on thyroid homeostasis characterized by decreased levels of thyroxine (T_4) and thyroid hyperplasia. Rats are believed to be more sensitive than humans to these thyroid effects. In reproduction and developmental studies, no adverse effects on pregnancy or standard developmental endpoints were reported, but decreased T_4 levels were noted in both dams and offspring. Some rodent studies observed changes in neurobehavioral parameters, but GLCC does not consider these reports sufficiently complete in experimental detail to be used for quantitative risk assessment because of a lack of information on experimental design, statistical analysis, and numbers of animals used.

The sponsor summarized each of the health endpoints and screening toxicity values used in their risk assessment of potential human exposures. The sponsor concluded that children's health was adequately protected by the benchmark doses that were calculated for decreased T_4 levels and for thyroid hyperplasia. The sponsor believes that the induction of hepatic enzymes in the absence of a histopathological correlate to indicate liver damage (basis of EPA-derived oral RfD, 1980) is not an appropriate toxicity endpoint.

Clarifying Questions from Panel

Referring to a sponsor handout on benchmark dose (BMD) modeling (Appendix F), a panelist asked the sponsor if all the BMD data were based on the Taylor abstract presented at the 2003 Society of Toxicology meetings. The sponsor confirmed this and added that the comments in the handout prepared by Judy Buelke-Sam of Toxicology Services (a separate organization not affiliated with GLCC) relate to developmental neurobehavioral alterations and experimental designs. These written comments were provided to the panel to further explain why the sponsor did not use the Viberg data (Viberg et al. 2002) quantitatively for hazard assessment.

A panelist questioned whether describing the liver enzyme induction produced by pentaBDE as "phenobarbital-like" was entirely accurate, noting that recent papers demonstrate that the Ah receptor also is involved in the effects of pentaBDE administration. These reports indicate pentaBDE may have broader implications than phenobarbital on the induction of hepatic enzymes.

Regarding the relationship between degree of bromination and half-life, a member asked if the sponsor's data were consistent with the literature (Sjodin et al. 1999). The sponsor replied the data were consistent, adding that confusion may arise from differences between ingestion and internal exposure. The half-lives of systemically absorbed doses of PBDEs are shorter for the less brominated congeners; however, following oral dosing, the less brominated congeners are systemically absorbed to a greater extent than the more brominated PBDEs.

When one panel member asked for comments on the relative susceptibility of rats and humans to the various consequences of T_4 changes, another panelist responded that much of the rat-human thyroid comparison data relate to hyperplasia, rather than to T_4 changes. The rat thyroid is more susceptible than the human thyroid to hyperplasia induced by thyroid stimulating hormone (TSH). It is less certain that rats are more susceptible than humans to T_4-related changes during the period of neurodevelopment. Epidemiology studies in humans with autoimmune disease (not induced by chemicals) show neurological changes in children from mothers who had T_4 decreases of 25% during their first and second trimesters. During these trimesters, the fetus receives all its T_4 from the mother, so fetal T_4 levels are likely to be decreased also. No rat studies exist showing that a 25% decrease in T_4 is enough to produce any neurodevelopmental changes in fetuses or dams, but 60% T_4 decreases do cause neurological changes in rats. These findings could indicate that rats are *less* sensitive than humans to potential neurodevelopmental consequences of T_4 decreases. Another panelist suggested that, alternatively, the differences noted in these studies might be caused by the different measurement methods used for rats and for humans. He noted that we are able to measure IQ in humans, but not in rats. The sponsor replied that if pentaBDE causes T_4 levels to be decreased by inducing uridine diphosphate-glucuronosyltransferase (UDPGT), then rats might be expected to be more susceptible than humans. This is because UDPGT is induced more readily in rats than in humans (Popp and Cattley 1991). A panelist disagreed with the sponsor on this point, saying no convincing data are currently available to determine the relative inducibility of UDPGT in rats versus humans. Another member reminded the panel of the wide variation in thyroid functional status within the human population, noting that during pregnancy up to 10% of women develop thyroid antibodies, and also that a substantial segment of the human population is hypothyroid.

A panelist said that even though the molecular structure of pentaBDE is not coplanar like the structure of the PCBs, the two chemical classes apparently share some similarity because they both can bind to the Ah receptor and cause enzyme induction. The sponsor replied that the congeners characterized to date in the pentaBDE commercial product have Ah binding affinities about 1000-fold less than some of the PCBs. Another panelist added that *in vitro* assays demonstrate that neither polychlorinated nor polybrominated biphenyls show much binding affinity for the Ah receptor compared to dioxin. Interestingly, *in vivo* studies with the pentaBDE commercial product show high levels of ethoxy-resorufin-o-deethylase (EROD) activity, indicative of Ah binding. This is inconsistent with data from *in vitro* binding assays that fail to demonstrate any interaction of PBDE congeners with the Ah receptor. The reason for this inconsistency is unknown. A panel member noted that various solvents could be used to test *in vitro* the ability of chemicals to bind with receptors that induce enzymes of interest in both rodents and humans. Such experiments could be considered in order to answer questions about the relative sensitivities of rats and humans to pentaBDE.

Asked whether any epidemiology studies exist on pentaBDE, the sponsor said one study evaluated a possible association with lymphoma but there was no good correlation. Since the data were not clearly presented, the study was not used in the submission. No epidemiology studies are known relating pentaBDE to enzyme induction, thyroid tumors, or other effects relevant to the toxicity benchmarks.

A panelist asked if the sponsor thought the T_4 decrease was related to thyroid hyperplasia, and, if so, why were both endpoints considered in calculating the benchmarks? Why not just use the lower endpoint? The sponsor said they believe all three of the health effects endpoints they had presented to the panel were related. They believe that pentaBDE induces liver enzymes including UDPGT, the UDPGT results in decreased T_4 levels, and the decreased T_4 levels increase TSH levels, which cause thyroid hyperplasia. Therefore, one could argue that only the benchmark for liver enzyme induction should be used. The sponsor did not use the liver enzyme benchmark because they do not believe the effect of increased liver enzymes is necessarily adverse, and the level of inducement that produces a significant or biologically relevant effect on T_4 is unknown. The sponsor said that, in the absence of this information, it does not make sense to use a NOEL or LOEL for enzyme induction as a point of departure.

Public Comments on Hazard Assessment

Dr. Lynn Cannon, representing The Learning Disabilities Association of America (LDA) read a statement that was excerpted from the organization's written comments on pentaBDE and on the entire class of PBDE flame-retardants. These comments are found in Appendix D.

Clarifying Questions from Panel and Sponsor

When asked by a panel member what safer alternatives to pentaBDE exist as flame retardant chemicals, Dr. Cannon replied that other substances such as aluminum trihydrate might be used.

The sponsor asked what conclusive neurobehavioral data exist that were not mentioned in the submission. Dr. Cannon responded that she did not have that information.

Panel Discussion of the Hazard Assessment

The panel discussion on Hazard Assessment addressed two charge questions.

- 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?

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

Adequacy of the Hazard Information

Panel members noted several areas where information is not available. No human data are available on inhalation effects, metabolism, or bioaccumulation. Half-life measurements range widely among species, suggesting human data should be obtained. No studies have been conducted on fertility or reproduction, *in vivo* genotoxicity, carcinogenicity, or developmental neurotoxicity. Pharmacokinetics data related to fetal development are also lacking. These data would be helpful for comparisons among species.

The panel recognized that most of the toxicity data were generated on commercial products. One panelist noted that, as these products are mixtures, the exact identity of the substance causing the observed effects is not known. If a metabolite of a component in the commercial product is the active moiety (e.g., hydroxylated pentaBDE), then induction of the enzyme that increases metabolism to this moiety should be viewed as an adverse event, perhaps the critical event.

The mechanism of action for pentaBDE appears to be via changes in thyroid homeostasis. It is not precisely clear how this occurs or which steps are critical, but changes in thyroid function may be secondary to induction of hepatic enzymes, especially UDPGT. Several panelists suggested that if it could be shown that all adverse effects of pentaBDE were mediated via thyroid changes (i.e., decreased T_4 levels) then identifying the threshold dose causing these thyroid changes would also identify the threshold dose for all observed toxicities.

One panelist thought all the existing toxicity data on pentaBDE argued for a thyroid-related mode of action (MOA), but he was not certain that developmental neurotoxicity could be related to it. Another member was not convinced that a thyroid MOA was sufficient by itself to completely explain the pentaBDE toxicity. He recited PCB literature indicating involvement of cell-cell signaling, arachidonic acid release, kinases, and direct-effects on neurotransmitter systems that did not act via the thyroid, and he noted monkey studies with non-coplanar PCBs that showed effects not likely to be thyroid-related. In addition, he noted that two studies show PCBs and PBDEs are additive, one examining thyroid hormone disruption (Hallgren and Darnerud 2002) and one examining neurodevelopmental effects in mice (Eriksson et al. 2003). Other panelists said PCBs and pentaBDE effects might be additive, but mechanistic data were

needed to conclude that they had similar MOAs. PBDEs and PCBs both induce glucoronyl transferase enzymes that conjugate thyroid hormone and facilitate its removal from the body (Zhou et al. 2001; 2002). Metabolites of PBDEs and PCBs also mimic thyroid hormones, as evidenced by high affinity for the thyroid transport protein transthyretin (Meerts et al. 2000), suggesting a possibility of common modes of action for thyroid hormone disruption between the two classes of molecules. Another panelist advised that extreme caution should be used when discussing and comparing MOAs. Although evidence suggests pentaBDE and PCBs influence the same mediators, this does not mean they will cause similar adverse effects. He thought the most valuable lesson from comparing pentaBDE to PCBs may be the direction given for further research. One member added that pentaBDE and the PCBs have similar octanol water partition coefficients, and in some cases their absorption, distribution, and elimination profiles are similar. This may indicate they have common metabolites, and these metabolites may be the active moieties. Other members said pentaBDE has a reasonably large dataset and making comparisons to other chemical classes may not be necessary. They thought that enough is known about pentaBDE itself to say the existing data are adequate for a Tier 1 assessment.

The panel discussed several studies investigating neurobehavioral changes in mice (Eriksson et al. 1998, 1999, 2001, 2002; 2003; Viberg et al. 2002; Branchi et al. 2001, 2002) and in rats (Taylor et al. 2002). In mouse studies from the Eriksson laboratories, pentaBDE (BDE-99) caused dose-related developmental neurotoxic effects after oral dosing on post-natal day 10. Branchi reported an inverse dose-response effect on locomotion after dosing mice *in utero* and through lactation. Taylor did not see any neurobehavioral, sensory, or motor effects, but their studies were in rats rather than mice and used a commercial product (DE-71). Two panelists noted that the experimental conditions and results of Eriksson's studies have not been reproduced completely by other labs, although some findings have been replicated. Some members thought the data suggest that mice are more sensitive than rats; others thought the differing results may simply reflect the range of experimental conditions employed by the various investigators. The panel was undecided whether the observed neurobehavioral changes could best be explained by a MOA related to T_4 or by some other mechanism. One member stated that he did not think the mouse studies on neurotoxicity should be used for risk assessment because they are inconsistent, used small numbers of animals, and show results that may not be reproducible.

Speaking more broadly about available hazard data, a panel member suggested several data gaps appear to exist. One gap is a two-generation reproductive study in rats. He thought this data gap may be a data need if the MOA appears to involve more that T_4. A second gap is determining what uncertainty factors to use. The uncertainty factors will be governed by whether the MOA is a T_4 decrease alone or a T_4 decrease and something else. A third gap is pharmacokinetics. Comparative pharmacokinetics data would allow determination of uncertainty factors. The panelist thought that without these pharmacokinetics data, additional toxicity testing would be needed.

While agreeing that one key issue is whether a T_4 MOA is sufficient to explain reproductive/developmental effects, a member added that another key issue is how to view studies conducted on a commercial product. The product tested is a specific mixture of PBDE congeners, but humans are not exposed to this same mixture; instead, human exposures are to a

variety of different mixtures. For example, in fish and in breast milk the major PBDE is tetraBDE. If it could be assumed that a T_4 MOA is the only MOA involved for all components of the tested commercial product, then additional toxicity testing might not be necessary. If this cannot be assumed, it is difficult to be satisfied with a dataset that does not include at least a reproduction study. Other panelists agreed, with one member giving his opinion that a T_4 decrease clearly was not the only MOA.

One member said he wanted to step back and make some general observations. He noted that pentaBDE is being assessed for its potential effects on children. It is bioaccumulative and toxic. Its production volume is increasing. Its effects on humans may include such things as loss of intellectual functioning (e.g., reduced IQs) that cannot be easily detected. These effects may or may not have a threshold. Given this information, the panelist thought that being certain of the MOA is critical in order to protect against adverse effects. Without being sure of the MOA, he thought no risk assessment could be considered conservative.

Another member voiced concern that none of the toxicity endpoints could be attributed to a specific chemical. It is not known which component of the commercial product is the most responsible. It is not clear how to deal with mixtures. Another panelist responded that an RfD for pentaBDE would, in fact, be the RfD for the commercial mixture.

The sponsor noted that, given the comments from panel members regarding unclear mechanisms of action and non-identified active product components, it might be more useful to conduct human physiologically based pharmacokinetic (PBPK) modeling to help clarify issues than to do additional animal toxicity studies on commercial products. A panelist replied that PBPK modeling with current data was likely premature, but it might help identify information still required. Another member did not think PBPK by itself would be useful; she suggested that comparing steady state values across species would be more useful. She thought that defining the differences in half-lives across species is critical for a risk assessment.

Appropriateness of the Quantitative Information for Risk Characterization

The panel discussed several issues regarding quantification. One panelist mentioned the difficulty in comparing results of the animal toxicity studies to one another and interpreting their relevance for humans, given that different strains of rats were used and some studies used only one sex. However, he concluded the hazard and dose-response information used by the sponsor for risk characterization was appropriate.

A second panelist thought it would be insightful to compare the pentaBDE doses and body burdens from the animal studies to the levels found in human maternal and fetal blood samples (reported in Mazdai et al. 2003). He noted that although the human database is small (12 maternal-fetal pairs) the study might have implications for calculating uncertainty factors. This human study also is of interest because the investigators measured T_4 concentrations in the blood samples. They found no correlation between the levels of T_4 and levels of pentaBDE (or any of the five other PBDEs measured). If a decrease in T_4 levels is truly the MOA for pentaBDE, the panel member thought that the Mazdai T_4 data may provide information on no-effect levels in humans.

Other members discussed ways to determine the relative sensitivity of humans and rodents to the effects of pentaBDE on T_4. One member thought it would be necessary to compare the intakes and body burdens among the species. A second panelist described work he had done attempting to compare the body burdens of the human and the mouse based on assumptions of body fat content. He believed that obtaining intake values was not necessary, because the more important parameter was steady state levels. He noted that, given similar intakes, humans would reach higher steady state levels of pentaBDE than would rodents because of a longer pentaBDE half-life (nine months in humans, less than one month in rodents).

One panelist said the sponsor used two different approaches to calculate the Hazard Quotient (HQ). One approach used the Margin of Exposure (MOE) and focused on one toxicity endpoint. The second approach used the Reference Dose (RfD) and considered the summation of all the toxicity endpoints. He thought that if T_4 is the precursor for all other effects, then the approach the sponsor used for the HQ does not matter. Otherwise, it does matter, and the sponsor should use different database uncertainty factors for the different approaches. The sponsor responded that they did not use a single approach to calculate the HQ because the assessment deals with a commercial product that is a mixture and because they wanted to use all the endpoints that were reproducible. These reproducible endpoints are T_4 decrease, thyroid hyperplasia, and hepatic enzyme induction. Two panelists agreed with the sponsor's rationale, noting that subchronic studies showed consistent effects in the liver and thyroid, and the sponsor used the lowest BMD. They added that the only items needing further discussion were the uncertainty analyses and the appropriate uncertainty factors values to use. Because it is not possible to state with certainty that the T_4 decrease is the only MOA, they suggested that standard uncertainty factors should be applied for all areas.

Exposure Assessment

Sponsor Presentation

Mr. Richard Wenning of ENVIRON International Corporation presented the highlights from the sponsor's submitted exposure assessment (see Appendix E for the presentation slides). He informed the panel that commercial pentaBDE product is a mixture composed primarily of pentaBDEs (~50-62%), tetraBDEs (~24-38%), and hexaBDEs (~4-12%). Very small amounts (<1%) of hepta- through decaBDEs have been reported in early commerce versions of the product. Given that the product is a mixture, understanding and evaluating its occurrence and fate in the environment presents a challenge. The sponsor did not rely on environmental fate models to predict exposure point concentrations, but used U.S. environmental and biomonitoring data on levels of tetra- through hexaBDE congeners as indicative of commercial product exposure. Data from other countries were used where U.S. data were not available.

Three exposure scenarios were considered for both children and adults: workplace/worker's home, general home/school/office, and ambient environment. The potential exposure pathways (inhalation, dermal, incidental ingestion, food consumption) for each of these scenarios were identified, and the exposure amounts were estimated. Theoretical total daily intakes were then

calculated for children in seven age bins and for adults. Exposures from breast milk and from mouthing of furniture cushions were included for children in the younger age bins. Theoretical total daily intake was greatest for children less than one year of age (mean of 0.0009 mg/kg-day), with the great majority of exposure (92%) coming from breast milk. In children older than one year, the major source of exposure shifted to food products, especially fish. The sponsor acknowledged that the available U.S. fish data are limited and may not exactly represent the types of fish consumed by adults and children. However, even if it is assumed that the level of total PBDEs were 10-fold higher than the maximum level reported in U.S. fish (174 ng/g on a lipid weight basis), the assessment results are not significantly changed.

The sponsor noted that after the exposure assessment was prepared, new data became available on pentaBDE in house dust (unpublished information from Rudel et al.[3]) and in breast milk (personal communication, Schecter et al.[4]). Rudel reported total PBDE levels in indoor dust collected in Cape Cod houses nearly two-fold higher than the highest levels reported by Knoth et al. (2002) in German house dust. Schecter reported total PBDE levels in breast milk from women in Austin and Dallas that are generally consistent with the levels reported previously in Canada (Ryan et al. 2002; Ryan and Patry 2001). When the sponsor used the maximum PBDE levels from the Rudel and Schecter unpublished data in its screening exposure model, the new values did not significantly change the assessment results.

If the new and unpublished data for breast milk and house dust are incorporated into the exposure assessment along with a higher theoretical estimate of the level in fish consumed by adults and children, the theoretical aggregate total daily intake of PBDEs would be greatest for children one to two years of age (mean of 0.0013 mg/kg-day). The majority of exposure (between 90 and 95%) for all age groups with the exception of the children less than one year of age would still be attributable to the consumption of fish. For children less than one year of age, the ingestion of human milk would still be the primary source of exposure.

Clarifying Questions from the Panel

Asked about small samples possibly not being representative of the entire U.S. population, the sponsor acknowledged that regional variations do exist. The exposure assessment accounted for this variation by using samples considered to be near the upper ends of the exposure spectrum. Some natural sources of pentaBDE may exist, but most of the chemical found in the environment is assumed to be from industrial production. A panel member added that environmental levels resulting from industrial emissions may be understated because the fish data are from non-point sources; he said fish located near emission points would be expected to have higher levels of PBDEs.

One panelist was concerned that the exposure values did not represent the highest exposed populations, and asked why the predicted values were substantially below the human blood levels in the Mazdai report (Mazdai et al. 2003). Additionally, she wondered why no data on *in utero* exposures were provided. The sponsor said he could not explain why the Mazdai results

[3] This study now has been published (Rudel et al. 2003)
[4] This study now has been published (Schecter et al. 2003)

showed human blood levels above those predicted, but data from Mazdai indicated that fetal exposures were similar to those of the mothers, at least at the time of delivery

Others asked about the increases of pentaBDE in the environment over time from increased production and from decomposition and disposal of products containing the chemical. They voiced concern regarding increased body burdens in the future. The sponsor said they did not believe that human body burdens would necessarily increase in the future. Although pentaBDE production volume is increasing at 3-4% per year, the number of companies making this commercial product has decreased from a half dozen to only one, with only one location involved in manufacture. This enables improved product stewardship practices and reduced worker and environmental exposures. In addition, the previous uses of pentaBDE in hydraulic fluids, roofing shakes, and other applications that resulted in high emissions have now been discontinued. Studies in Europe have demonstrated that pentaBDE contained in products discarded to landfills was largely immobilized via binding to sediments. The European Union has estimated volatilization of pentaBDE from furniture to be only one-tenth of one percent. The sponsor had no estimate available for the half-life of pentaBDE in the environment.

Several members had questions about the sponsor slides (Appendix E) that showed bar graphs revised to include the recent unpublished data for breast milk and house dust and higher estimates of fish consumption. One panelist asked why the Schecter data did not cause PBDE intake for breast-feeding infants to be increased more than from 0.0009 to 0.0011 mg/kg-day. The sponsor answered that this age group had exposure sources other than breast milk, and these other sources were not increased. Another panelist noted that when the new exposure data were included in the bar graph, the differences between the three age groups with the highest exposures and the RfD was reduced to about two-fold. A third member, referring to his own investigations of pentaBDE in aquatic biota, noted that the actual fish concentrations were likely to be less than the sponsor had estimated and so the maximum exposure estimates in the bar graph might be too high. However, this panelist was concerned the data covered only the time period of birth to one year of age without addressing the *in utero* exposure occurring previously.

Panel Discussion of the Exposure Assessment

The panel discussion on the exposure assessment addressed three charge questions.

