American Chemistry Council *Good Chemistry Makes It Possible*

September 15, 2003

✓ VIA E-MAIL AND EXPRESS MAIL

Dr. Scott Masten
Office of Chemical Nomination and Selection
NIEHS/NTP
P.O. Box 12233
MD A3-07
Research Triangle Park, NC 27709

Received 9/19/03

Re: Comments on the Substances Nominated to the NTP for Toxicological Studies and Testing Recommendations; 68 Fed. Reg. 42068 (July 16, 2003)

Dear Dr. Masten:

The Brominated Flame Retardants Industry Panel (BFRIP) of the American Chemistry Council is providing comments to the National Toxicology Program (NTP) on certain substances nominated to the NTP for toxicological studies and on the testing recommendations made by the Interagency Committee for Chemical Evaluation and Coordination (ICCEC) on June 10, 2003. BFRIP's members consist of Albemarle Corporation, Ameribrom Inc.[1] and Great Lakes Chemical Corporation. BFRIP members manufacture and distribute two of the substances (tetrabromobisphenol A [TBBPA -- 79-94-7] and tetrabromobisphenol A bis (2,3-dibromopropylether) [TBBPA – DBPE -- 21850-44-2] listed in the NTP's recent Federal Register notice. BFRIP supports an NTP program to test TBBPA and TBBPA-DBPE. BFRIP also has comments concerning the testing program and the supporting documents prepared for nominating these substances.

As indicated in our more detailed comments (which are enclosed as Attachment 1), there are existing data which apparently were not considered in the review of toxicological literature as reflected by the supporting documentation prepared for NTP by Integrating Laboratory Systems. These additional data should be considered and the scope of the NTP testing program adjusted accordingly in order to avoid unnecessary use of test animals and to assure that future studies are designed appropriately. Nevertheless, BFRIP's member companies are willing to provide support for NTP's efforts in the form of technical expertise, materials, experience in analytical methods and other assistance.

**Concerns Regarding Use and Exposure Characterization**

BFRIP is concerned about the statements concerning exposure to these substances which appear in the rationale for supporting testing. These statements are not supported by available data to characterize the nature of potential exposure to these substances. As indicated in the enclosed comments, both substances are considered to be "high production volume" chemicals that are manufactured, imported and used within the US. In fact, TBBPA is produced in greater quantities than any other brominated compound used for providing ignition resistance to polymeric substances. However, TBBPA and TBBPA-BDPE have dramatically different uses and these uses are such that the



[1] Ameribrom Inc. belongs to the Dead Sea Bromine Group.

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potential for human exposures to these substances can be minimized. Thus, for the reasons discussed below, and in greater detail in Attachment 1, it appears misleading for the NTP and its supporting documents to say there is "widespread human exposure" to TPPBA (or to TBBPA-BDPE).

As indicated in the review of TBBPA, the major use for TBBPA is as a reactant in the production of thermoset epoxy-type resins. These resins in turn are typically used in the production ignition resistant (FR 4 type) printed wiring boards (PWB). As a result, once TBBPA is reacted into the epoxy system, it no longer exists as TBBPA. By the time the finished PWB is produced, there is essentially no free TBBPA in the hard, thermoset matrix; and the opportunities for exposures to TBBPA are eliminated. Another major use of TBBPA is as a reactant used to make TBBPA derivatives; including TBBPA-BDPE. In these uses, TBBPA is reacted and no longer exists (other than possibly in trace amounts) in the final derivative; also virtually eliminating the opportunity for exposure to TBBPA. There is some use of TBBPA as simply an additive in thermoplastics. However, this use is minor (compared to other uses of TBBPA), and involves incorporating TBBPA along with other additives (e.g. colorants, stabilizers, etc) into a polymer matrix from which TBBPA is not expected to be released.

Despite the contained and controlled uses of TBBPA, the NTP and its supporting documents characterize human exposure as "widespread." The exposure data reported in the TBBPA toxicological review would not seem to support this conclusion. The report of occurrence of TBBPA in electronic equipment is not unusual (given the primary use in plastics and circuit boards used in electronics). However, occurrence does not constitute exposure. The literature that was cited did support an indication that small amounts of TBBPA could be found in areas around electronic dismantiling and near TBBPA production facilities, but does not seem to demonstrate significant portions of the US population are routinely exposed to TBBPA. In circumstances where TBBPA exposure was found, TBBPA levels observed in humans and the environment are in the low part per billion range and levels in the air are in the ng to μg/m3 range. Although the data on the number of workers potentially exposed to TBBPA (224 people) is based on the NOES database, which is quite old, it is not foreseeable that this number has changed dramatically. Even if the estimate were an order of magnitude low, it would not be indicative of widespread human exposure.

