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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