- Is the fate of pentaBDE adequately understood?

- 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?
    - 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?

- Are the estimates of exposure calculated appropriately and correctly?

Fate of PentaBDE

A panel member made a number of comments regarding the fate of pentaBDE. He said the fate of pentaBDE is not well understood because of scarcity of data, but environmental levels of pentaBDE are known to be increasing about five percent per year. The panelist thought that products like FPUF, rather than emissions from manufacturing plants, might be the major sources of pentaBDE found in the environment. PentaBDE has a low vapor pressure and is relatively stable, with a half-life likely to be years. Some debromination and hydroxylation occur. A small amount likely goes to dioxins and furans, but this is probably negligible. Microbial biodegradation is low, but metabolism occurs in fish, with metabolites varying with the fish species. Landfills generally do a good job containing pentaBDE from discarded products, but pentaBDE has been found at mg/kg concentrations in sludge, and some sludges are applied to farmlands. The exact manner in which pentaBDE gets into sludge is unknown, but it may be the same way that it gets into house dust. This is likely to involve crumbling of FPUF during the use and aging of products. FPUF is also used as polyurethane foam carpet underlayment, so it may become a component of vacuum cleaner waste. The amounts of pentaBDE found in sewage sludge are remarkably similar across the U.S. Longer-range transport also occurs, as evidenced by findings of pentaBDE in the Arctic. Bioconcentration of tetraBDE (BDE-47), one of the major components of the pentaBDE commercial product, is known to be very high, exceeding the bioconcentration of PCBs. Levels in fish have increased between 10 and 100 times in the past decade, and it has been found in ospreys. In the U.S. the ingestion of fish is a major source of human exposure.

Another panelist suggested that pentaBDE might diffuse out of the plastic components of end products. He noted two models might be used to estimate diffusion from plastics: one is used primarily in the European Union (EC Report 1998) and another in the U.S. (the A.D. Little Migration Estimation Model; AMEM). Although the lack of data on pentaBDE prevents input values from being precisely defined, the panelist thought it would be possible to make bounding estimates with the models. He said that one estimate using the AMEM model predicts up to 80% per year of pentaBDE will diffuse out of plastics.

The same panelist distributed and discussed calculations (Appendix G) he had done to estimate potential pentaBDE inhalation exposures from people sitting on pillows or cushions. In one assumed scenario, a 1 kg pillow is made of FPUF that contains 4% pentaBDE. Sitting on the pillow compresses it and expels air with pentaBDE into the room. Depending on the room size, the number of pillow compressions, the FPUF void volume, and many other variables, the inhalation exposure to pentaBDE from this scenario might be as high as 50 ug/day. Other panelists thought the scenario might be reasonable, adding that the estimate of 50 ug/day is an order of magnitude greater than the inhalation exposure estimated from pentaBDE in house dust (Rudel et al. in press[5]). Several members agreed that diffusion from FPUF-containing products in general, and scenarios such as the one described in particular, might be major pathways of pentaBDE entry into indoor air and the environment. These members said testing might be conducted to explore the contribution of these types of pathways. If confirmed as meaningful, ways should be identified to block or reduce this entry pathway to the environment.

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

Characterizing Exposure to Children and Prospective Parents

One panel member stated that the lack of data on half-life and exposure pathways, together with the problems differentiating between the pentaBDE commercial product mixture and individual congeners, indicated that insufficient information was available to adequately determine exposure conditions or populations of concern. Another member said the sponsor did an adequate job identifying exposure pathways, but additional information in several areas would be useful. For example, since various fish species metabolize the chemical differently, it would be helpful to know levels of pentaBDE and its metabolites in different types of fish and how much of each fish type is eaten. Since breast milk levels appear to be increasing, more sampling might be indicated.

Another panel member noted that levels of the commercial pentaBDE mixture in root crop vegetables taken from the EU report (European Chemicals Bureau, 2000) and from Wenning (2002) listed in Table 3-27 on p.111 of the submission seemed inconsistent with the VCCEP assessment value (in the same table). He said it also was unclear how the values were chosen for exposures – sometimes the mean value and other times the upper bound was reported. The sponsor explained that the root crop data appear to be inconsistent because the data used in the VCCEP screening model were adopted from market basket data reported from outside the U.S. The EU risk assessment (European Chemicals Bureau, 2000) relied on a theoretical fate model (the EUSES Environmental Fate model) to predict all of the environmental data used in their risk assessment. An inherent flaw in the EUSES model, which is recognized by many scientists, is the reliance on the physical/chemical properties of different categories of chemicals, rather than on the use of chemical-specific data. Consequently, the EUSES model classified PBDEs as members of a group of persistent, high K_{ow} chemicals that are assumed to migrate through soil and accumulate in root plants. Wenning (2002) used Monte Carlo modeling to highlight the range of uncertainty associated with the values EUSES calculated for different environmental compartments. The limited environmental data indicated that very few PBDEs are measurable in below-ground plant tissues, hence the large difference between the EUSES value and the VCCEP value. The sponsor emphasized that the value used in the submission relied on measured data and did not use predictive modeling to define the concentrations in different exposure-source compartments.

The high blood levels in people not working in the brominated flame retardant industry reported by Mazdai concerned some panelists. They noted that some subjects had blood levels from 10 – 40 times higher than the high-end exposures estimated in the submission, and they emphasized the importance of determining the sources of non-occupational exposures. The sponsor responded that the median values in the Mazdai report were not that different from the estimates. Other members agreed that the high values found in the Mazdai study indicated the upper bounding estimates of human exposure might not be conservative. They thought these data raise questions about whether human exposures might be approaching levels of toxicity. Some panelists expressed less concern, noting that outliers often exist that are difficult to explain, and accurate bounding estimates should not be expected from a screening level assessment. They reasoned that if unknown exposure sources exist, the exposure assessment would not predict the mean exposure values so accurately. They thought a more likely explanation for the high values

is that the range of distribution is greater than expected; however, they said it makes sense to look more closely at exposures occurring from breast milk and from fish consumption. Others noted the importance of understanding whether the highest values measured in human studies were really outliers. They pointed out that, considering approximately 160 samples were obtained from four human studies, it appears unlikely that the high samples can be dismissed as outliers.

Addressing the issue of whether all the relevant time periods of potential exposure were covered by the submission, one panel member said adults in the workplace were adequately considered. He added that no *in utero* exposure data from workers were available and *in utero* exposures in the general population were not explicitly covered, but the Mazdai samples of cord blood provided some relevant data. Another panelist noted that the fish consumption data in the submission were typical rather than upper bound, and consumption from recreational fishing was applied only to adult males, not to the fisherman's family or to the entire population.

Exposure Estimates

One panelist stated that overall the exposure estimates were calculated appropriately. Two other members said in some instances the sponsor used mean exposure values when the panelists thought bounding screening assessments should have been calculated. Another member said the range of potential exposures should be defined more clearly, but he thought nothing indicated the assumptions used for the major exposure pathways (breast milk, fish) are wrong.

Several panel members expressed concern that the sponsor's exposure estimates employed European input data in cases where North American data were unavailable. Since PBDE levels in wildlife are often higher in the U.S. and Canada than elsewhere, they thought use of European data might result in underestimating exposures to the North American population.

Panel members noted the following typographical errors in the submission: (1) on page 111 of the report, the breast milk *VCCEP Assessment* value should be changed from 76 to 43 ng/g lipid, and (2) on page 4 of the *Calculations for Hypothetical Exposure of Consumers to Commercial PentaBDE Product at Home* section of Appendix VI, the *Indoor Dust Ingestion Rate* values for the three groups of children less than five years old should be changed from 10 to 100 mg/day.

Risk Characterization and Data Needs

Sponsor Presentation

Dr. Tessa Serex of GLCC summarized the risk characterization and data needs that were presented in the sponsor's written submission (see Appendix E for the presentation slides). She reviewed the data supporting the sponsor's decision to use three screening benchmarks: change in neonatal T_4 homeostasis, thyroid hyperplasia, and liver enzyme induction. She also reviewed the data supporting the exposure assessment. Based upon the data available when the submission was prepared, the age group with the highest potential exposure appeared to be children less than one year of age (mean of 0.0009 mg/kg-day), with exposure coming mostly from breast milk.

However, subsequent calculations incorporating the unpublished data for breast milk and house dust into the exposure assessment and making a higher theoretical estimate of levels from fish consumption resulted in the theoretical aggregate total daily intake of pentaBDE (to make the risk assessment conservative, all detected PBDEs were assumed to be pentaBDE) being highest for children one to two years of age (mean of 0.0013 mg/kg-day). The majority of exposure (between 90 and 95%) for all age groups with the exception of children less than one year of age was still attributable to the food pathway, specifically the consumption of fish. For children less than one year old, the ingestion of human milk remained the primary source of exposure.

The sponsor emphasized that with the revised exposure values including the more recent data on fish, human milk, and house dust, the total aggregate exposure in the highest exposed age group is still below the estimated screening toxicity benchmark values for pentaBDE for T_4 changes (0.2 mg/kg-day), thyroid hyperplasia (0.04 mg/kg-day), and neurobehavioral changes consisting of changes in the low frequency auditory threshold (0.007 mg/kg-day). Theoretical aggregate total exposures to all age groups and adults also are below the U.S. EPA RfD of 0.002 mg/kg-day. Estimated exposures of children and adults of the general population were below screening toxicity benchmark values.

The sponsor identified the following possible data gaps for the commercial pentaBDE product. For hazard assessment: a two-year bioassay, a multi-generation reproductive toxicity study, and mechanistic studies to determine the human relevance of thyroid and neurobehavioral effects observed in rodents. For exposure assessment: increased source-specific data on lower brominated PBDEs in the U.S. and clarification of the pathways by which the pentaBDE commercial mixture and its constituents could be released into the environment and possibly accumulate in biotic and abiotic compartments. The sponsor noted that Health Canada and the National Toxicology Program (NTP) are planning to conduct toxicity studies that may address some of the data gaps in the hazard dataset. These studies include a 2-generation reproduction study by oral gavage, a 90-day oral dietary study, a 26-week study in mice (2 strains), and a 2-year study in rats and mice.

The sponsor said filling these identified data gaps would reduce uncertainty, but not necessarily change the Tier 1 assessment results, and that closing the data gaps is not necessary to adequately assess the risks to children's health for the Tier 1 program.

Panel Discussion of the Risk Characterization

The panel discussion on the risk characterization addressed the following charge question:

Integration of Exposure and Hazard Information

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

A panel member commended the sponsor for presenting revised calculations in the slide presentation that incorporated the new, unpublished data on exposures to dust, breast milk, and

fish, and included the blood sampling data from Mazdai. He said that, although panel members had voiced disagreements with some of the assumptions used to determine uncertainty factors and other values, the overall approach the sponsor used to calculate the toxicity benchmarks, BMDs, and Hazard Indices (HIs) appears to be sound. However, he thought *in utero* exposures and exposures to prospective parents needed to be more fully presented. Another member added that the point of departure for a risk value depends on many things, and the choices made will affect the values of the final RfDs and BMDs. He suggested the panel try to discern overall trends rather than events that may not be of key biological importance (i.e., hepatic enzyme induction). Nevertheless, he acknowledged that using the event that occurs at the lowest dose is conservative, and he thought conservatism is essential because the MOA is not fully known.

Another member also commended the sponsor for the manner in which they had calculated and presented the total aggregate exposures; however, she wondered if aggregation of all potential maximum exposures was appropriate for the U.S. population. She thought perhaps no real target population for the total aggregate exposure existed in the U.S; however, if it did exist, the risk characterization indicates this population may be approaching a range of toxicity. Others added that while pregnant women and people with iodine deficiency may not be target populations for total aggregate exposures, they are vulnerable subpopulations to consider.

Referring to the different uncertainty factors used for the various toxicity benchmark values, one member said she did not necessarily agree with the assumptions the sponsor had used in arriving at the uncertainty factor totals. For some of the benchmarks, one could argue that the uncertainty factors should be 10 or even 30 times greater. The sponsor acknowledged that the particular values chosen were often a matter of judgment. The sponsor noted, however, that even if the uncertainty factors were increased, the margins of exposure (MOEs) between the benchmark values and exposure estimates were large in most cases. Another panelist said that he had calculated BMDs using his own assumptions and obtained different results. He said in some cases the sequence of events the sponsor followed in choosing the datasets for BMD derivations did not seem correct. He also noted that the sponsor did not define uncertainty factors in the same way for every endpoint. His major concern was with the benchmark dose low estimate (BMD_{LO}) for the T_4 change, and he volunteered to work with the sponsor to assure the correct values are being used.

One panel member suggested a conservative risk assessment could be assured by attributing all the toxicities observed from the total commercial mixture to the pentaBDE moiety. Another member disagreed with this approach saying that, if the most toxic moiety in the mixture had different kinetics than pentaBDE, it could accumulate undetected in the environment and in human target populations.

One member said the risk characterization failed to account for potential additive effects of pentaBDE and other chemicals. He noted that PCBs are found in breast milk together with PBDEs, and these two classes of chemicals are known to be additive in reducing T_4 levels. He also noted that the risk characterization did not address the possibility of pentaBDE exposure increasing over time.

One panelist felt strongly that the exposure uncertainty is so great that it severely limits the ability to perform a reasonable risk characterization. Several panelists agreed that the exposure uncertainty is high, citing as evidence the higher-than-predicted Mazdai data discussed above.

Panel Discussion of Data Gaps and Needs

Panel members addressed the following two charge questions:

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

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

Reflecting on areas the sponsor had identified as possible data gaps in the hazard assessment, a panelist wondered whether the planned Health Canada and NTP toxicity studies might be modified or expanded to provide information to fill the data gaps. The sponsor replied that some data gaps would be filled by the existing study protocols. In addition, the sponsor will inform the agencies conducting these studies of the outcome of this VCCEP meeting.

Individual Panelist Data Needs

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. A single consensus opinion from the panel is not sought.

In discussing the two charge questions above, the panel members went beyond recommending studies from the next VCCEP Tier. They provided comments on all areas where they believed additional information would be useful to better characterize the potential hazards, exposures, and risks to children. Similar data needs identified by the individual panel members have been grouped, and the number of panel members identifying each data need (out of the 13 panel members) is indicated. The number of items identified as data needs by individual panelists ranged from 2 items (4 panelists) to 6 items (4 panelists). A majority of the 13 panel members thought it was important to obtain more measurements of pentaBDE in humans and to identify more completely the possible sources of human exposure.

The following 9 items were listed as data needs by 2 or more panelists:

- Obtain more measurements in humans (10 panelists in total: of these panelists, 5 specified samples from breast milk, 3 specified blood serum, and 4 specified workers with potentially high occupational exposures)

- Identify sources of human exposure more completely (7 panelists)

- Determine mechanism of action and whether all observed toxicities are related to thyroid hormone changes (6 panelists)

- Obtain more information on pharmacokinetics, including body burden comparisons between human and laboratory animals (6 panelists)

- Determine the potential effects on fertility (5 panelists)

- Determine how toxicity results from commercial products can be interpreted and related to individual congeners (5 panelists)

- Determine environmental fate more completely (4 panelists)

- Obtain more measurements in fish (3 panelists)

- Characterize the risk for potentially sensitive subpopulations (e.g., pregnancy, obesity, iodine deficiency) (2 panelists)

In addition, these other items were mentioned by single panelists:

- Evaluate diffusion from end products and resulting effects on indoor air

- Study the toxicity of hydroxy metabolites in humans

- Determine the toxicity of pentaBDE alone, with other PBDEs, and with other chemical classes such as polybrominated and polychlorinated biphenyls (PBBs, PCBs)

- Measure levels in foods that might contain pentaBDE as a result of sludge applications to soil

- Rework the BMD calculations

- Determine the complete identity of the pentaBDE commercial mixtures, including the nonbrominated compounds

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APPENDIX A

Pre-meeting Comments from Ruthann Rudel on PentaBDE and OctaBDE

Ms. Ruthann Rudel of Silent Spring was selected as an *ad hoc* panel member, but was unable to attend the meeting. She provided written premeeting comments that the panel considered in its discussions. Because she could not participate in the discussions, data needs from Ms. Rudel are not listed in the report.

Pre-meeting comments from Ruthann Rudel on PentaBDE and OctaBDE

The most critical issues for the Hazard Assessment are:

- The lack of a reproductive study
- An inappropriate choice of uncertainty factors in deriving the RfDs
- Liver enzyme induction should be considered to be a relevant endpoint
- The assessment must address the combined toxicity of these compounds with the other polybrominated diphenyl ethers, with polychlorinated biphenyls, with polyhalogenated aromatic hydrocarbons, and with other chemicals that act via similar mechanisms

The Exposure Assessment does not adequately consider the following issues:

- Blood, breast milk, and adipose levels of PBDEs should be used to "reality check" the exposure estimates presented based on exposure models and calculations that rely on assumptions and limited data about intake rates and media concentrations. As we saw in the case of decabromodiphenyl ether, the single exposure estimate based on a dozen blood samples taken in the U.S. in the 1980s was associated with higher levels of exposure than any of the exposure scenarios calculated based on what seemed to be "extremely conservative" exposure assumptions. We do not know very much about how people get exposed to these compounds – so the exposure calculations presented are very likely to have uncertainty of multiple orders of magnitude. Biological monitoring data should be combined with available data on pharmacokinetics to provide additional estimates of exposure levels.

- No effort is made to estimate exposures in the future – this is important because these compounds are persistent and bioaccumulative and biological measures have been shown to be increasing over time.

- Assumptions used for exposure calculations are not appropriate for a screening level assessment and appear to underestimate potential exposures to the general population by orders of magnitude. Because there is a high degree of variability observed in virtually every measurement study that has been done for the PBDEs, it is important to include estimates of "high end" exposures in this assessment.

  Specific examples:
  Table 3-18 (pentabromodiphenyl ether submission p. 91) gives assumptions used in the exposure calculations. Many of the choices are means or 95th percentile UCL estimates of the means. Means and estimates of means are not appropriate choices for a screening-level assessment such as this one. Maximum reported values should be used instead. So, for example, for breast milk concentrations, the report uses the mean from Ryan (42.8 ng/g lipid) rather than the maximum (282 or 589 ng/g lipid) reported from that (relatively

small) Canadian study. Data from Papke are not considered at all in this assessment, although they report breast milk concentrations substantially higher than those reported by Ryan (about 200 ng/g lipid in a pooled US sample).

For house dust concentrations, the report uses an estimate of the mean from Knoth (0.410 micrograms/g) rather than the maximum reported (about 5 micrograms/g). Furthermore, because the Knoth data were from Europe, where these compounds are much less used than in the U.S., they are probably an underestimate of U.S. levels. For example, my data on PBDE in housedust (see table below) show a max of about 36 micrograms/g dust in a sample of 89 homes.

Rudel et al. (2003) house dust data:

Summary data on PBDE levels in house dust samples on Cape Cod, MA (micrograms/g)

Statistic	PBDE-47	PBDE-100	PBDE-99
Approximate method detection limit	0.4	0.3	0.4
Minimum	<LOD	<LOD	<LOD
Median	<LOD	<LOD	0.30
90th%ile	2.3	0.67	4.1
Maximum	9.9	3.4	23
Number of homes	89	89	89
Percent with detectable levels	45%	20%	55%

from Rudel R, D Camann, JD Spengler, D Barr, and JG Brody. 2003. Household exposure to phthalates, pesticides, alkylphenols, PBDEs, and other endocrine active compounds. SOT 2003 Abstract # 896 (and subsequently published as Rudel et al. (2003) in Environ. Sci. Tech.)

Assuming a 1-2 year old child ingests 200 mg/day of house dust through hand-mouth activity, total intake of these three congeners would be up to 7.3 micrograms/day or 0.0007 mg/kg/day for a 10 kg child. Compare this with tables 3-25 and 3-26, which estimate child intake by hand-mouth activity at about 0.000001 mg/kg/day.

APPENDIX B

List of Attendees

List of Attendees

Ms. Mary Albert
Health Canada

Mr. Matthew Barkhurst
Toxicology Excellence for Risk Assessment

Dr. Richard A. Becker
American Chemistry Council

Dr. Dan Briggs
Toxicology Excellence for Risk Assessment

Mr. John Bowser
US EPA

Mr. Robert Campbell
Great Lakes Chemical Corp.

Dr. Lynne Cannon
Learning Disabilities Association of America

Ms. Lynn Delpire
U.S. EPA/ OPPT/ EETD/ EAB

Mr. Chuck Elkins
Chuck Elkins & Associates

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

Dr. Hend Galal-Gorchev
US EPA/ HECD

Mr. William F. Gentit
Akzo Nobel Functional Chemicals LLC

Dr. Pertti J. Hakkinen
European Commission

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

Ms. Kathleen Lawson
Learning Disabilities Association of America

Mr. Greg Miller
US EPA/ National Center for Environmental Economics

Ms. Patricia Nance
Toxicology Excellence for Risk Assessment

Ms. Jacqueline Patterson
Toxicology Excellence for Risk Assessment

Ms. Bebe Raupe
Bureau of National Affairs, Inc.