Unlike TBBPA, TBBPA-BDPE is used strictly as an additive, predominantly in polyolefins used in electrical and electronic wiring and other electrical components requiring ignition resistance. TBBPA-BDPE is not expected to be readily released from such materials. The annual production of TBBPA-BDPE is a fraction of TBBPA's. BFRIP is not aware of any monitoring data or other information that attempts to quantify the concentration of TBBPA-DBPE in biota or the environment. Based on TBBPA-BDPE's much lower production volume and its typical uses, it is expected that the magnitude of exposure and number of persons potentially exposed to TBBPA-BDPE would be considerably lower than TBBPA.

**Publicly Available Health Effects Test Data**

*TBBPA Data:* TBBPA has been well studied and characterized during the past two decades and BFRIP members (either on their own or as part of BFRIP) have conducted a number of *in vitro* and *in vivo* health effects studies on these commercial products using standardized protocols which have assisted in the characterization. BFRIP sponsored TBBPA for the US Environmental Protection Agency (EPA) High

Production Volume (HPV) Chemical program and therefore robust summaries (including a summary of the available data) and a test plan were prepared and submitted to the EPA. This information can be found at the following website: http://www.epa.gov/chemrtk/phenolis/c13460tc.htm. In addition to the studies that are reported in this document, there are several additional studies that have been performed since that time that have not yet been incorporated in this submission. These additional studies are listed in Attachment 2 and are reflected in our technical comments. Furthermore, BFRIP is updating is HPV documentation to reflect studies completed since its original submission and it is planned that the amended version will be provided to EPA soon. NTP should be aware that TBBPA is one of many substances which are being reviewed pursuant to the European Union (EU) Existing Substances Directive and the EU's assessment will be ongoing during 2004. Industry is working with the EU on the assessment, and of course, BFRIP will be glad to advise NTP of any additional studies the Panel undertakes.

BFRIP has prepared detailed comments on the Review of the Toxicological Literature prepared for NTP concerning TBBPA. These comments are enclosed as Attachment 1. BFRIP has concluded that there are sufficient data available to eliminate the need for certain studies recommended in NTP's proposed test program. This would enable NTP to concentrate its resources on other toxicological studies where more useful analysis can be developed.

*TBBPA-BDPE Data:* Unlike TBBPA, TBBPA-BDPE is not being studied under the EPA's HPV program and is not in the EU risk assessment process. Consequently, the available hazard data on that substance have not been summarized or made as widely available as data concerning TBBPA. However, the WHO publication, Environmental Health Criteria 172 Tetrabromobisphenol A and Derivatives (Geneva 1995), contains a summary of the data available at that time. Since publication of the WHO report, additional studies on TBBPA-DBPE have been completed. A list of the studies available on this compound has been compiled and is enclosed (Attachment 3). These existing studies may be useful to NTP and should be considered carefully before a final testing program is generated. If NTP would like to obtain a copy of these studies, please let me know.

**Conclusion**

The two substances recommended for study by the ICCEP are good candidates for further evaluation by the NTP. The BFRIP member companies already have invested a considerable amount of time and effort working cooperatively with government agencies here and abroad to support the analysis of TBBPA. We hope that the data BFRIP has generated in support of such assessments will be taken into consideration by the NTP before it decides on a final testing plan. The data available for TBBPA-BDPE are not as extensive as the data for TBBPA. However, as with TBBPA, the member companies of BFRIP would be glad to provide NTP with copies of any existing studies in the members' possession if such data will assist NTP in development of a final study plan. BFRIP also can help to provide test articles, analytical methods and other expertise to NTP that could be useful in studying these two products.

If you have any questions or need additional information, you can contact me at 703/741-5639 or by e-mail at [Wendy_Sherman@americanchemistry.com].

Sincerely,

Wendy K. Sherman

Wendy K. Sherman
BFRIP Panel Manager
CHEMSTAR

Enclosures

Cc: BFRIP Members, w/ attachments

Attachment 1
Detailed Comments on the Toxicological
Assessment Prepared by
Integrated Laboratory Systems for NIEHS

**BFRIP COMMENTS ON THE JUNE 2002 DOCUMENT**

**TETRABROMOBISPHENOL A: REVIEW OF TOXICOLOICAL LITERATURE[1]**

COMMENTS SPECIFIC TO THE EXECUTIVE SUMMARY

**Basis for Nomination**

This section states that Tetrabrombisphenol A (TBBPA) was nominated for neurodevelopmental and carcinogenicity testing by National Institute of Environmental Health Sciences (NIEHS) based on TBBPA's high production volume (HPV), alleged widespread human exposures and suspicion to cause thyroid toxicity and thyroid tumors. TBBPA is a HPV chemical; however, we question, based on its pattern of use, that there is significant human exposure. Further, repeated dose testing in rats indicates that TBBPA does not cause toxicity in the thyroid. We also question the suspicion of thyroid tumors, because any effect on the thyroid by TBBPA appears mediated by a mechanism that is not applicable to humans. These points will be addressed in detail in these comments.