Ms. Lee Salamone
American Chemistry Council

Dr. Chad B Sandusky
Physicians Committee for Responsible Medicine

Dr. Tessa L. Serex
Great Lakes Chemical Corporation

Mr. Richard Wenning
Environ International Corporation

Ms. Andrea Wullenweber
Toxicology Excellence for Risk Assessment

Dr. Jay Zhao
Toxicology Excellence for Risk Assessment

APPENDIX C

Voluntary Children's Chemical Evaluation Program (VCCEP) Peer Consultations on Octabromodiphenyl ether and Pentabromodiphenyl ether

Meeting Materials

June 3-5, 2003

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

Table of Contents

Overview of the Peer Consultation Process

Introduction

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

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

The purpose of this meeting is to provide a science-based peer consultation on the data needs for octabromodiphenyl ether and pentabromodiphenyl 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 (BFRIP) has volunteered to sponsor a Tier 1 assessment for octabromodiphenyl ether and pentabromodiphenyl 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 data, the depth of exposure information increases with each tier, with Tier 1 a screening level assessment and Tiers 2 and 3 more advanced assessments using exposure studies, monitoring data, and modeling. The Federal Register notes that the Tier 1 assessment should use all available data, and therefore some of the chemical assessment documents will include more than what is in the Tier 1 level.

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

The VCCEP program is a voluntary program. 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.

Octabromodiphenyl ether and Pentabromodiphenyl ether Peer Consultation Panel

The VCCEP Peer Consultation Panel for octabromodiphenyl ether and pentabromodiphenyl ether consists of fourteen members: the nine VCCEP Core Panel Members for Year 1 and five additional *ad hoc* members specifically selected for this meeting. The 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 octabromodiphenyl ether and pentabromodiphenyl ether panel, with the nomination period closing in November 2002. *TERA* independently selected five additional *ad hoc* scientists for the panel. *Ad hoc* panelists have the same status and responsibilities as the core group panelists.

Each panel member has disclosed information regarding potential conflicts of interest and biases related to the VCCEP program, the sponsor, and octabromodiphenyl ether and pentabromodiphenyl 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, to ensure adequate time to carefully review the document and be prepared for the discussions.

The meeting will be organized to make the best use of the time available to hear the opinions of the experts on the charge questions and the data needs for octabromodiphenyl ether and pentabromodiphenyl 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 that adequate space is available, we ask people to register in advance for the meeting. The public was also given the opportunity to prepare brief technical comments on the assessment document and submit these in writing prior to the meeting. *TERA* shared the comments with the Panel and Sponsors prior to the meeting and copies are available for all attendees at the meeting. Observers will be permitted to make brief technical comments at the meeting as time permits. Panel members and Sponsors may ask clarifying questions of those making comments.

Meeting Report

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

Agenda for the VCCEP Peer Consultation for Pentabromodiphenyl Ether

June 3-4, 2003

University of Cincinnati, Kingsgate Conference Center, Salon AB

Tuesday June 3, 2003

8:00 **Registration and Check In**

8:30 **Meeting Convenes6**
Welcome: Ms. Jacqueline Patterson, *TERA*
Introductions and Disclosures, Panel
Meeting Process: Dr. Michael Dourson, Chair

9:00 **Sponsor Introduction and Background on Pentabromodiphenyl Ether**
Presenter: Mr. Bob Campbell, Great Lakes Chemical Corporation

9:15 **Sponsor Presentation on Hazard Assessment**
Presenter: Dr. Tessa Serex, Great Lakes Chemical Corporation

Clarifying Questions from Panel

Public Comments on Hazard Assessment
Clarifying Questions from Panel and Sponsors

Panel Discussion
Discussion of panel charge questions regarding Hazard Assessment

12:30 **Lunch**

1:30 **Sponsor Presentation on Exposure Assessment**
Presenter: Mr. Rick Wenning, Environ

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**

6:30 **Reception for all attendees**

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

Wednesday June 4, 2003

8:00 **Registration**

8:30 **Meeting Re-convenes**

Sponsor Presentation on Risk Characterization and Data Needs
Presenter: Dr. Tessa Serex, Great Lakes Chemical Corporation

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

Panel Discussion on Data Needs
Discussion of panel charge questions regarding Data Needs

12:30 **Adjourn**

Agenda for the VCCEP Peer Consultation for Octabromodiphenyl Ether
June 4-5, 2003
University of Cincinnati, Kingsgate Conference Center, Salon AB

Wednesday June 4, 2003

1:30 **Meeting Convenes***[7]

Sponsor Introduction and Background on Octabromodiphenyl Ether
Presenter: Mr. Bob Campbell, Great Lakes Chemical Corporation

1:45 **Sponsor Presentation on Hazard Assessment**
Presenter: Dr. Tessa Serex, Great Lakes Chemical Corporation
Clarifying Questions from Panel

Public Comments on Hazard Assessment
Clarifying Questions from Panel and Sponsors

Panel Discussion
Discussion of panel charge questions regarding Hazard Assessment

5:00 **Adjourn**

Thursday June 5, 2003

8:00 **Registration**

8:30 **Meeting Re-convenes**

Sponsor Presentation on Exposure Assessment
Presenter: Mr. Richard Wenning, Environ

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

12:00 **Lunch**

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

1:00 **Sponsor Presentation on Risk Characterization and Data Needs**
Presenter: Dr. Tessa Serex, Great Lakes Chemical Corporation

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

Panel Discussion on Data Needs
Discussion of panel charge questions regarding Data Needs

Closing Remarks and Evaluation of Meetings

4:30 **Adjourn**

Octabromodiphenyl Ether and Pentabromodiphenyl 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 this chemical 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?

    - 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 this chemical 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,

    - Are any additional toxicity studies 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 fourteen 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 Octabromodiphenyl ether and Pentabromodiphenyl ether and their Sponsor, the Great Lakes Chemical Company.

Dr. John Balbus

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

Dr. Balbus received his M.D. from the University of Pennsylvania, an M.P.H. from the Johns Hopkins School of Hygiene and Public Health, and an A.B. in Biochemistry from Harvard University. He completed residencies in internal medicine at Pennsylvania Hospital and in occupational and environmental medicine at Johns Hopkins School of Hygiene and Public Health. Dr. Balbus has also held a variety of additional academic appointments that include: Assistant Professor of Medicine at George Washington University Medical Center, Clinical Fellow in 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 panels on octa and pentabromodiphenyl ethers. 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, and is a designee to the Virginia Toxics Advisory Board.

Dr. Hale has served on a number of review panels, program reviews, and national or international research programs. Specifically, he has served as a peer reviewer on a number of US EPA panels, including participating in the EPA Forum on the Extent and Severity of Contaminated Sediments, serving as a peer reviewer for revisions to "Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health," and reviewing the Design Document for the National Study of Chemical Residues in Lake Fish Tissues. He also served on the Science Advisory Panel for the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). Dr. Hale also participates in community toxics programs and has served as a panel member for the Chesapeake Bay Toxics of Concern Scientific and Technical Advisory Committee Review and for the Scientific and Technical Advisory Committee, Chesapeake Bay Program Toxics Subcommittee. He is a manuscript reviewer for multiple scientific journals, books, and proposals. Dr. Hale has also 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 panels on octa and pentabromodiphenyl ethers. 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 and continues to do so.

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 panels on octa and pentabromodiphenyl ethers. He is active on several working groups of the American Chemistry Council (ACC). 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.

Dr. Thomas A. McDonald

Dr. Thomas McDonald is a Toxicologist with the Office of Environmental Health Hazard Assessment (OEHHA), California Environmental Protection Agency (Cal/EPA), Oakland, California. His primary activities include hazard identification and dose-response assessment of carcinogens, development of children's cancer guidelines, peer review, and technical support to the state's science advisory boards. Current research interests include mechanisms of carcinogenesis, thyroid hormone disruption, and children's health. Dr. McDonald is actively involved in the assessment of polybrominated flame retardants, as evidenced by the recent publication "A perspective on the potential health risks of PBDEs" in Chemosphere, 2002.

Dr. McDonald received his Ph.D. in Environmental Health Sciences from the University of North Carolina, Chapel Hill, and holds degrees in molecular biology and public health from the University of California at Berkeley. He has been a toxicologist at Cal/EPA since 1994; and during his tenure at Cal/EPA received a Cal/EPA Customer Service and Technical Award. In 1993, he also received the Hoechst Celanese Award for Excellence in Research. He currently serves as a University of California at Davis Mentor/Supervisor to a graduate student working on the Cal/EPA children's cancer project.

Dr. McDonald's professional activities include membership in scientific societies and participation as a reviewer for journals and government documents, and on peer review panels. Dr. McDonald has published over a dozen manuscripts in peer-reviewed journals and authored two book chapters. He has also been the primary author on at least seventeen environmental health hazard assessment documents for Cal/EPA. Dr. McDonald has also presented numerous invited lectures and abstracts on the topics of brominated flame retardants and age-related carcinogenesis.

DISCLOSURE:

Dr. McDonald has been selected as an *ad hoc* member for the VCCEP panels on octa and pentabromodiphenyl ethers. He is employed by the Office of Environmental Health Hazard Assessment (OEHHA), California Environmental Protection Agency (Cal/EPA), Oakland, California. Cal/EPA has taken public positions on polybromodiphenyl ethers and is currently monitoring ambient air concentrations of these chemicals throughout California. In 2002 Dr. McDonald published an article on PBDEs in *Chemosphere*, and in 2000 co-authored an article on PBDEs in *Environmental Health Perspectives*.

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 panels on octa and pentabromodiphenyl ethers. 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 Associate 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. Tessa L. Serex

Ph.D., D.A.B.T. (Toxicology)
Great Lakes Chemical Corporation

Dr. Tessa Serex is currently employed as Toxicologist at Great Lakes Chemical Corporation. Her activities consist of product safety evaluations including placing and monitoring studies under OPPTS and OECD guidelines as well as conducting risk assessments on products, and evaluating products from a product stewardship perspective. She is the Lead Technical Advisor to the International Antimony Oxide Industry Association and in this capacity she serves as the industry representative for the European Union risk assessment on antimony trioxide.

Dr. Serex served as a Post Doctoral Research Associate at Oak Ridge National Laboratory in the Toxicology and Risk Analysis Section between September 1998 and April 2000. Activities included: evaluation of general toxicity studies (acute, subchronic, chronic/oncogenicity) as well as neurotoxicity and reproductive studies submitted under FIFRA, according to U.S. EPA pesticide registration regulatory requirements. At Oak Ridge Dr. Serex also participated in the hazard assessment for the development of concentration exposure limits for airborne chemicals deemed acutely toxic or high-priority. This project was commissioned by the National Advisory Committee for Development of Acute Exposure Guideline Levels (AEGLs).

In 1998 Dr. Serex received a Ph.D. in Pharmacology/Toxicology from Quillen College of Medicine, East Tennessee State University. Her dissertation research was entitled "*In vitro* assessment of the toxicity of cocaine and its metabolites in the human umbilical artery". She is an associate member of the Society of Toxicology and a diplomat of the American Board of Toxicology.

Mr. Richard J. Wenning

Senior Scientist
ENVIRON International Corporation, Inc.

Mr. Richard Wenning is a senior scientist in the health sciences practice at ENVIRON International Corporation, an engineering and scientific consulting firm with offices located worldwide. Mr. Wenning is an environmental toxicologist with fifteen years of consulting experience in several aspects of chemical risk assessment, including chemical source fingerprinting, exposure assessment, ecological food web modeling, and probabilistic risk analysis. He has been involved in developing environmental sampling strategies and quantitative exposure studies to supplement, refine, or verify screening or detailed human or ecological exposure models addressing dioxins, PCBs, and metals in food products, soil, sediment, indoor air, and fish. Mr. Wenning has performed exposure assessments and risk assessments for children, occupationally exposed individuals, recreational anglers, and other potentially exposed populations exposed to a range of persistent organic contaminants in the environment such as the dioxins, PCBs, chlorinated pesticides, and brominated flame retardant chemicals.

Mr. Wenning is active on the science advisory boards of several professional organizations. He was a member of the National Organizing Committee for the International Dioxin2000 Symposium (Monterey, CA) and International Advisory Committee for Dioxin2001 (Kyongju, South Korea) and Dioxin1999 (Venice, Italy). He is a member of the organizing committee for BFR2004 (Toronto, Canada). Mr. Wenning has also published extensively in the scientific literature on human health and ecological risk assessment. He serves as Associate Editor of the journals *Archives of Environmental Contamination & Toxicology*, and *Ecotoxicology & Environmental Safety*. Until 2002, Mr. Wenning was the editor-in-chief of the peer-reviewed journal *Environmental Forensics*. He recently completed work as co-editor of a special issue of the journal *Chemosphere* (February, 2002) devoted to a state-of-the-science review of brominated flame retardant chemicals in the environment. Mr. Wenning was recently named editor-in-chief of the new peer-reviewed journal *Integrated Environmental Assessment and Management*. He received his B.S. in environmental science from the University of Denver (1985) and an M.E.M. in environmental toxicology from Duke University (1987).

APPENDIX D

Voluntary Children's Chemical Evaluation Program (VCCEP) Peer Consultation on Pentabromodiphenyl Ether and Octabromodiphenyl Ether

Observer Policy & Submitted Comments

June 3-5, 2003

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

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VCEEP Peer Consultation Policy and Procedures for Observers

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

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

Written Comments

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

Oral Comments

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

Meeting Report

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

Dr. Fredric C Arnold
U.S. Environmental Protection Agency
Economics, Exposure, and Technology Division

May 21, 2003

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

Dear Ms. Patterson:

My comments on the Voluntary Children's Chemical Evaluation Program Submission for pentabromodiphenyl ether are given below.

On page 63, the VCCEP submission for pentabromodiphenyl ether (pentaBDE) dismisses consideration of the chemical in water saying "It is highly unlikely that BDEs will be detected in water because of the hydrophobic nature of this class of compounds." As a result, ingestion of water containing pentaBDE is not included in the pathways of exposure to the chemical and, more importantly, transport of pentaBDE in water may not be included in future studies of the distribution of this chemical in the environment. However, as reported by Peltola et al, "Although pentaBDE has low water solubility, it has been found in water (Lake Ontario, 1999). BDE-47 and BDE-99 made up >70% of the total amount of PBDEs and approximately 90% of all PBDEs were in the soluble phase (Luckey et al. 2001). Total PBDE concentrations were between 4 and 3 pg/l. BDE-47, BDE-99, and BDE-100 have been detected in Sweden where water contained them as a total 0.3 ng/l (study summarized by de Wit 2000). BDE–47, BDE-99 and BDE-100 were also found in urban stormwater leachate in level of ca. 10 ng/l as the sum of the three congeners." The Submission should consider ingestion of water as a source of pentaBDE uptake and that if future studies include the fate and transport of pentaBDE in the environment, transport with water either as a solute or attached to a particulate, should not be neglected.

The Submission bases several assessments on a concentration of flame retardant formulation in products of 2% to 5% with a concentration of pentaBDE product within the formulation of 60% to 71%. Anecdotal evidence suggests that the amount of flame retardant formulation added to flexible polyurethane foam is more nearly 17% or 20 pounds of flame retardant formulation per hundred pounds of foam. This concentration used in the Submission should be verified and corrections made, if appropriate.

References

De Wit, C.A., 2000. Brominated Flame Retardants. Report 5065, Swedish Environment Protection Agency, Stockholm. IBSN 91-620-5065-6.

Luckey, F., Fowler, B., and Litten, S., 2001. Establishing baseline levels of polybrominated diphenyl ethers in Lake Ontario surface waters. The Second International Workshop on Brominated Flame Retardants, May 14-16. The Swedish Chemical Society, Stockholm, pp. 337-339.

Peltola, J. and Yla-Mononen, L., 2002. Pentabromodiphenyl ether as a global POP. Finnish Environment Institute, Environment Division.

The opportunity to comment on the Submission is appreciated.

Sincerely yours,

/s/

Fredric C Arnold
Economics, Exposure, and Technology Division
(7406M)

Mr. Robert Boethling
U.S. Environmental Protection Agency
Office of Pollution Prevention and Toxics
Exposure Assessment Branch

I reviewed the fate and chemical property sections of these documents. My only substantive comment concerns bioacumulation, especially for the penta PBDEs. The penta document states only that the tetra and penta PBDEs "have been reported to be more bioaccumulative than other BDE congeners." This statement is accurate, but in my opinion does not do justice to currently available information and its implications for bioaccumulation potential. There are two studies in particular which indicate that certain PBDEs including penta are bioaccumulative and bioavailable.

In the Sellstrom et al. (1998) study, they reported fish/sediment ratios for BDE99 and 100 up to 36, based on actual measurements (monitoring). This is strong evidence that these BDEs "are bioavailable and taken up readily by fish." And in the more recent work of Booij et al. (2002), log bioaccumulation factors (log BAF) up to approx. 9 were reported for BDEs 99 and 100. According to these authors, "all accumulation factors were much larger than expected on the basis of the most simple thermodynamic equilibrium model (log BAF = log Kow)." The two studies examined pike and mussels, respectively. An interesting technical sidelight is that these substances exceed the molecular cross-sectional area value (9.5 Angstroms) above which uptake is allegedly impossible.

References

Sellstrom U, A Kierkegaard, C de Wit, B Jansson. 1998. Polybrominated diphenyl ethers and hexabromocyclododecane in sediment and fish from a Swedish river. Environ. Toxicol. Chem. 17:1065-1072. Booij K, BN Zegers, JP Boon. 2002. Levels of some polybrominated diphenyl ether (PBDE) flame retardants along the Dutch coast as derived from their accumulation in SPMDs and blue mussels (Mytilus edulis). Chemosphere 46:683-688.

Last, the reference for Burreau et al. (1997) in the penta document has an error: volume number is 16 not 46.

Ms. Barbara McElgunn
Learning Disabilities Association

Learning Disabilities Association ***ofAmerica***

4156 Library Road · Pittsburgh, PA 15234-1349 · 412/341-1515 · FAX 412/344 0224

Submission for the TERA VCCEP Pentabromodiphenyl Ether Peer Consultation Meeting, June 3-5

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. There is evidence the prevalence of ADHD[8], learning disabilities[9] and autism[10] are increasing in recent years. A report in the Journal of the American Medical Association (2000) reported that the number of children prescribed psychotropic drugs increased by a factor of three between 1990 and 1995. Between 1990 and 1995 Health Canada data found an increase in the quantities of methylphenidate (Ritalin) prescribed increased by a factor of 3-4. The drug-tracking firm, IMS Canada reported another 55% increase in prescriptions for Ritalin between 1996 and 2001. Society must consider the contributions of chemicals that disrupt the developing nervous system in the etiologies of these disorders. The evidence from both experimental animal and clinical research from the few neurotoxic chemicals that have 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.

The LDA Research Committee has been aware for some time of the warnings from the scientific community about rising levels of the high-volume industrial chemicals - polybrominated diphenylethers (PBDEs) everywhere in the 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[11], and varying levels of PBDEs have been found in most commercial foods[12]. PBDE concentrations in foods in Canada ranged between 0.04 ng/g for pasta, and 1.2 ng/g for wieners – these values resulted in an estimated daily intake of 44ng, which is higher than PCDD/Fs (2.4.ng) but lower than PCBs (285 ng)[13]. These chemicals have

[8] 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.
[9] Center for Learning Disabilities. Students with learning disabilities: A national review. Annual Report to Congress, 2001.
[10] Byrd RS. Report to California legislature re jump in autism rates, 2002.
[11] Environment Canada (2002) S&E Bulletin, June, Ottawa.
[12] Alaee M, Bunce N, Ikonomou, M, et al. Determination of the impact of polybrominated Dephenyl Ethers in the Canadian environment and health of Canadians. TSRI report, 2002.
[13] Ryan, J. & Patry, B.Body burdens and exposure from food for PBDEs in Canada. The second International Workshop on Brominated Flame Retardants. BFR 2001, 103-104

been found to be persistent, bioaccumulative, highly lipophilic, developmentally neurotoxic and disruptive to thyroid systems 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 Petreas et al. indicates that California women have levels 3-10 times higher than European women measured during the same period[14]. The activity and structural similarity of PBDEs and PCBs, known developmental neurotoxicants, are another cause for concern to LDA.

The penta brominated diphenyl ether (penta-BDE) formulation is produced and used in high volume in North America. Penta-BDE is used is as a flame retardant additive in the manufacture of polyurethane foam; added to polymer in the manufacture of computer and TV boards and housing at levels from 5- 20% (WHO). The EU risk assessment report for Penta-BDE states that volatilization from the polymer matrix constitutes a probable inhalation exposure route; breakdown and transformation by combustion can form brominated dibenzo-p-dioxin and brominated dibenzofurans; and other recycling practices may have the potential to release these toxicants into the environment[15]

The levels of PBDEs in the tissues of 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 from 15-580 ng/g lipid in maternal serum and from 14- 460 ng/g in fetal samples[16] --far exceeding levels that moved Sweden to ban PBDEs in that country to protect the health and development of its citizens. Levels of PBDEs in breast milk rose form a mean of 0.2 ng/g lipid weight for samples collected across Canada in 1982, to a mean of 42.5ng/g lipid weight from milk samples taken in the Vancouver area in 2001-2002[17]. The highest concentrations can be compared to the PCB concentrations (expressed in terms of the fat concentrations in maternal milk) reported by Jacobson and Jacobson [18] as being associated with a 6.2 point loss in full-scale IQ scores and strong effects related to memory and attention at 11years of age 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). It is important to note that the PCB concentrations in the Jacobson study were only slightly higher than those found in the general population, indicating possible population effects.

A study by Walkowiak et al (2001) found negative associations between breast milk PCBs and mental/motor development at all ages followed – to 42 months. At age 30 months, for a PCB increase from 173 to 679 ng/g lipids in milk, there was a decrease of 8.3 points on the Bayley Mental Scales, and a decrease of 9.1 points on the Motor Scales.

[14] Petreas et al. (2003) High body burdens of 2, 2', 4, 4'-tetrabromo diphenyl ether (BDE-47) in California women. Environmental Health Perspectives, doi: 10. 1289/ehp.6220

[15] European Union Risk Assessment Report. Bis(Pentabromophenyl) Ether. European chemicals Bureau, 2000.

[16] Mazdai et al. (2003) Polybrominated diphenyl ethers in maternal and fetal blood samples. Environmental Health Perspectives, doi: 10. 1289/ehp.6146.

[17] Ryan, J. & Patry, B.Body burdens and exposure from food for PBDEs in Canada. The second International Workshop on Brominated Flame Retardants. BFR 2001, 103-104

[18] Jacobson J.L, Jacobson SW. Intellectuel impairment in children exposed to polychlorinated biphenlys in utero. New England J. Med., 335, (11) 783-789, 1996

A study by Ericksson et al.[19] linked exposure to tetra-BDE and penta-BDE, 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-old animals, increasing with age. In addition, neonatal exposure to PBDE 99 (penta BDE) 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.

The chemical structure of the commercial penta BDEs closely resembles that of thyroid hormones, and bind to transthyretin and thyroid hormone receptors. All the PBDEs have been found to disrupt the normal functioning of thyroid hormone balance and action, known to be essential for brain development[2021]. Learning and behavioral effects have been noted from alterations in thyroid in experimental animal studies, and from clinical studies of the effects of thyroid hormone deficiency before birth, or beyond[22]. Thyroid hormone is critical to the orchestration and expression of many vital processes necessary for normal brain development[23] [24] [25]. 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[26].

Despite their close relationships with PCBs, no NOEL for developmental neurotoxicity has been established for the 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 then only if negotiated and triggered by the other two tiers.

An economic analysis by Muir et al.[27] makes this point: "This analysis suggests that a business-as-usual scenario, where environmental concentrations of brominated flame retardants, such as PBDEs, are allowed to continue their increasing upward trend, especially in human mothers'

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[19] Ericksson P, Jacobsson W, & Fredriksson, A. (2001) Brominated Flame Retardants: A novel class of developmental toxicants in our environment? Environmental Health Perspectives, 109 (9)

[20] McDonald, TA, A perspective on the potential health risks of PBDEs. Chemosphere, 46 (2002) 745-755.

[21] Fowles, JR, Fairbrother, A. et al. (1994) Immunologic and endocrine effects of the flame-retardant pentabromodiphenyl ether (DE-71) in C57BL/6j mice. Toxicology 86, 49-61.r

[22] 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.

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

[24] Howdeswell, KL. (2002) A model of the development of the brain as a construct of the thyroid system. Environmental Health Perspectives, 337-348

[25] Zoeller, RT., Amy, LS. et al. Thyroid hormone, brain development and the environment. Environmental Health Perspectives, 355-361.

[27] Muir T, Alaee M. (2003). The costs and benefits of brominated flame retardants (BFRs) and alternatives. Organohalen Compounds, in press.

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 took precautionary action to ban penta-BDE in July 2003 – Directive 76/769/EEC.

The EU Commission has recommended further testing and information in some areas, e.g. on risks to infants who will continue to be exposed via milk, and for workers, to characterize lifetime exposure risks.

In conclusion our organization recommends:

- That precautionary action be taken without delay to ban penta-BDE in order to mitigate exposures to the public from the penta-BDEs, as has been done in the European Union.

That this measure be followed by studies regarding secondary exposures – to workers, consumers, and children, from current and persistant environmental levels of penta-BDEs:

- To adequately characterize the risk regarding the exposure of infants to breast milk or cow's milk.

"There is concern whether the concentration in milk might increase during the time it would take to obtain the information needed to refine the risk characterization and remove some of the uncertainties" EU Commission Recommendation March 5, 2001

- To establish a NOEL for developmental neurotoxicity for penta-BDE.

- To include the cumulative neurotoxic and endocrine effects of environmental exposures from various PBDE congeners and PCBs with a similar mode of action, since the main environmental properties and mechanisms of toxicity of the PBBs and PBDEs are similar to those of the structurally related PCBs and dibenzodioxins

- To conduct a multi-generation study to assess effects on thyroid function and actions with associated neurodevelopmental studies in rodents; these studies should include the use of lower dose levels as well as iodine-deficient animals to better assess the risks to sensitive human populations.

- To obtain biomonitoring data to investigate the exposures of women of childbearing age and others who work on computers for long periods of time to these substances.

A Swedish study (Sjodin, A, 1995) found surprisingly high levels of these substances in the serum of clerks working full time at computer screens.

The Learning Disabilities Association of America, 2003

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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.

Ms. Lynn A. Delpire
U.S. Environmental Protection Agency
Exposure Assessment Branch

May 20, 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 pentabromodiphenyl ether.

Page 63 of the pentaBDE submission states, "With the exception of one study conducted in the United Kingdom...none of the studies found in the scientific literature measure the commercial octaBDE product or attribute the occurrence of individual BDEs to the commercial pentaBDE product." Rice et al. (2002) explained how releases of commercial octaBDE and commercial pentaBDE could account for the occurrence of several of the BDE congeners they found in fish obtained from the Des Plaines River, IL. Rayne and Ikonomou (2002) found that "Reconstructed PBDE congener patterns from SPMDs [semipermeable membrane devices] deployed in Fraser River near Vancouver [British Columbia, Canada] suggest that commercial penta- and octa-BDE mixtures are the source of PBDEs in aquatic systems from this urban and industrial area."

There are some inconsistencies (or typographical errors) that make it more difficult to understand the assumptions used in the consumer exposure assessment. Pages 71 and 91 show 410 ng/g as the concentration of BDEs in indoor dust, while page 97 and the appendix show 784 ng/g as the concentration of BDEs in indoor dust. Page 111 shows 170 ng/g as the concentration of BDEs in fish, while page 63, page 91, and the appendix show 72 ng/g as the concentration of BDEs in fish. Page 111 shows 67 ng/g as the concentration of BDEs in breast milk, while page 76, page 91, and the appendix show 42.8 ng/g as the concentration of BDEs in breast milk. In each case, the concentration shown in the appendix is the one that was most likely used in the exposure assessment. It will be easier for the Panel to review the submission if these inconsistencies can be clarified before the meeting.

References

Rayne S and Ikonomou MG. 2002. Reconstructing Source Polybrominated Diphenyl Ether Congener Patterns from Semipermeable Membrane Devices in the Fraser River, British Columbia, Canada: Comparison to Commercial Mixtures. Environmental Toxicology and Chemistry, 21 (11): 2292-2300.

Rice CP, Chernyak SM, Begnoche L, Quintal R, Hickey J. 2002. Comparison of PBDE composition and concentration in fish collected from the Detroit River, MI and Des Plaines, River, IL. Chemosphere, 49: 731-737.

I look forward to attending the Peer Consultation Meeting as an observer.

Sincerely yours,

/s/

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

Ms. Barbara McElgunn
Learning Disabilities Association

Learning Disabilities Association
ofAmerica
4156 Library Road · Pittsburgh, PA 15234-1349 · 412/341-1515 · FAX 412/344 0224

Submission to theVoluntary Children's Chemical Evaluation Program (VCCEP) Peer Consultation Meeting on Octabromodiphenyl Ether and Pentabromodiphenyl Ether

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. There is alarming evidence the prevalence of ADHD[28], learning disabilities[29] and autism[30] are increasing in recent years. A report in the Journal of the American Medical Association (2000) reported that the number of children prescribed psychotropic drugs increased by a factor of three between 1990 and 1995. Between 1990 and 1995 Health Canada data found an increase in the quantities of methylphenidate (Ritalin) prescribed increased by a factor of 3-4. The drug-tracking firm, IMS Canada reported another 55% increase in prescriptions for Ritalin between 1996 and 2001. Society must consider the contributions of chemicals that disrupt the developing nervous system in the etiologies of these disorders. The evidence from both experimental animal and clinical research from the few neurotoxic chemicals that have been studied to date is compelling.

The PBDEs are chemicals that are in widespread use, and have been found in all media to date, including human tissue at levels that appear to be doubling every three to five years. This large population distribution may well become a major health problem in the near future and brings into focus the inadequacies of our current regulatory systems to evaluate chemicals that have environmental properties and mechanisms of toxicity that are similar to those of the structurally related PCBs and dibenzodioxins, and that are also ubiquitous, and rising, in the environment.

These chemicals have been found to be persistent, bioaccumulative, highly lipophilic, developmentally neurotoxic and disruptive to thyroid systems 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 Petreas et al. indicates that California women have levels 3-10 times

[28] 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.
[29] Center for Learning Disabilities. Students with learning disabilities: A national review. Annual Report to Congress, 2001.
[30] Byrd RS. Report to California legislature re jump in autism rates, 2002.

higher than European women measured during the same period[31]. The activity and structural similarity of PBDEs and PCBs, known developmental neurotoxicants, are another cause for concern to LDA.

Petreas et al[32] found no evidence of BDE-47 in stored samples of breast milk from California in the 1960s, but BDE-47 was present in all of the fat samples and in 24 of 50 tissue samples during the late 1990s. US body burdens were reported to be 3-10 times higher than those in Europe. A study of PBDE levels in maternal and cord blood (Mazdai 2003) found relatively high levels from 15- 580 ng/g lipid in maternal serum and 14- 460 ng/g in fetal samples[33] --far exceeding levels that moved Sweden to ban PBDEs in that country to protect the health and development of its citizens. These concentrations can be compared to the PCB concentrations (expressed in terms of the fat concentrations in maternal milk) reported by Jacobson and Jacobson [34]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.[35] linked exposure to tetra-BDE and penta-BDE, 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-old 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.

PBDEs have been found to be able to disrupt the normal functioning of thyroid hormones in several ways. It is recognized that normal maternal, fetal, and infant thyroid hormone levels are critical for brain development. Learning and behavioral effects have been noted from alterations in thyroid in experimental animal studies, and from clinical studies of the effects of thyroid hormone deficiency before birth, or beyond[36]. Thyroid hormone is critical to the expression of many vital processes necessary for normal brain development[37]. 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[38]. Many other chemicals and compounds have anti-thyroid actions, but these have not been studied for their possible links to neurodevelopmental effects.

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[32]Petreas M., She, FR., et al. High body burdens of 2, 2'4, 4'-tetrabromo diphenyl ether (BDE-47) in California women. Environmental Health Perspectives, doi: 10. 1289/ehp.6220

[33] Mazdai et al. Polybrominated diphenyl ethers in maternal and fetal blood samples. Environmental Health Perspectives, doi:10. 1289/ehp.6146, 2003.

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

[35] Ericksson P, Jacobsson W, & Fredriksson, A. (2001) Brominated Flame Retardants: A novel class of developmental toxicants in our environment? Environmental Health Perspectives, 109 (9)

[36] 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.

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

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.[39] makes this point: "This analysis suggests that a business-as-usual scenario, where environmental concentrations of brominated flame retardants, 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 precautionary Principle, as codified in several international treaties, states that there is an ethical imperative to act on the weight of evidence to prevent harm through timely action, even if the science is incomplete.

The European Union has moved to ban the octa-BDEs in July 2003

In conclusion our association recommends:

- That precautionary action be taken to ban the production of Octa-BDE in order to mitigate exposures to the public, as in the European Union. Further studies are recommended, but will take a decade or more complete, during which time the public will be exposed to rising levels of these substances, with unknown but possibly serious consequences.

- That USEPA immediately work to 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 environmental levels of mixtures of various PBDE congeners, PCBs and other compounds with similar modes of action.

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

- That further risk assessments be based on current practices related to the life-cycle of the substance imported or produced in the United States.

[39] Muir T, Alaee M. (2003). The costs and benefits of brominated flame retardants (BFRs) and alternatives. Organohalen Compounds, in press.

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The Learning Disabilities Association of America, 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.

June 2003
The Learning Disabilities Association of America
.

Ms. Lynn A. Delpire
U.S. Environmental Protection Agency
Exposure Assessment Branch

May 20, 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 octabromodiphenyl ether.

Page 57 of the octaBDE submission states, "With the exception of one study conducted in the United Kingdom...none of the studies found in the scientific literature measure the commercial octaBDE product or attribute the occurrence of individual BDEs to the commercial octaBDE product." Rice et al. (2002) explained that releases of commercial octaBDE and commercial pentaBDE could account for the occurrence of some of the BDE congeners they found in fish obtained from the Des Plaines River, IL. Rayne and Ikonomou (2002) found that "Reconstructed PBDE congener patterns from SPMDs [semipermeable membrane devices] deployed in Fraser River near Vancouver [British Columbia, Canada] suggest that commercial penta- and octa-BDE mixtures are the source of PBDEs in aquatic systems from this urban and industrial area."

References

Rayne S and Ikonomou MG. 2002. Reconstructing Source Polybrominated Diphenyl Ether Congener Patterns from Semipermeable Membrane Devices in the Fraser River, British Columbia, Canada: Comparison to Commercial Mixtures. Environmental Toxicology and Chemistry, 21 (11): 2292-2300.

Rice CP, Chernyak SM, Begnoche L, Quintal R, Hickey J. 2002. Comparison of PBDE composition and concentration in fish collected from the Detroit River, MI and Des Plaines, River, IL. Chemosphere, 49: 731-737.

I look forward to attending the Peer Consultation Meeting as an observer.

Sincerely yours,
/s/

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

APPENDIX E

Sponsor Presentation Slides

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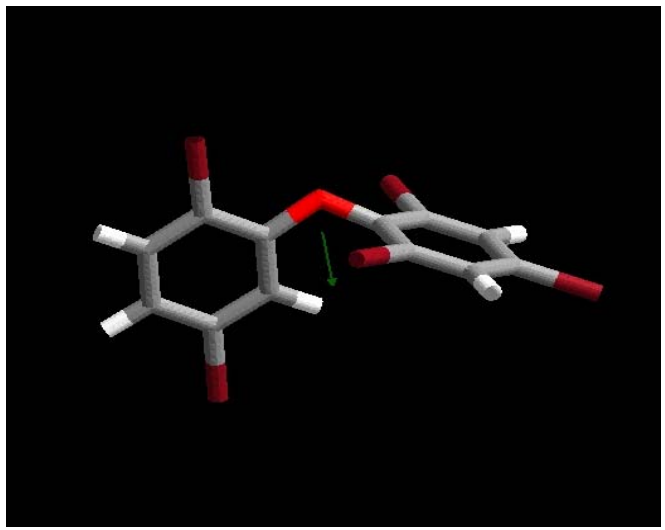
VCCEPP Tier 1 Review of the Commercial Pentabromodiphenyl Ether Product: Introduction



Robert Campbell
MS Industrial Hygiene
Great Lakes Chemical Corporation
June 3, 2003

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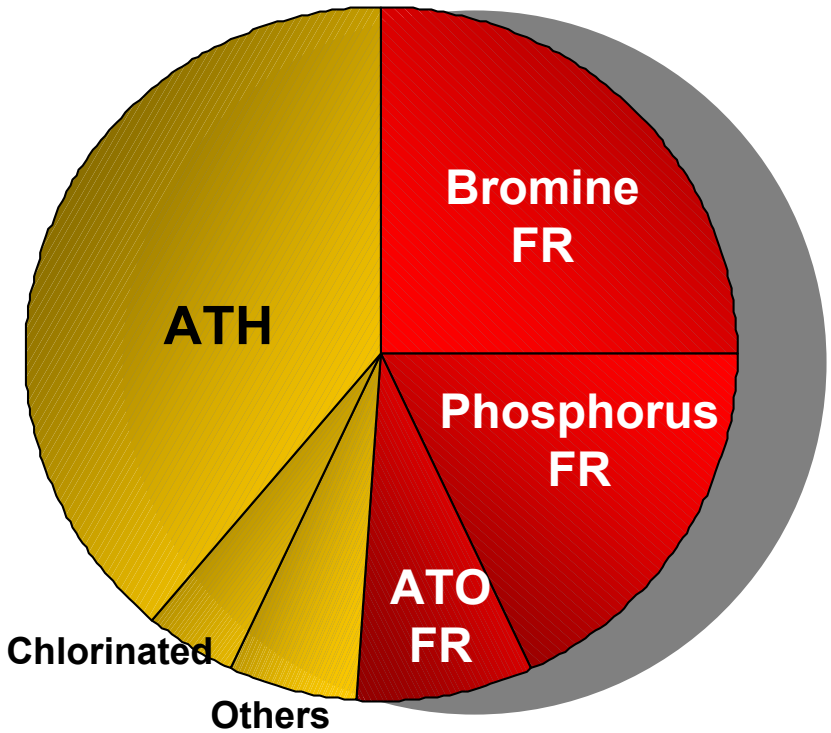
Global FR Market



Total Market Size ~ 2,200M lbs

Source: Townsend Associates

GLCC Markets in **RED**

GLCC Supports Innovation and Stewardship in all major FR markets

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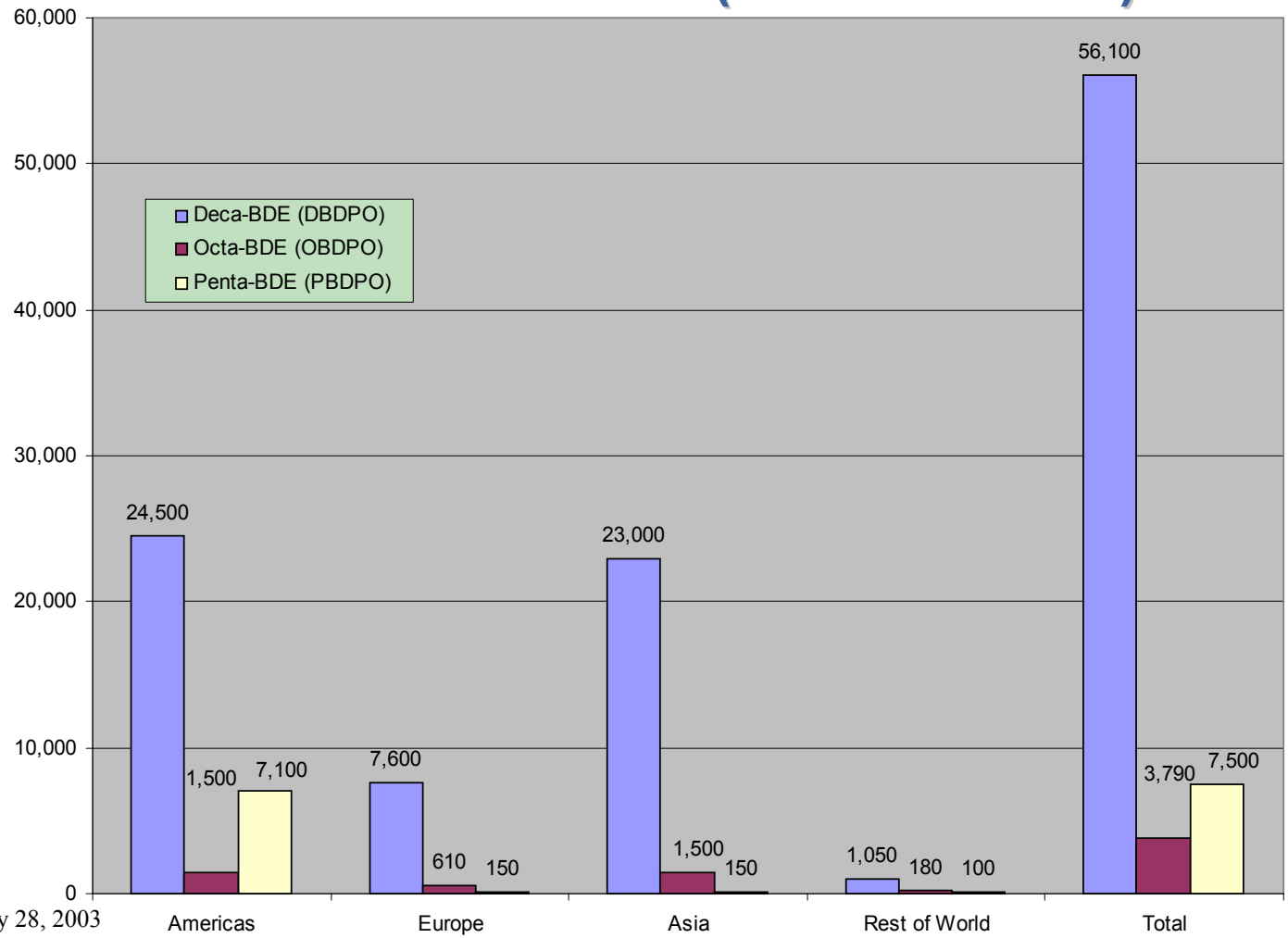
Brominated Diphenylethers Estimated Market Demand in 2001 (in metric tons)



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FR's Used in Foam

• Penta-BDE	• EU Ban July 2004
• TDCP	• EU Risk Assessment Underway
• TCPP	• EU Risk Assessment Underway
• *Chlorinated Paraffins*	• *Risk Reduction Planned*

Chlorinated Phosphates and Chlorinated Paraffins Are On EU Agenda

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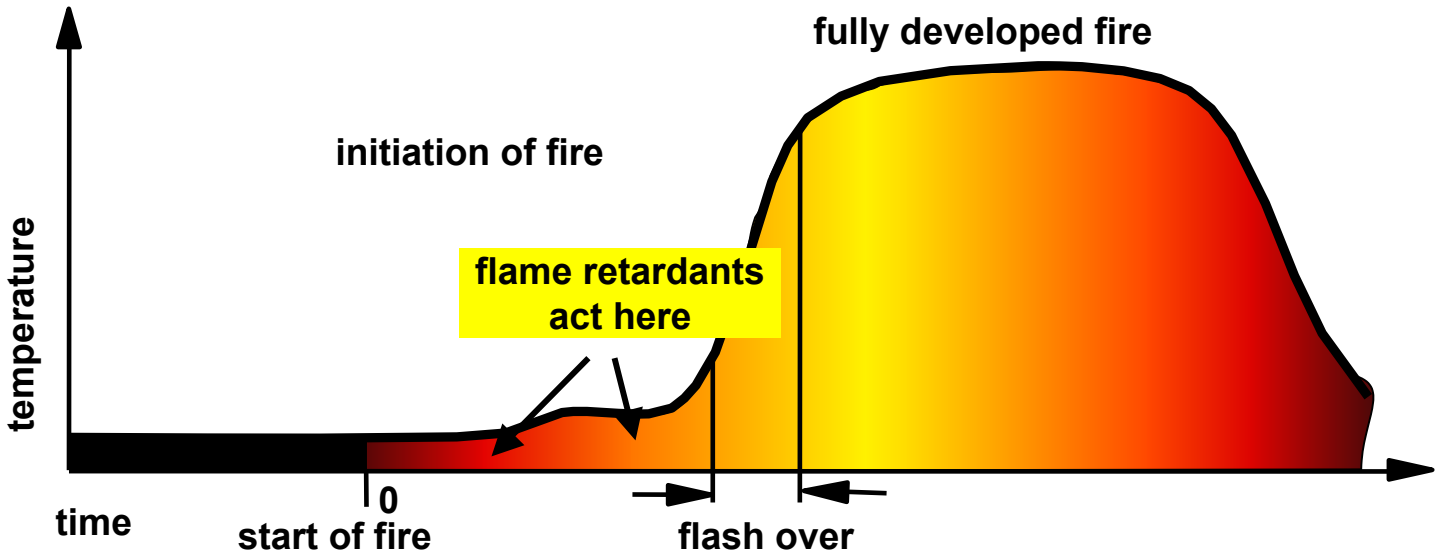
Why Are FRs Used?



- FRs save lives, reduce injuries as well as reducing the costs and impacts of fire damage
- FRs increase the time and temperature needed to ignite a product
- FRs reduce the rate of fire spread

Key Point: The FR must match the matrix

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Fire Safety Statistics: US vs Europe

80,000 people injured in fire incidents every year in Europe (burns, smoke inhalation), 60,000 of these are injured in their homes

In the U.S., 400,000 residential fires (3,500+ fire deaths / 20,000+ injuries)

Dormitory fire at Seton Hall University claims 3 lives and injures 58 students. Source - Non-flame retardant furniture.

80 x's more TV set fires per capita in Sweden than in the United States (Swedish National Testing and Research Institute)

2 people/day die from furniture fires in the US

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Non-FR Small Flame Fire Test

Incipient to Flashover in 3.5 minutes

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Accidental Fires Contribute to Environmental Pollution

- **Air -**
  - Particulates and gases
- **Water-**
  - Surface Run off
- **Solid Waste**
  - Demolition waste to landfill
- **Resources**
  - Replacement & reconstruction materials

LCA of FR vs. Non-FR TV's Demonstrated Much Lower PAH, HDD/DF Emission, etc.

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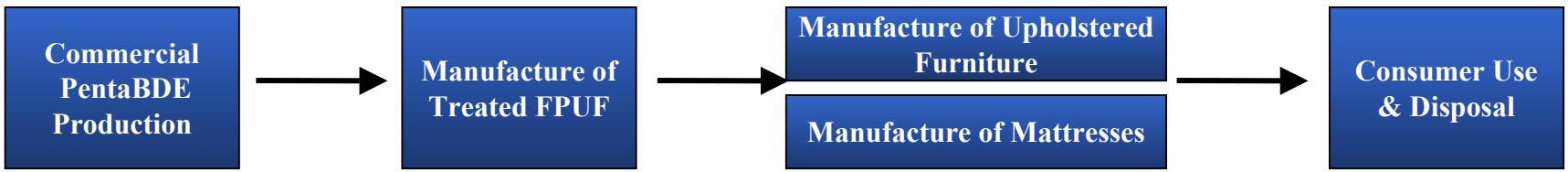
Commercial PentaBDE Product VCCEPP Review

- History -
  - Commercially available since the late 1960's
  - ~12 different manufacturing sites (US and Europe)
  - Used in hydraulic fluids, oil well completion fluids, roofing shakes, underground mine conveyor belting, Printed Circuit Boards, flexible PU foam, epoxies, textile treatments
- Present-
  - Focussed Manufacturing and Market
    - GLCC manufacturers at one site in the U.S.
    - Enhanced Product Stewardship Activities



>98% in the US goes to flexible polyurethane foam

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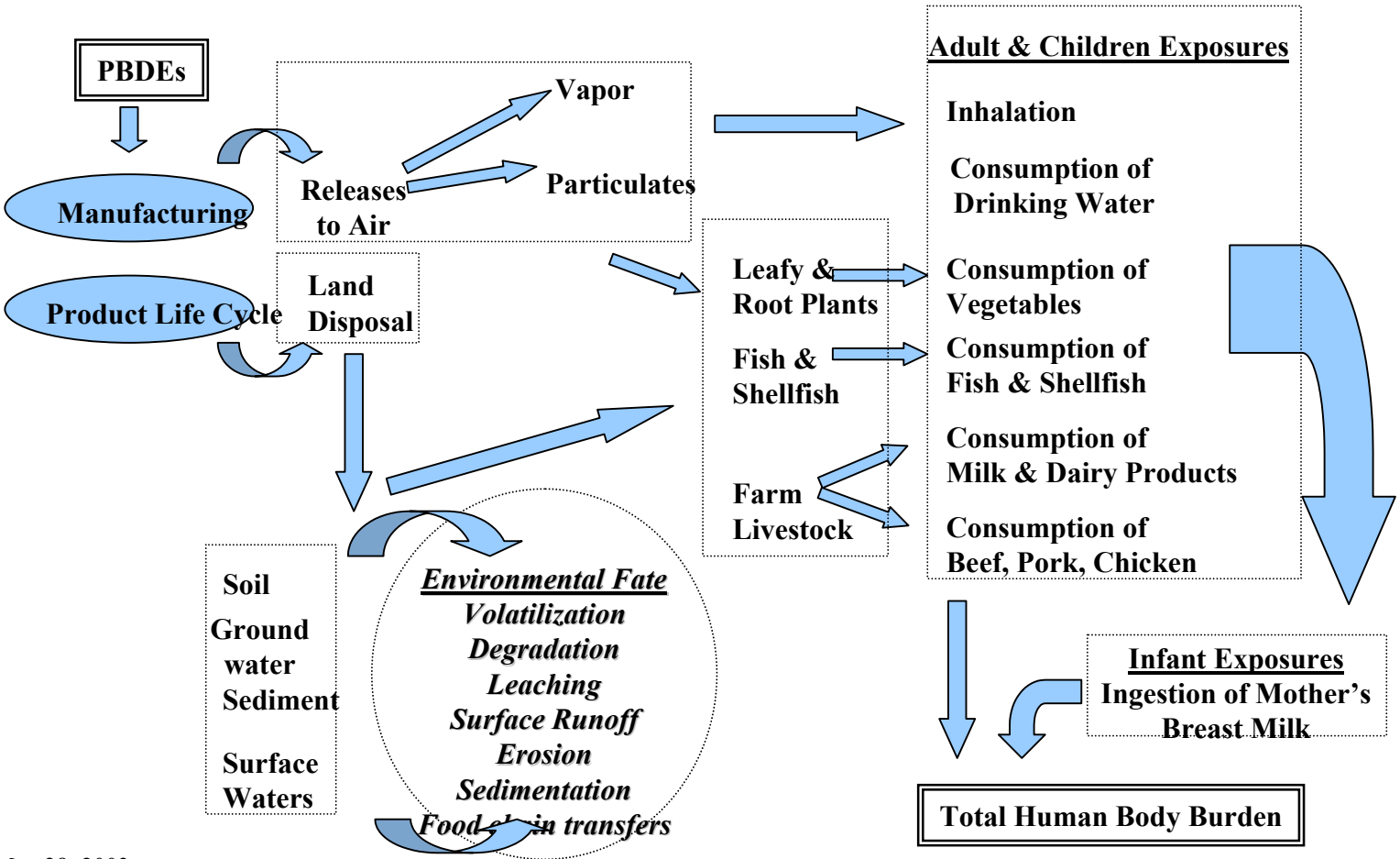
Human Exposure Model for PentaBDE



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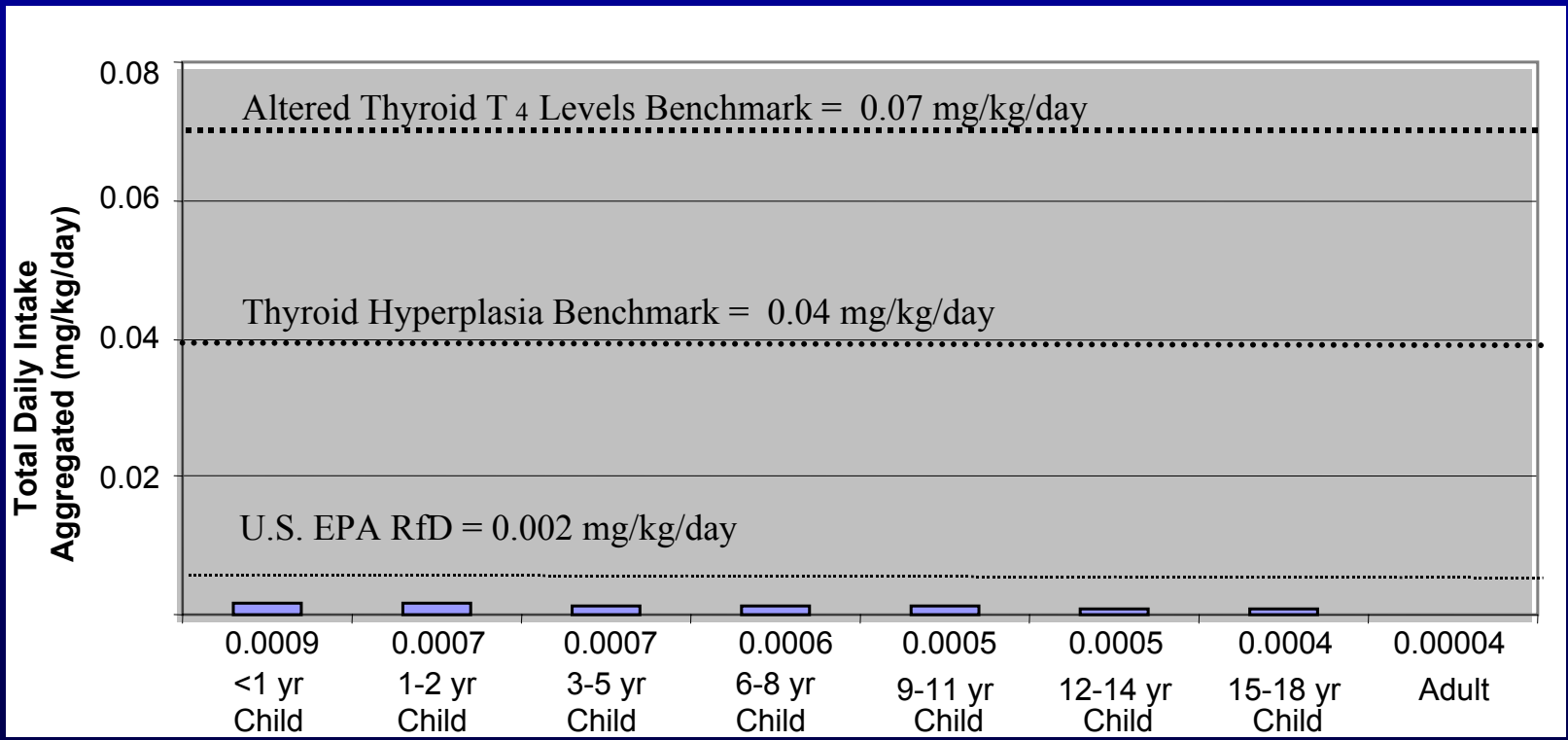
Theoretical Daily Intake vs Toxicity Benchmarks



Intake is Below the Relevant Effect Levels

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Industry Information Sites

- http://www.BSEF.COM
  - Bromine Science and Environmental Forum
- http://www.EBFRIP.ORG
  - European Brominated Flame Retardant Industry Panel
- http://www.Cefic.EFRA.ORG
  - European Flame Retardant Association

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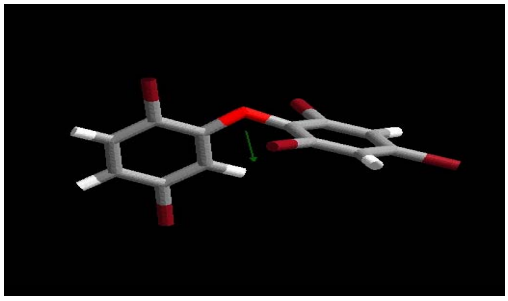
VCCEPP Tier 1 Review of the Commercial Pentabromodiphenyl Ether Product: Hazard Assessment



Tessa Serex, Ph.D., D.A.B.T.
Great Lakes Chemical Corporation

June 2003

May 28, 2003

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Commercial PentaBDE Product Toxicokinetic Profile

- Absorption
  - Oral absorption varies greatly among species
    - TetraBDE for example:
      - Mouse 46%
      - Rat 86%
      - We used 86% for the exposure assessment
  - Percutaneous *in vitro* dermal absorption is 3.13%
  - For inhalation exposures a default estimate of 75% was used

May 28, 2003

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Commercial PentaBDE Product Toxicokinetic Profile

- Distribution
  - Adipose tissue
  - Liver
- Elimination
  - Major pathway: feces
  - Minor pathway: urine, breastmilk
  - Half-lives increase with degree of bromination
  - TetraBDE eliminated faster than pentaBDE or hexaBDE

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Commercial PentaBDE Product Toxicology

- Not acutely toxic
  - Oral, Inhalation, Dermal
  - Sensitization
- Not Genotoxic
  - no reverse mutations, with or without S9 activation
  - no chromosome aberrations in human lymphocytes, *in vitro*

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Commercial PentaBDE Product Toxicology

- Subchronic studies revealed characteristic adaptive response in liver of treated animals:
  - induction of enzymes involved in xenobiotic metabolism
    - increased liver weights and increased size of hepatocytes
    - cytoplasm described as “ground glass” in appearance
    - NO ↑ enzymes that indicate liver damage, SGOT, etc.

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Commercial PentaBDE Product Toxicology

- Subchronic studies also revealed effects on thyroid homeostasis
  - Typically characterized by ↓ in T_4, small or no change in TSH or T_3
  - Possibly related to the induction of UDPGT, resulting in ↓ free T_4
  - Thyroid hyperplasia
  - Rats likely more sensitive to this effect than humans, differences in buffering capacity

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Commercial PentaBDE Product Toxicology

- Reproductive/Developmental Findings
  - ↓ T_4 levels have been reported in treated dams and offspring (T_3, TSH levels not affected).
  - Developmental data in rats and mice, no effects on pregnancy or standard developmental endpoints have been reported.
  - Changes in neurobehavioral parameters in some, but not all, studies of rodents exposed to pentaBDE or other relevant congeners

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Commercial PentaBDE Product Toxicology

- Developmental Neurobehavioral Alterations: Current data set not suitable for quantitative analysis
  - Sporadic changes in levels of activity observed
  - Inconsistent dose-response effect
  - Small numbers of subjects
  - Repeated measures not employed
  - Litter based statistics not employed
  - New data (Taylor et al., 2003), suitable for quantitative analysis?

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Commercial PentaBDE Product
Possible Relevant Health Endpoints

- Characteristic adaptive response in the liver, enzyme induction - cannot be said *a priori* this is adverse
- Effects on the thyroid appear to be key non-cancer hazard.
  - Changes in T_4 homeostasis in neonate
  - Thyroid hyperplasia

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Table 1. Health endpoints and screening toxicity values used in the Tier 1 risk assessment of hypothetical exposures to children and adults.

Human Health Endpoint	Toxicity Value	Relevant Study
Change in T4 Homeostasis	0.2 mg/kg/day	Zhou et al. (2002)
Thyroid Hyperplasia	0.04 mg/kg/day	IRDC (1976)
Liver Enzyme Induction	0.002 mg/kg/day	U.S.EPA IRIS Reference Dose, based on Carlson (1980)

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Commercial PentaBDE Product Changes in T4 Homeostasis

- Toxicity value was based on changes in T_4 levels in the fetus or neonate exposed *in utero* (Zhou et al., 2002):
  - The $BMDL_{10}$ was **4.5 mg/kg/day** for data from PND 4 and **5.9 mg/kg/day** for data from PND 14.
  - By applying an uncertainty factor of 30 (3 for interspecies extrapolation and 10 intraspecies variation), the resulting value is **0.2 mg/kg/day.**

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Commercial PentaBDE Product Changes in T4 Homeostasis

- Children's health is adequately protected by this benchmark
  - Humans are more resistant to changes in circulating thyroid hormone levels due to significant buffering capacity of binding proteins and lower sensitivity to alterations
  - The relevance of changes in T_4 and TTR binding in rats to humans is questionable. Rat thyroid more sensitive to physiological perturbations than humans due to the shorter half-life of T_4 in rats, also differences in transport proteins and more easily induced UDPGT in rats compared to humans
- Therefore, rats are more susceptible than humans to decreases in circulating thyroid hormone levels and associated effects

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Commercial PentaBDE Product
Thyroid Hyperplasia

- $BMDL_{10}$s were derived using data from Zhou et al. 2001; female rats after 4 days of exposure, Zhou et al. 2002; dams on GD 20 or PND 22, WIL 1984 and IRDC 1976; male and female rats after 28 or 90 days of exposure and Fowles et al. 1994; male and female mice after 14 days of exposure
- $BMDL_{10}$s for thyroid hyperplasia ranged from 4 mg/kg/day for male rats to 9.6 mg/k/day for female rats
  - The lowest $BMDL_{10}$, **4 mg/kg/day**, selected as point of departure
  - Uncertainty factor of 100 (3 for interspecies extrapolation, 10 for human variability, and 3 for duration of dosing), resulting value was **0.04 mg/kg/day**

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Commercial PentaBDE Product
Thyroid Hyperplasia

- This benchmark is adequately protective of human health
  - Both rats and humans have significant capacity to compensate for small changes in T_4 and maintain homeostasis. Severity did not increase with longer exposure duration in rats.
  - Thyroid hyperplasia likely occurs in the rat in response to increased demand for thyroid hormone from an organ that is functioning near maximum capacity to maintain homeostasis.
  - Thyroid hyperplasia would not be expected in humans due to the presence of binding proteins (e.g., thyroid binding globulin) that allow humans to compensate for small decreases in thyroid hormone levels.
- Therefore, rats are more susceptible than humans to decreases in circulating thyroid hormone levels and associated effects

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Commercial PentaBDE Product Liver Enzyme Induction

- Liver enzyme induction is not an appropriate endpoint
  - U.S. EPA RfD for the commercial pentaBDE product is based on increased hepatic enzyme induction in rats reported by Carlson (1980)
  - Enzymes induced were those involved in endogenous and xenobiotic metabolism, enzymes indicative of cellular damage in the liver e.g., SGOT and SGPT were unchanged even at high doses
  - A higher NOAEL (1.77mg/kg/day) might have been identified if Carlson (1980) had examined the livers of rats in the high-dose series (0, 5.01, 10.02, or 20.04 mg/kg/day) microscopically
  - In the WIL (1984) 90-day study, rats were exposed to higher doses (up to 100 mg/kg/day), the microscopic changes in the liver were considered adaptive changes, consistent with enzyme induction
  - It can not be said *a priori* that enzyme induction is an adverse effect

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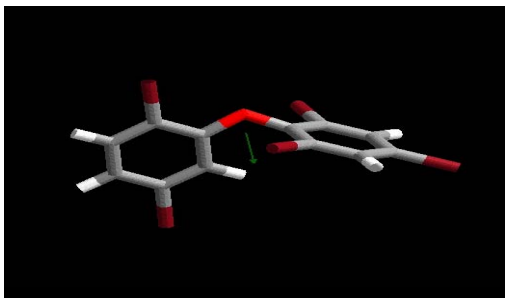
VCCEPP Tier 1 Review of the Commercial Pentabromodiphenyl Ether Product: Exposure Assessment



Richard J. Wenning
ENVIRON International Corporation

June 2003

Mary 21, 2003

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Commercial PentaBDE Product
BDEs in the Environment

- Very few data focus on understanding the fate of the commercial product in the environment.
- Among the 209 individual PBDEs, abiotic and biotic studies conducted over the past decade typically report levels of 10 to 12 BDE congeners:
  - triBDE = BDE-28,
  - tetraBDE = BDE-47, BDE-49, BDE-66,
  - pentaBDE = BDE-85, BDE-99, BDE-100,
  - hexaBDE = BDE-153, BDE-154,
  - heptaBDE = BDE-183, BDE-190,
  - decaBDE = BDE-209

Commercial PentaBDE Product
tetraBDEs (~ 24-38%)
pentaBDEs (~ 50-62%)
hexaBDEs (~ 4-12%)

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Commercial PentaBDE Product
Overall Approach

- Did not rely on environmental fate models to predict exposure point concentrations.
  - Hypothetical exposures were based on the most representative (yet protective) levels reported in available U.S. environmental studies. Data from other countries used where U.S. data was unavailable.
- U.S. environmental and biomonitoring data on levels of tetra- through hexa-BDE congeners were assumed to be indicative of exposure to the commercial pentaBDE product.
  - Where data was reported for individual BDE congeners or groups, the congeners associated with the commercial pentaBDE product were summed and used in the Tier 1 assessment.

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Commercial PentaBDE Product Exposure Scenarios

Receptor Group	VCCEPP Tier 1 Exposure Scenarios		
	Workplace	Home, School, & Office	Ambient Environment
Children (0-18 yrs old)	✓ Worker's home	✓ Home ✓ School	✓Air, soil, foods ✓Human milk (<1 yr old)
Adults	✓ PentaBDE production ✓ Chain of Commerce ✓ Worker's home	✓ Home ✓ School ✓ Office	✓Air, soil, foods ✓Recreational fishing

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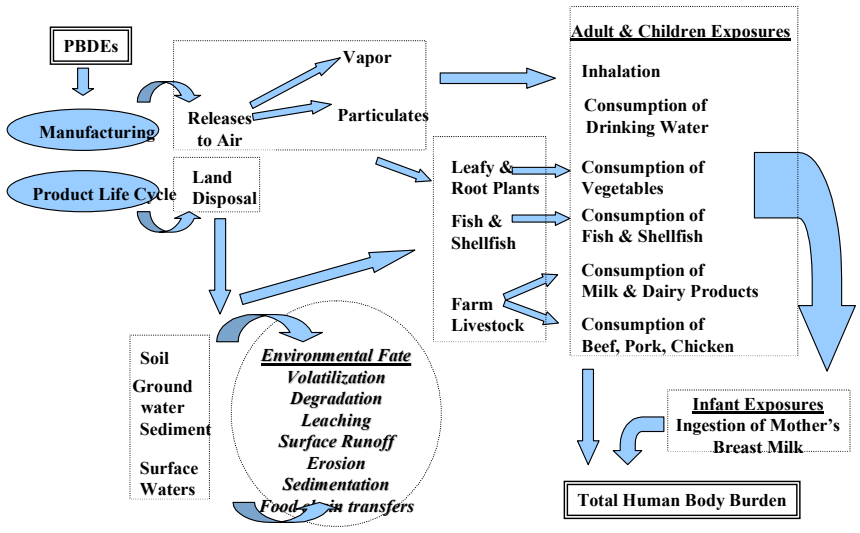
Human Exposure Model for PentaBDE



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Commercial PentaBDE Product Exposure Pathways

Exposure Scenario	Exposure Routes			
	Inhalation	Dermal Contact	Incidental Ingestion	Consumption of Foods
Primary & C-of-C Workplaces	✓ Vapors	✓ On the job ✓ Doing laundry ✓ House floor dust	✓ On the job ✓ Doing laundry ✓ House floor dust	--
Home, School, & Office	✓ Particulates (inhaled & swallowed)	✓ Indoor dust	✓ Indoor dust ✓ Mouthing cushions at home (<1 to 5 yr olds)	--
Ambient Environment	✓ Particulates (inhaled & swallowed)	✓ Soil	✓ Soil	✓ Meat ✓ Vegetables ✓ Dairy ✓ Fish ✓ Fats & oils ✓ Eggs ✓ Human milk (<1 yr old) ✓ Recreationally caught fish

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Commercial PentaBDE Product Exposure Point Concentrations

Exposure Scenario	Media	Concentration	Reference
Workplace	Indoor Air	18 ug/m^3	ECB (2000), based on saturated vapor pressure
Home, School & Office	Indoor Air	1.3 ng/m^3	Sjodin et al. (2001a)
	Indoor Dust	410 ng/g	Knoth et al (2002)
	Saliva	14 ug/L	ECB (2000), based on water solubility at 25ºC
Ambient Environment	Ambient Air	52 pg/m^3	Stranberg et al. (2001)
	Soil	76 ug/kg	Hale et al. (2002)
	Leafy & Root Vegetables	0.13 ng/g wet wt.	Ohta et al. (2002)
	Meat	0.05 ng/g wet wt.	Darnerud et al. (2000), unpublished Swedish market basket survey
	Dairy	0.02 ng/g wet wt.	
	Other Fats & Oils	0.16 ng/g wet wt.	
	Eggs	0.04 ng/g wet wt.	
	Fish Fillets	72 ng/g wet wt.	Manchester-Neesvig et al. (2001)
	Human Breast Milk	43 ng/g lipid wt.	Ryan et al. (2002)

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Commercial PentaBDE Product
Comparison to OctaBDE Exposure Levels

- Home, school, and office levels are assumed the same, with exception of transfer to saliva during mouthing activity by children < 5 yrs old.
- Ambient environmental levels are assumed the same for both products.

Exposure Scenario	Media	Concentration	
		OctaBDE Product	PentaBDE Product
Workplace	Indoor Air (primary manufacturing)	4.6 mg/m^3 (measured DE-79™ particulate)	18 ug/m^3 (saturated vapor pressure)
	Indoor Air (C-of-C)	1.7 ug/m^3 (measured decaBDE particulate)	--
	Indoor Air (recyclers/shredders)	0.0003 ug/m^3 (measured ΣPBDE particulate)	--
Home, School & Office	Transfer to Saliva	0.5 ug/L (from ABS Plastic Surfaces)	14 ug/L (from FPUF-treated cushion)

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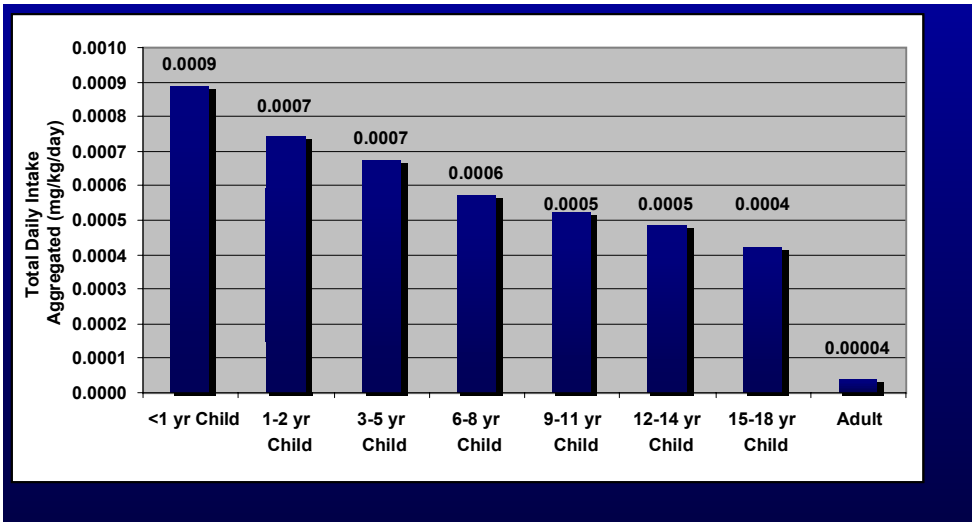
Commercial PentaBDE Product
Theoretical Total Daily Intake



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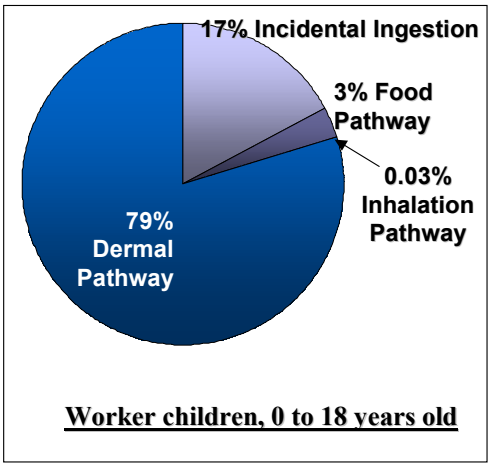
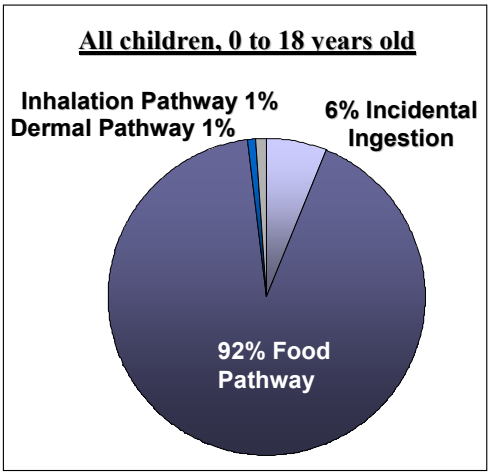
Commercial PentaBDE Product
Pathway Contributions to Total Exposure





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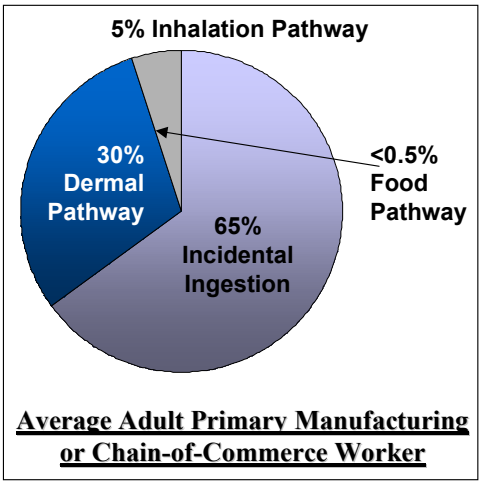
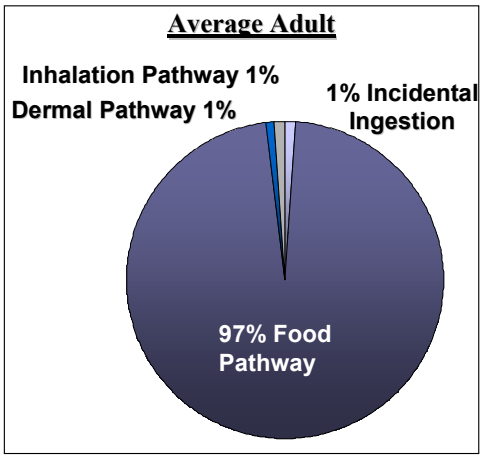
Commercial PentaBDE Product
Pathway Contributions to Total Exposure





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Commercial PentaBDE Product
Contributions to Food, Human Milk, and Mouthing Cushion Pathways

Receptor	Food Consumption Pathways						Breast Milk	Mouthing Cushions
	Fish	Vegetables	Dairy	Meat	Fats & Oils	Eggs		
<1 yr Child	4%	2%	2%	0.1%	0.03%	0.1%	92%	0.01%
1-2 yr Child	82%	10%	5%	1%	0.7%	0.8%	--	0.03%
3-5 yr Child	85%	9%	3%	2%	0.8%	0.6%	--	0.01%
6-8 yr Child	86%	8%	3%	1%	0.9%	0.5%	--	--
9-11 yr Child	86%	8%	3%	1%	0.7%	0.4%	--	--
12-14 yr Child	88%	8%	2%	1%	1%	0.5%	--	--
15-18 yr Child	88%	8%	2%	1%	0.8%	0.4%	--	--
Adult	90%	1%	2%	0.8%	0.2%	6%	--	--

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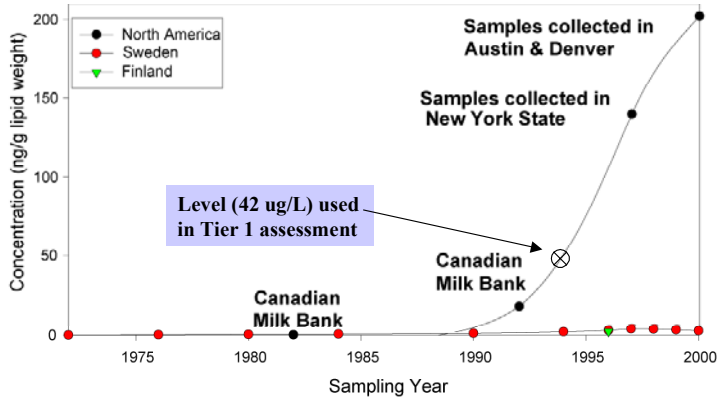
Commercial PentaBDE Product
Total BDE Levels in Breast Milk



Total BDE concentrations reported in North America and Europe [1].

[1] Results from the Canadian Milk Bank and New York State are from Ryan and Patry (2001); results from Denver and Austin are from Päpke et al. (2001); Swedish results are from Meironyté-Guvernius and Norén (2001), and Finnish data are from Strandman et al. (2000).

Mary 21, 2003

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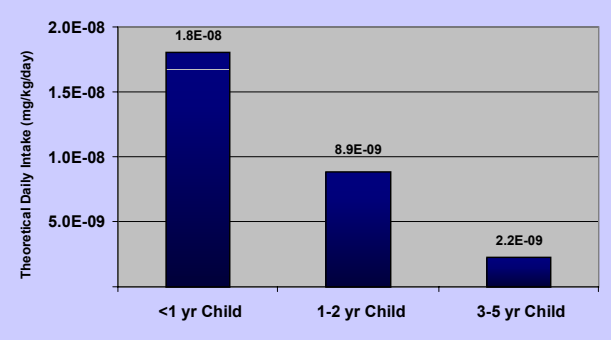
Commercial PentaBDE Product
Mouthing Treated FPUF Cushions



Theoretical daily intake of the commercial pentaBDE product by mouthing cushions with exposed treated FPUF.

$$\text{Daily intake} = \text{Water solubility limit} \times \text{Salivary flow rate} \times \text{Extraction Rate from FPUF} \times \text{Absorption rate} \times \text{Exposure frequency} \div \text{Body weight}$$

$$= \left[14\ \text{ug/L} \times 0.22\ \text{mL/minute} \times 4\ \% \times 90\% \times \text{Up to 9 minute/day} \right] \times 0.001\ \text{mg/ug} \times 0.001\ \text{L/ml} \div \text{Body weight}$$

Mary 21, 2003

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New Data and
a Reality Check

Mary 21, 2003

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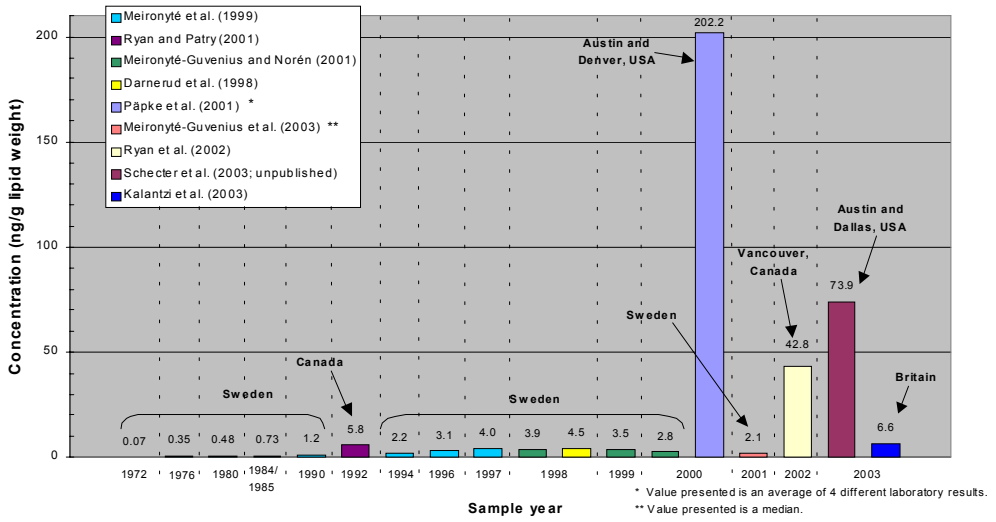
Mean Total BDE Levels in Breast Milk Over Time



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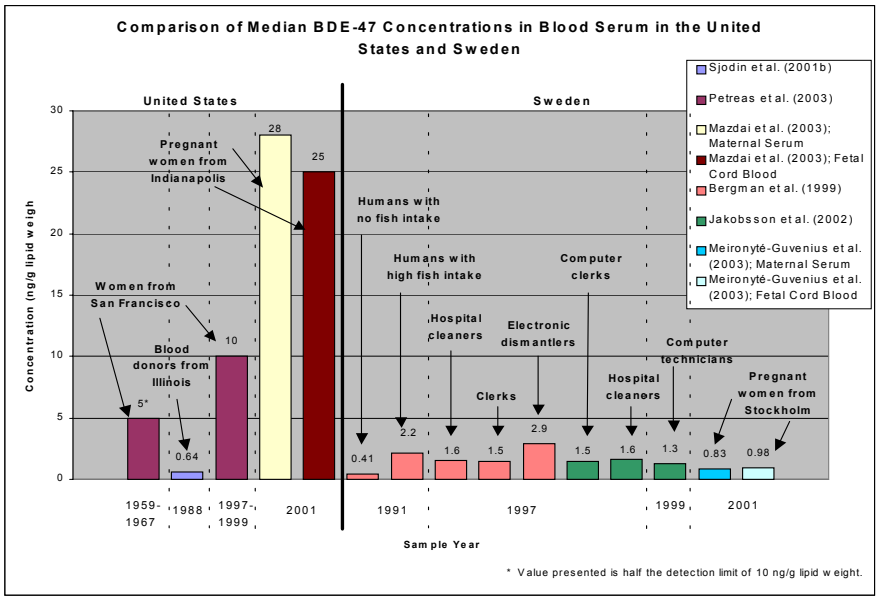
Measured Blood Serum Levels



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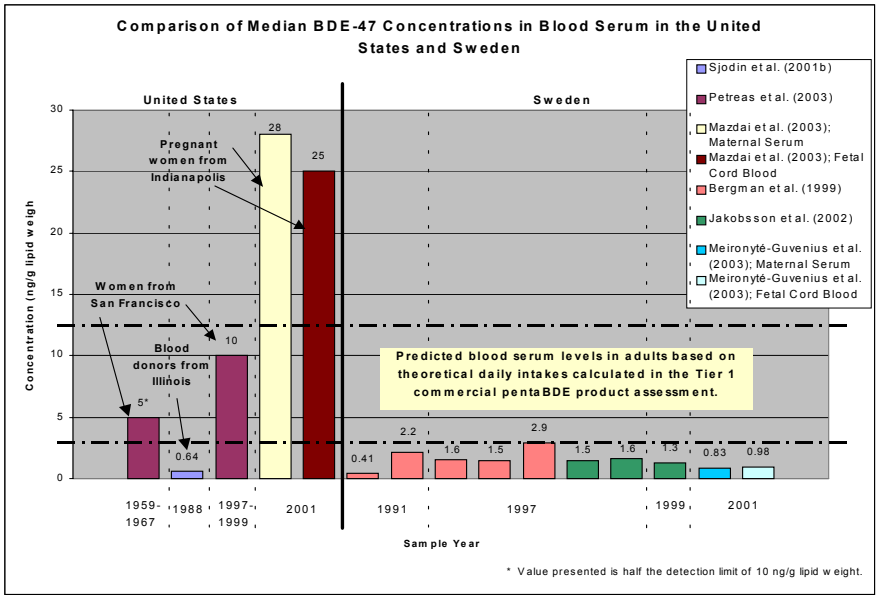
Measured vs Predicted Blood Serum Levels



Mary 21, 2003

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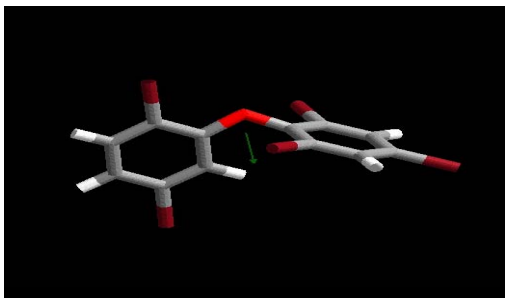
VCCEPP Tier 1 Review of the Commercial Pentabromodiphenyl Ether Product: Additional Exposure & Hazard Information



Tessa Serex, Ph.D., DABT
Great Lakes Chemical Corporation
Richard J. Wenning
ENVIRON International Corporation

May 28, 2003

June 2003

Great Lakes
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"Overnight Revelations"

Hazard information

- Screening toxicity benchmark for neurobehavioral changes in Long Evans female rats from Taylor et al. (2002)
- Consideration of human serum versus T_4 concentrations in Mazdai et al. (2003)

Exposure information

- Upper-bound estimates of exposure for key potential exposure pathways
  - Indoor house dust (dermal & incidental ingestion)
  - Fish consumption
  - Human milk ingestion by <1 year old children

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Commercial PentaBDE Product
Tier 1 Health Endpoints and Screening Toxicity Benchmarks

Human Health Endpoint	Toxicity Value	Uncertainty Factors	Relevant Study
Change in T_4 Homeostasis	0.2 mg/kg-day	10 intra-species	Zhou et al., 2002
Thyroid Hyperplasia	0.04 mg/kg-day	3 intra-species 10 human variability 3 dosing duration	IRDC, 1978
Neurobehavioral Changes	0.02 mg/kg-day	10 intra-species 10 inter-species 3 database	Taylor et al., 2002
	0.007 mg/kg-day	10 intra-species 10 inter-species 10 database	
Liver Enzyme Induction	0.002 mg/kg-day	10 intra-species 10 interspecies 10 dosing duration	U.S. EPA IRIS Reference Dose based on Carlson et al., 1980

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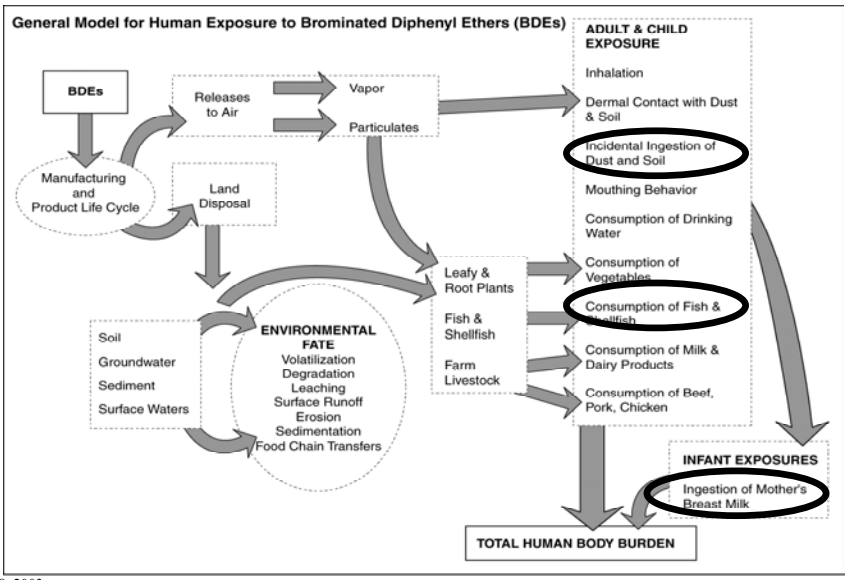
Human Exposure Model



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Indoor House Dust, Dermal & Ingestion Pathways for Children and Adults

Total PBDEs (ng/g)		CDI ** (mg/kg-d)	Hazard index *				
			Thyroid Effects	Dvlpmt Effects	LEI	Neurobehav. Effects	
36,000	Maximum; Rudel et al., unpublished; Cape Cod, MA houses	5×10^{-5} to 6×10^{-6}	0.001 to 0.0002	0.0002 to 0.00003	0.02 to 0.003	0.002 to 0.0003	0.007 to 0.001
19,124	Maximum; Knoth et al., 2002; German houses	Did not calculate					
748 ***	95UCL on mean; Knoth et al., 2002; German houses	1×10^{-6} to 1×10^{-7}	0.00004 to 0.00001	0.00001 to 0.000002	0.0008 to 0.0002	0.001 to 0.00002	0.0002 to 0.00005

* HI represents total hypothetical exposure in the home scenario and also includes theoretical intake via inhalation / incidental ingestion of indoor particulate and ingestion from mouthing cushions (parameters not varied).

** Calculation based on exposure factors in EFH (1997)

*** Value used in the exposure assessment.

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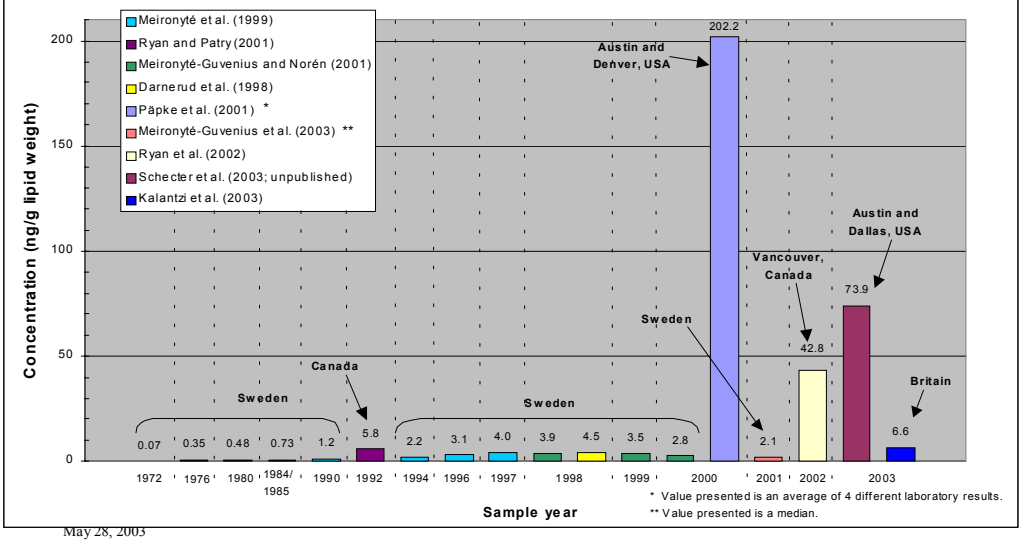
Mean Total BDE Levels in Breast Milk Over Time



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U.S. Human Milk, Ingestion by < 1 year old child

Total PBDEs (ng/g)		CDI (mg/kg-d)	Hazard index *				
			Thyroid Effects	Dvlpmt Effects	LEI	Neurobehav. Effects	
34	Median; Schecter et al., unpublished	1.3×10^{-4}	0.004	0.0007	0.07	0.007	0.02
42.8 **	Mean; Ryan et al., 2002	1.7×10^{-4}	0.005	0.0009	0.09	0.009	0.03
74	Mean; Schecter et al., unpublished	2.9×10^{-4}	0.008	0.002	0.2	0.02	0.04
282	Maximum; Ryan et al., 2002	1.1×10^{-3}	0.03	0.006	0.6	0.06	0.15
418	Maximum; Schecter et al., unpublished	1.6×10^{-3}	0.04	0.008	0.8	0.08	0.2

* HI represents total hypothetical exposure in the ambient environment scenario and also includes theoretical intake via the soil, ambient air, and food pathways (parameters not varied).

** Value used in the exposure assessment.

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Fish Consumption by Adults and Children

Total PBDEs (ng/g ww)		CDI (mg/kg-d)	Hazard index *				
			Thyroid Effects	Dvlpmt Effects	LEI	Neurobehav. Effects	
72 **	95UCL on mean; U.S. freshwater fish fillet dataset (n=95)	7×10^{-6} to 2×10^{-5}	0.004 to 0.0006	0.0009 to 0.0001	0.09 to 0.01	0.009 to 0.001	0.03 to 0.003
174	Maximum; U.S. freshwater fish fillet dataset	2×10^{-5} to 5×10^{-5}	0.005 to 0.001	0.001 to 0.0003	0.1 to 0.03	0.01 to 0.003	0.03 to 0.007
1,740	10x current maximum U.S. freshwater fish fillet result	2×10^{-4} to 5×10^{-4}	0.009 to 0.01	0.002 to 0.0025	0.2 to 0.25	0.02 to 0.025	0.05 to 0.07

* HI represents total hypothetical exposure in the ambient environment scenario and also includes theoretical intake via the soil, ambient air, breast milk, and food pathways (parameters not varied).

** Value used in the exposure assessment.

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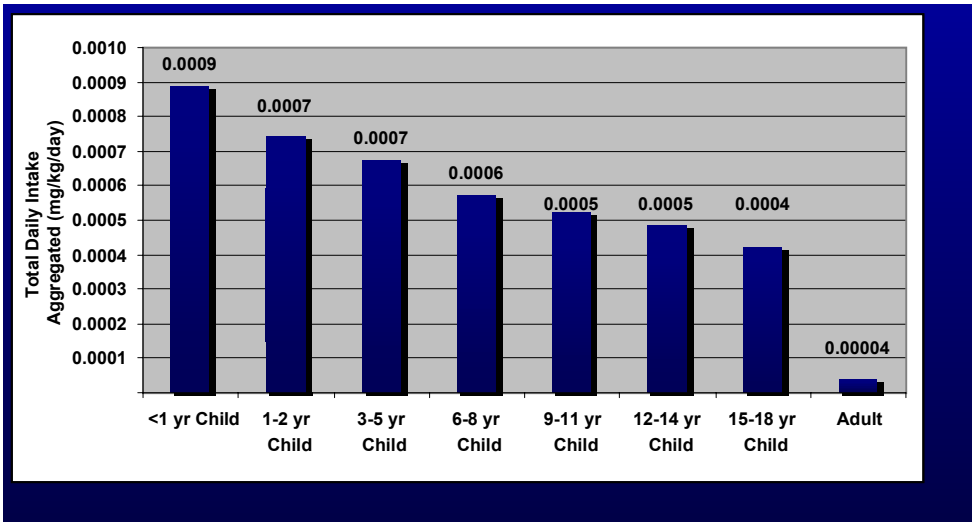
Commercial PentaBDE Product Theoretical Total Daily Intake Presented in the Tier 1 Assessment Report



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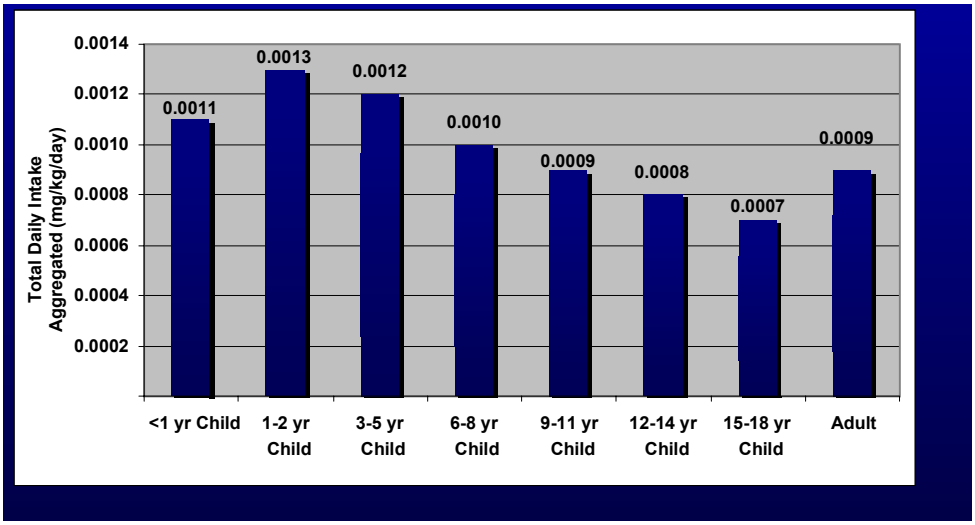
Commercial PentaBDE Product
Theoretical Total Daily Intake – Using Maximum EPCs for Fish, House Dust and Human Milk Pathways



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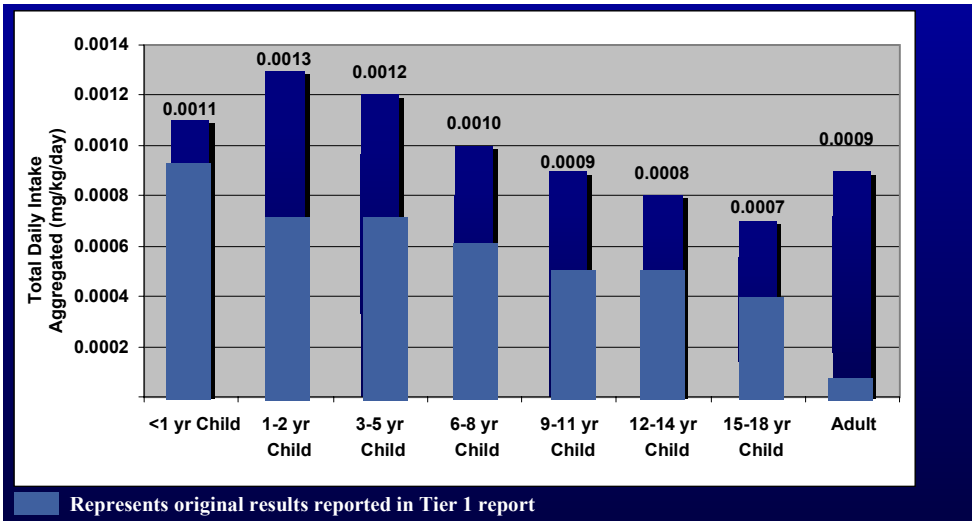
Commercial PentaBDE Product
Change in Theoretical Total Daily Intake Using Maximum EPCs for Fish, House Dust and Human Milk Pathways



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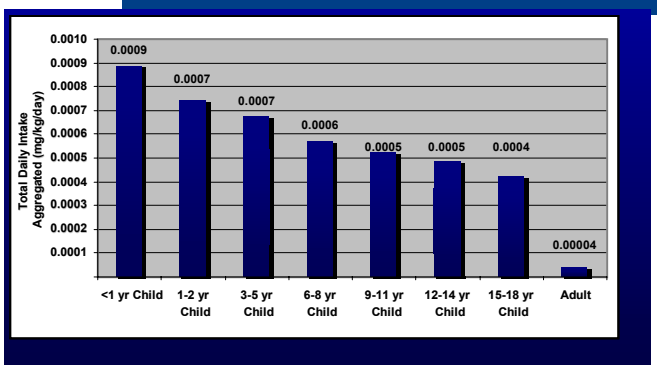
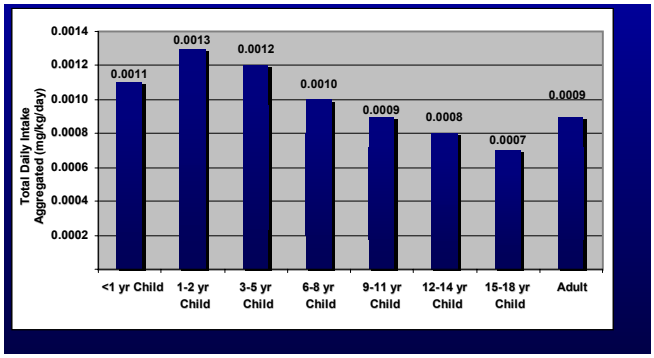


CDI Results reported in Tier 1 Assessment

CDI Results using maximum EPCs for fish, indoor dust, and human milk



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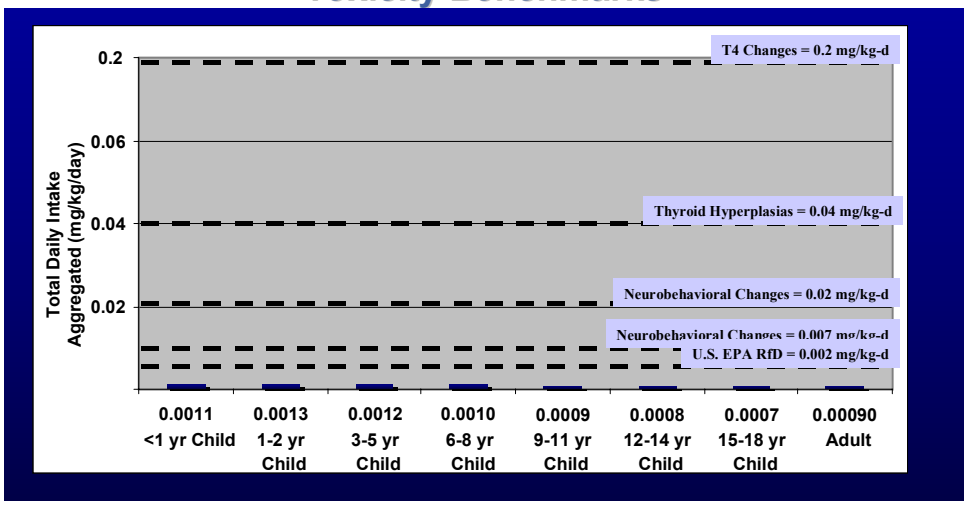
"Revised" Theoretical Daily Intake vs Toxicity Benchmarks



Intake is Below the Relevant Effect Levels

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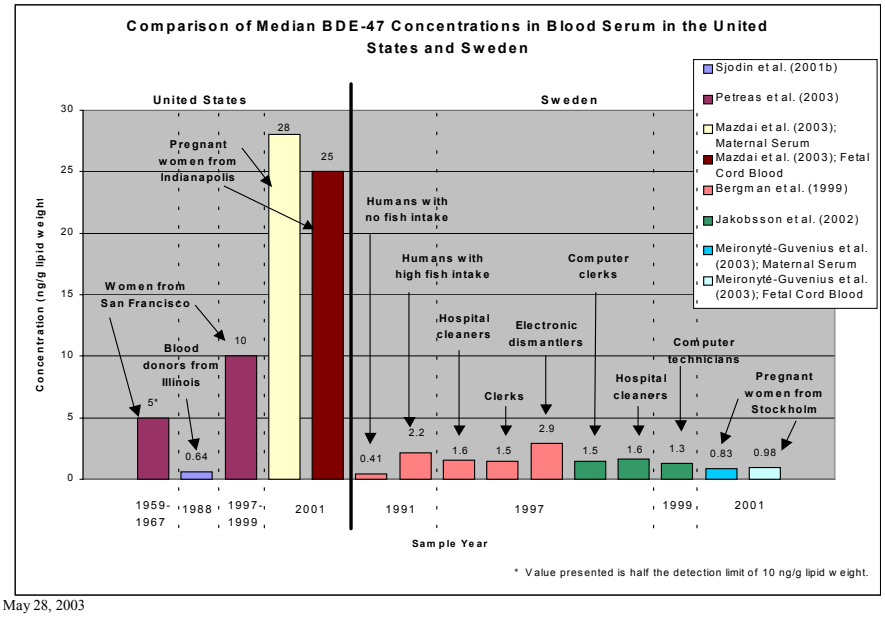
Measured Blood Serum Levels



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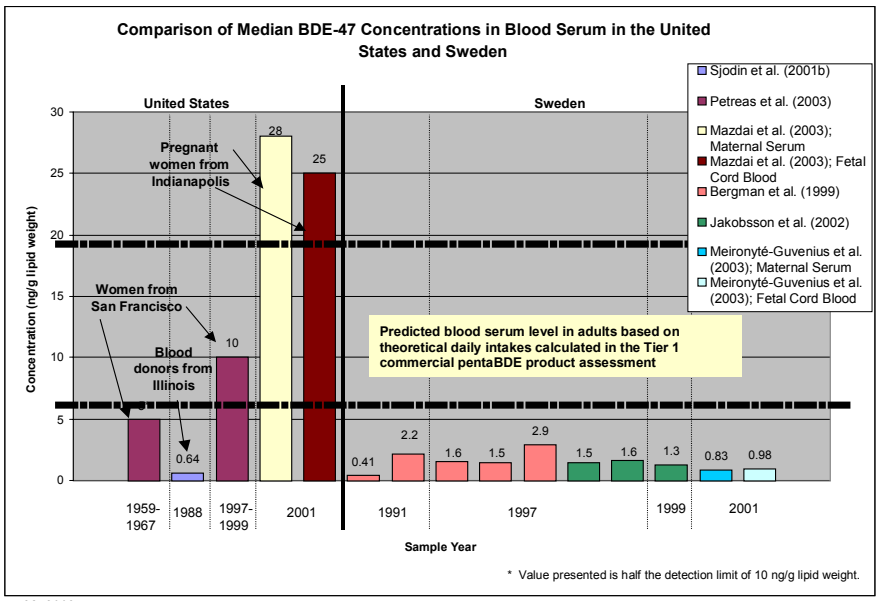
Measured vs Predicted Blood Serum Levels



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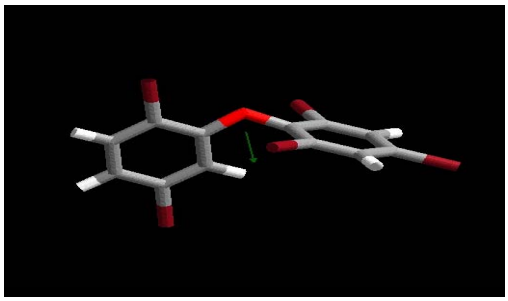
VCCEPP Tier 1 Review of the Commercial Pentabromodiphenyl Ether Product: Risk Characterization & Data Needs Assessment



Tessa Serex, Ph.D., DABT
Great Lakes Chemical Corporation

June 2003

May 28, 2003

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Commercial PentaBDE Product Assumptions and Major Findings

Hazard Assessment

- 3 screening benchmarks:
  - Change in neonatal T_4 homeostasis
  - Thyroid hyperplasia
  - Liver enzyme induction
- Absorption factors;
  - 3% dermal
  - 86% oral
  - 75% inhalation

Exposure Assessment

- Food pathways are predominant exposure in children and adults
- Children = Potential exposures highest for children <1 yr old
- Adults = Potential exposures highest in the primary or c-of-c workplace
  - All other sources of exposure are >4-fold lower in adults

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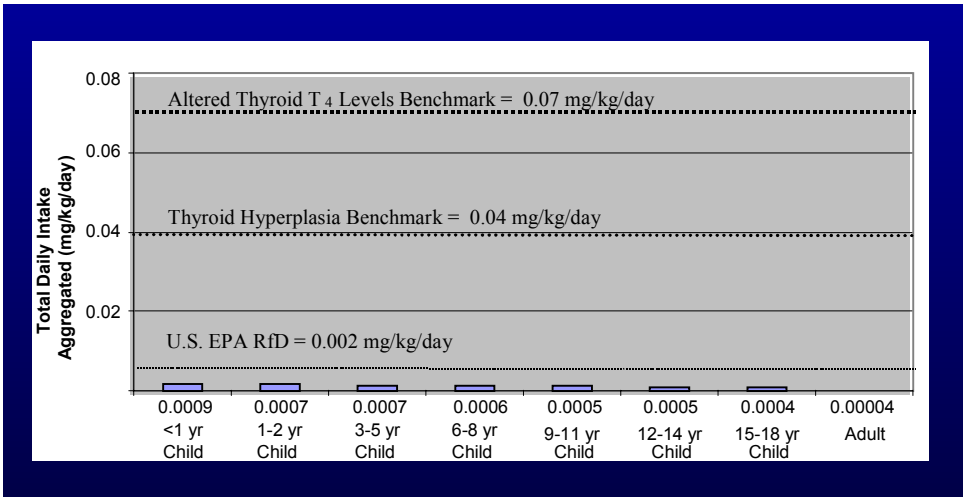
Theoretical Daily Intake vs Toxicity Benchmarks



Intake is Below the Relevant Effect Levels

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Commercial PentaBDE Product Conclusions

- Estimated exposures of children were below screening toxicity benchmark values.
- Estimated exposures of adults were also below screening toxicity benchmark values.

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Commercial PentaBDE Product Conclusions

	Hazard Indices for Potential Non-Cancer Effects		
	Liver Enzyme Induction U>S> EPA oral RfD	Thyroid Hyperplasia	Disruption of T_4 Homeostasis
Children	Not Appropriate	**0.006 to 0.02**	
Adults	Not Appropriate	**0.00001 to 0.0006**	
Workplace Adults	Not Appropriate	**0.4 to 0.7**	

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Commercial PentaBDE Product Uncertainties

Hazard Assessment

- Relevance of current IRIS oral RfD
- Extrapolation of endpoints from animals to humans
- Completeness of hazard dataset
- Sensitivity of children vs. adults

Exposure Assessment

- Sources of exposure
- Overlap of penta and octa congeners
- Levels in different food products not specific to the U.S.
- Overestimates of exposure, double counting

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Data Needs Assessment

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Commercial PentaBDE Product
Possible Data Gaps

The following data gaps were addressed by using worst case exposure estimates in the Tier 1 evaluation

Exposure Assessment

- Scanty source-specific exposure data on lower BDEs in the United States.
- Pathways by which the commercial mixture or constituents are released to the environment and accumulate in different biotic and abiotic compartments.

Hazard Assessment

- Absence of a two-year chronic bioassay
- Mechanistic studies to determine relevance of rat data on thyroid and neurobehavioral function in humans
- Multi-generation reproductive toxicity study.

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Commercial PentaBDE Product
Overall Interpretation of Data Gaps

- Hazard Indices allow for uncertainties, both in terms of exposure and hazard assessment.
- Filling these gaps would reduce uncertainty, but may not change the Tier 1 assessment results.
  - Due to the highly conservative approach used for the exposure assessment.
- There is high confidence that this risk assessment has adequately assessed any potential health risks to children.
  - Closing data gaps is not needed to provide an adequate assessment of the risks to children's health.

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Commercial PentaBDE Product
Health Canada Planned Studies

- 28-day oral gavage
  - Tissue distribution, elimination
  - Neural Markers
  - Neuro- and Immuno-Pathology
  - Cancer Biomarkers

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Commercial PentaBDE Product
Health Canada Planned Studies

- One-generation reproductive pilot (rats), oral gavage
- Two-generation reproductive study (rats), oral gavage
  - Developmental Neurobehavioral Segment
  - Spermatogenesis Evaluation
  - Ovary/Estrous Cycle Evaluation
  - Endocrine Function Analysis
  - Blood Serum/Breast Milk Ratio

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Commercial PentaBDE Product
NTP Planned Studies

- Request for Proposals closed March 2003 for:
  - 90-day oral dietary study in rats with tissue concentration and cytochrome-P450 determinations
  - 14-day range finding study in mice
  - 26-week study in mice, 2 strains
  - 2-year study in rats and mice

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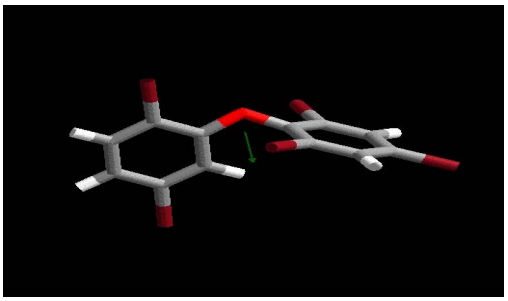
VCCEPP Tier 1 Review of the Commercial Pentabromodiphenyl Ether Product: Additional Exposure & Hazard Information



Tessa Serex, Ph.D., DABT
Great Lakes Chemical Corporation
Richard J. Wenning
ENVIRON International Corporation

June 2003

Great Lakes
CHEMICAL CORPORATION

"Additional Overnight Revelations"

- Exposure information
- Presentation of the results of a "typical scenario" to improve the evaluation of theoretical exposures to workers
  - Better frames the worst-case scenario (no respiratory or dermal protection) that was included in the Tier 1 assessment

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Exposure Estimates for Primary Production Workers

PentaBDE Product Hypothetical Exposure Pathway	Worst-Case Scenario * CDI (mg/kg-d)		Typical Scenario ** CDI (mg/kg-d)	
	Drummer & Cleaner, male	Drummer & Cleaner, female	Drummer & Cleaner, male	Drummer & Cleaner, female
Inhalation of vapor	0.001	0.001	0.0001	0.0001
Dermal contact	0.005	0.005	0.0005	0.0006
Incidental ingestion, hand-to-mouth contact	0.01	0.01	0.001	0.001
Other (minor) Pathways	0.0002	0.0002	-- ‡	--
Total	0.017	0.018	0.0019	0.0022

* The worst-case scenario (no respiratory or dermal protection) was included in the Tier 1 assessment.
** The typical scenario assumes the use of PPE; i.e., workers wear gloves and respiratory protection.
‡ Not calculated because results do not contribute significantly to total exposure estimates.

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Hazard Estimates for Primary Production Workers

PentaBDE Product Primary Production Worker	CDI (mg/kg-d)	Hazard index *		
		Thyroid Effects	Dvlpmt Effects	LEI
		0.04 mg/kg-day	0.2 mg/kg-day	0.002 mg/kg-day
Worst-Case Scenario **				
Drummer & Cleaner, male	0.017	0.4	0.2	9
Drummer & Cleaner, female	0.018	0.5	0.3	9
Typical Scenario ***				
Drummer & Cleaner, male	0.0019	0.05	0.01	1
Drummer & Cleaner, female	0.0022	0.06	0.01	1

* The toxicity benchmark for developmental effects (change in T_4 homeostasis) represents the correct value based on the Zhou et al. (2002) bioassay.
** The worst-case scenario (no respiratory or dermal protection) was included in the Tier 1 assessment.
*** The typical scenario assumes workplace air particulate does not exceed the GLCC workplace exposure limit (WEL; 0.14 mg/m^3) and workers wear gloves.

APPENDIX F

Sponsor Handout: BMD Modeling from Taylor et al. 2003

and

Personal Communication from Judy Buelke-Sam, Toxicology Services to Tessa Serex, Great Lakes Chemical Corp.

BMD Modeling from Taylor et al. 2003

Data Set	Endpoint	Model	Log-Like	BMD10 (mg/kg)	BMDL10 (mg/kg)
Taylor_FearAdult_330.dat	Taylor et al. Fear Conditioning Adult 330 sec Cued	K-Power	-536.19	78.31	46.52
Taylor_FearAdult_60.dat	Taylor et al. Fear Conditioning Adult 60 sec Cued	K-Power	-421.84	20.18	13.34
Taylor_Auditory_ThresholdLow.dat	Taylor et al. Auditory Threshold - Low Freq.	K-Power	-339.89	10.20	6.70
Taylor_DamT4PND22.dat	Taylor et al. Dams Cohort 4 - PND22 T4	K-Power	-160.18	57.90	31.32
Taylor_PupT4PND5.dat	Taylor et al. Pups Cohort 4 - PND5 T4	K-Power	-160.61	51.86	35.53
Taylor_PupT4PND14.dat	Taylor et al. Pups Cohort 4 - PND14 T4	K-Power	-118.66	55.66	32.11

29 May, 2003

To: Tessa L. Serex, Ph.D., D.A.B. T.
Toxicologist
Great Lakes Chemical Corp.

From: Judy Buelke-Sam
Toxicology Services

Opinion: Developmental Neurotoxicity of PBDEs 47, 99, and 71.

I have reviewed the articles sent to me, as listed at the end of this document. I also have reviewed a copy of the Taylor et al. poster presentation from the 2003 Society of Toxicology meetings, and discussed some of the procedures/results with one of the authors (Dr. Kevin Crofton of the U.S. EPA). In addition, I have looked over the review by Dr. McCartney on this class of compounds, and the submissions provided.

In general, I agree with the numerous points made by Dr. McCartney on several aspects of study design and interpreting outcome from neurobehavioral toxicity studies. The points that she makes are relevant to both adult and developmental studies. The majority of data I reviewed comes from academic laboratories, using very few litters of animals, and most often, single dose levels. Dose response and behavioral testing batteries that include overlap in functional assessments plus a broad range of CNS functional domains (e.g., neuromotor, sensory systems, learning and memory, etc.) are key components for interpreting patterns of agent-related effects for risk assessment purposes. It also appears to me that Dr. Eriksson publishes portions of his data in multiple articles, making it seem that there is a greater database of replicated information available from his laboratory on the PBDEs than there actually is.

The core effect reported in the Eriksson studies is the "hyperactivity and lack of habituation" in the specific activity measure used. I have a couple issues with this interpretation. First, the control pattern of behavior is very unusual. In many different types of activity-recording apparatus, mice are very busy creatures. I have never seen any other control data that shows essentially no activity in mice after 40 minutes of testing (Figure 1, Viberg et al., 2002). Second, the authors are defining habituation here as a decrease in response to the novelty of the chamber. That occurs after a good bit of exploration, expressed here as locomotion and rearing. Since the PBDE-99 treated animals are notably less active during the first 20 min of the test session, they apparently explored less than controls. I agree here with the authors that they were hypoactive. If you estimate activity levels for the entire session, it appears that the treated animals show approximately the same or slightly less total behavior than the controls. As a result, the normal pattern in this apparatus is disrupted, the animals are hypoactive, but from my perspective, habituation is not affected. The mice are then treated with nicotine and replaced in the activity apparatus (Figure 2). The nicotine challenge increases control activity during the next hour of assessment, but decreases locomotion and rearing in the PBDE-99 treated animals. Interestingly, the overall levels of the PBDE-99 animals challenged with saline show much less decrease from the first hour of testing (refer back to Figure 1) than do saline challenged controls.

In addition to the numerous procedural comments made by Dr. McCartney that deal primarily with neurotoxicity assessment directly, I have a couple major issues with the design of these studies from a developmental toxicity perspective. First, in nearly all these studies, a very small number of litters/treatment group (only 3 or 4 dams/group) were used, and the individual pup, rather than the litter mean, was used as the statistical unit for analysis. This is an artificial inflation of the sample size - even for those pups treated directly.

Second, a basic principle of developmental toxicology is that there are critical periods of development during which exposure results in specific outcomes. Brain development occurs rapidly in rodents, and I find it very unusual that the same, very specific pattern of delayed developmental toxicity occurs following treatment on PND 3 and PND 10. In light of other exposure data, this suggests to me that there are no real consequences of exposure on PND 3 in mice within his limited assessments, but that the persistence of PBDE in tissue presumably through PND 10 results in the somewhat less dramatic, but suggested same specific effects later in development. Unless an agent has a very specific, single effect on development that requires specific receptors, one almost always expects that. exposure earlier in development will result in a broader profile or greater degree of toxicity than later in development. If, indeed, PND 10 is a single, critical period of CNS/cholinergic system development in the mouse, then other studies that cover or include this period ought to also produce behavioral changes that might be related to altered cholinergic development and alterations in activity and/or habituation patterns. I don't see these suggestions in study outcomes from other laboratories.

Only two of the studies I reviewed include multiple dose levels **and** a relatively broad functional testing battery (Branchi et al., 2002, PBDE-99 in mice; Taylor et al., 2003, PBDE-71 in rats). Both of these studies treated pregnant females from gestation day 6 through weaning of offspring at postpartum day 21. This is a standard treatment period from the OECD guideline and recent US EPA updated guidance (for pesticides) for a developmental neurotoxicity study. Neither study assessed the actual internal maternal or developmental exposure to the PBDE investigated. And neither study clearly met the sample size requirements (20 dams/group, 10 or 20/sex/group for postnatal assessment) of the guidelines. The mouse study used **only** 3 or 4 litters/group and evaluated 2-4 pups/litter, analyzing the majority of data based on individual pups; the rat study used cohorts of 10 litters/group (testing l/sex/litter for individual tests, with appropriate analyses conducted as confirmed by Dr. Crofton via telephone conversation).

Branchi et al. 2002, PBDE-99. The mouse study used **only** 3 or 4 litters/group and evaluated 2- 4 pups/litter, apparently analyzing all but the overall repeated measures data based on individual pups. The one variable that the collaborative behavioral teratology study in rats (reported in 1985) found was **always** the largest contributor to data variance was litter - even in the control groups. The older the animals became, the bigger the contribution of litter to differences in growth and behavioral parameters. Especially when dams are treated, but also when entire litters are treated directly with the same dose, sporadic findings of "treatment-related effects" determined from individuals of so few litters are likely to be "litter effects." Using multiple pups from the same litter as individual units for statistical analyses is very poor design - but one that still occurs repeatedly in the behavioral literature. Eriksson never tested any of his mice very early in development as was done here during continued maternal exposure. The only early

finding in this study was an apparent delay in 1 of 5 early neuromotor assessments - just as likely to be litter effects, as 4/litter were tested in these assessments. The activity findings in this laboratory's open field apparatus show a more usual pattern of behavior in mice, and do not support the Eriksson findings of only a delayed disruption in activity pattern. (As an interesting note, the Al254 pattern of effects reported in this study is similar to the pattern seen when Eriksson's laboratory investigated Al254 using the same testing apparatus the group employed for their PBDE work). There is no suggestion of dose-response relationship seen for apparent PBDE-99 increases in activity on PNDs 34 and 60, and the only "significant" effects on PND 120 occur in the low-dose group. These changes are likely due to litter effects, but still, they are in the opposite direction from those previously reported following a single postnatal dose, suggesting a slightly higher rate of habituation rather than increased activity as the session progresses that Eriksson reported. The modest, and isolated finding shown in Figure 6 - a significant decrease in thigmotactic behavior in the mid-dose group (n=3 litters tested in this group) is also most likely due to litter effects.

Taylor et al. 2003, PBDE-71 in rats. Sample size and analysis issues are not a concern in this study (based on my personal conversation with one of the authors), the dose-related decrease in serurriT41evels in dams and offspring are convincing data. These findings occur at dose levels that do not produce any alterations in parameters of growth, on pre-weaning activity patterns during the time of maximal decreases in T4levels, or on activity levels on PND 64. The only other remarkable findings are increased low-frequency auditory thresholds in the mid- and high-dose animals, an anticipated finding accompanying decreased T4levels during early postnatal life. The possible learning and memory finding occurs only when a combination of tone (ca 95 dB) and house-light cue is used in the procedure.

Summary

1. If, indeed, PND 10 is a critical period of CNS/cholinergic system development in the mouse for disruption by PBDE exposure, as repeatedly suggested by Eriksson in his reports, then other studies that cover or include this period ought to also produce behavioral changes that might be related to altered cholinergic development, including alterations in activity and/or habituation patterns. I don't see these suggestions in study outcomes from other laboratories.

2. The normal and disrupted activity profiles reported by Eriksson's laboratory are both very unusual. Whether these are testing environment specific, apparatus-specific, mouse-strain specific, study-design specific (relative to small sample sizes and litter-to-litter variability in this strain) or a combination of factors, cannot be directly determined from his publications. The most convincing finding he reports is the opposite effect on behavior in the PBDE and control animals following a nicotine challenge at 2 months of age. The ontogeny of this apparent finding deserves further research.

3. The suggested alterations in the Branchi et al. study are subject to sample size and inappropriate statistical issues, and do not follow a pattern of delayed effect suggested by Eriksson's work, but are more similar to the pattern produced by A1254. If anything, there is little or no change in early neuromotor development, and any suggested changes in activity patterns at PNDs 34 and 60 are much diminished at PND 120. With the likelihood of persistence

of internal exposure, it would seem to me that the broader period of exposure should produce more remarkable, if less specific effects, rather than more subtle changes that likely are confounded by the litter and statistical issues discussed above.

4. The majority of developmental neurotoxicity data used in risk assessment has been collected in the rat, not the mouse. The finding of greatest concern in the EP A rat study is the dose-related reduction in serum T4 levels during the pre-weaning period when maternal exposure, and presumably pup exposure is still going on. The only convincing finding at later post-exposure periods is the anticipated increase in auditory thresholds, and with a suggestion of sensory mediated (cued) disruption of a fear conditioning response. There were no activity changes detected in these animals either during the time of exposure and the remarkable decreases in T 4 levels, or later at PND 64.

5. When taken together, these studies suggest some interaction with CNS development may be occurring following PBDE exposure. With the exception of the T4-related changes in rats, there are too many design and analysis issues in most of the mouse studies to do more than suggest a subtle and perhaps species/strain specific effect.

Reviewed:

Branchi et al. (2002). **NeuroToxicology**, 23: 375-384. (pBDE-99, A1254)

Viberg et al. (2002). **Toxicological Sciences**, 67: 104-107. (PBDE-99)

Zhou et al. (2001). **Toxicological Sciences**, 61: 76-82. (PBDE-71, -79, -83R)

Zhou et al. (2002). **Toxicological Sciences**, 66: 1 05-116. (PBDE- 71)

Eriksson et al. (2002). **Toxicological Sciences**, 67: 98-103. (PBDE-99)

Eriksson et al. (2001). **Environmental Health Perspectives**, 109: 903-908. (PBDE-47, -99)

Eriksson et al. (1998). **Organohalogen Compounds**, 35:375-377. (PBDE-47, -99)

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Viberg et al. (2002). **Toxicologist**, 66: (I-S)132. (PBDE-153)

Taylor et al. (2002). **Toxicologist**, 66: (I-S)133. (PBDE- 71)

Taylor et al. (2003). Poster from SOT meeting (PBDE-71)

Breslin et al. (1989). **Fundamental and Applied Toxicology**, 12: 151-157. (PBDPO)

McCartney (July, 2002) Review of Eriksson's neonatal mouse studies.

Collaborative Study References:

Adams, J, Buelke Sam J, Kimmel CA, Nelson CJ, Reiter L W, Sobotka TJ, Tilson HA, Nelson BK.1985. Collaborative behavioral teratology study: protocol design and testing procedures. Neurobehav Toxicol Teratol 7(6):579 586.

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Kimmel CA, Buelke Sam J, Adams J. 1985. Collaborative behavioral teratology study: Implications, current applications and future directions. Neurobehav Toxicol Teratol 7(6):669673.

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APPENDIX G

Panelist Handout: Indoor Exposure Scenario

PBDE Indoor Exposure Scenario/Estimates
Mike Jayjock – June 4, 2003

ONE Foam Pillow Weighing 1000 grams
with 3.75% Penta in a 5m x 7m x 2m residential room

MW	VP PBDE torr	Csat ppm	Csat mg/m^3	**Csat ug/m^3**		dose **ug/day**	
564	3.50E-07	0.00046053	0.010645	**11**	@$5m^3$/da	**53**	**unrealistically high** Csat requires pure compound and a long time to establish

Inhalation Exposure will be very problematic to estimate: void volume within the foam could accumulate both "bloomed" or pure PBDE which could result in saturation air concentration of PBDE in that void volume but only after some time. Compression of the foam (sitting on a cushion) would expell this air into the room. The airborne concentration would be dependent on the volume of the room, air dispersion within the room, the generation rate (conc x vol/time) of this void air volume, "sink" effects within the room and the ventilation rate with outside air.

Maximum	ug/g	ingest g/day		
Dust conc	36	0.2	7	does not include hand to mouth transfer from "hard" surfaces. See below.
Rudel et al. 2003				

HARD SERFACE CONCENTRATIONS ??
TOTAL SURFACE AREA OF WALLS, FLOOR CEILING= 130 m^2
1300000 cm^2

Divided into the number of micrograms emitted but not exhausted **0.3** ug/cm2 on all surfaces after **one year ...**

Note. There could be multiplying factors for local deposition proximate to near field emission sources indoors (i.e. foam)
For example, if the above disposition were not distributed evenly over the walls there could be a significant concentration > 0.3 ug/cm^2. Some of the dispersed PBDE could go into deep (unavailable sinks such as wallboard) but some could settle onto hard surfaces to accumulate and be available for dermal or hand to mouth transfer or to be cleaned - washed to sewer.

Foam Pillow Weighs 1000 grams
with 3.75% Penta that's 37 grams PBDE

Bedroom Volume 2.5m x 5m x 7m
8.75 cubic meters with 11 ug/m^3
0.5 ACH will exhaust

1% per year diffused= 375,000 ug per year
Note: 0.4 %/yr predicted by EU Method
1% to 80%/yr predicted by AMEM

46657 micrograms OR **12 %** of the diffussed PBDE
328,343 ug/yr OR **88 %** **remaining in house on dust and surfaces**