**Nontoxicological Information**

We recommend deleting the pyrolysis information. Laboratory pyrolysis studies do not represent conditions of municipal waste incineration, manufacture, processing or use. Virtually any organic substance containing a halogen can produce some level of halogenated dioxins or furans when pyrolyzed. What is relevant is whether TBBPA contains 2,3,7,8-substituted polybrominated dibenzodioxins or furans or forms these substances when processed, used or disposed of in waste incinerators. This issue is addressed in greater detail in our comments on Section 2.2 Physical/Chemical Properties.

We suggest that the Executive Summary include only U.S. data on TBBPA levels in humans. Data from other countries can be provided in later sections of the review.

TBBPA's manufacture is essentially limited to Arkansas (Great Lakes Chemical Corporation, Albemarle Corporation), Israel (Dead Sea Bromine Group, DSBG/GLCC Joint Venture), and Jordan (Albemarle). There is one producer in Japan that manufacturers TBBPA for that market.

This section should make clear that TBBPA is the primary flame retardant used in epoxy resin printed circuit boards worldwide. The reasons for TBBPA's dominance is that it is highly effective as a flame retardant and needs only low load levels, highly cost effective, compatible with the circuit board's other components, able to maintain the board's physical properties, qualified for use, and has health and safety data supporting its use. In circuit boards, TBBPA is covalently bound into the epoxy resin, and thus is restricted in release either to the environment or the consumer.

We recommend deleting information in this section on the uses of TBBPA other than in printed circuit boards, electronic equipment housing made of ABS, and as a raw material for TBBPA-derivatives that are subsequently used as flame retardants. The other uses listed are minor and can be covered in later sections of the document.

The bioconcentration factors (BCF) cited are based on old data and should be revised. TBBPA's BCF in fish is 307, and its depuration half-life was < 24 hours. TBBPA's BCF in the oyster is 148. Thus, TBBPA's potential for bioconcentration is low. This is expected for a substance with 2 readily conjugated hydroxyl groups.

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[1] Prepared For Dr. S. Masten, NIEHS, by Ms. K. Haneke, ILS.

We recommend the information provided in BFRIP's HPV submission on environmental fate be consulted.

TBBPA is listed on the TRI. We believe the following statement best expresses that data:

> TBBPA was first listed for TRI reporting in 2000. The latest publicly available data are from 2001. In 2001, total on-site releases and off-site releases for disposal of TBBPA in the U.S. were 876,171 pounds. Of this, 625,482 pounds were sent off-site for disposal. On-site land releases, predominantly to one manufacturer's on-site landfill built to hazardous waste standards, were 196,675 pounds. On-site air discharges were 54,005 pounds, while surface water discharges were 9 pounds. The majority of the on-site releases were associated with TBBPA's manufacture. Total off-site transfers for further waste management were 47,300 pounds; of this, 44,299 pounds went to treatment and 2,979 to energy recovery. Discharges to publicly owned sewage treatment works were 9 pounds. Forty-eight facilities reported TBBPA releases in 2001.

**Human Exposure**

We question the Contractor's statement that inhalation, dermal, or oral exposure to the general population from polymers containing TBBPA is significant. While this type of exposure is possible in the absolute sense and TBBPA has been detected in vacuum cleaner dust collected in Europe, the levels are extremely low and likely represent our increasing ability to detect smaller and smaller quantities of substances in the environment. The reference to TBBPA in drinking water does not mention that the TBBPA was present from *de novo* synthesis of Bisphenol A (BPA) leached from the container's walls and subsequently brominated by substances used to sanitize the reusable container. It was not due to its use as a flame retardant component in the polymer matrix. The reference to TBBPA's detection in fish and shellfish should mention that this report was on samples collected in Japan and is several decades old.

We believe the point at which human exposure to TBBPA is most likely to occur is during its manufacture or processing, and specifically in operations where TBBPA is transferred to bags for shipping or emptied into hoppers for mixing with other substances. Once TBBPA is reacted into or incorporated in resins, exposure is negligible. The most relevant route of exposure in the workplace is inhalation via dusts generated in the bagging or mixing operations. These exposures can be mitigated in the workplace through protective equipment or engineering controls.

We question the statement that there is "ongoing increase in human exposure to brominated flame retardants, including TBBPA". The available data has to do with tissue levels in samples obtained in Europe and deals with certain polybrominated diphenyl ether (PBDE) congeners rather than the broader class of brominated flame retardants. The data cited regarding occupational groups was collected in Europe, not the US, and the levels are very low.

**Toxicological Data**

Firemaster PHT4 is a trade name for tetrabromophthalic anhydride, a substance totally unrelated to TBBPA. Reference to studies performed on PHT4 should be deleted.

We recommend shortening the discussion on disposition, metabolism and toxicokinetics to the pertinent points with respect to TBBPA, and providing the details on the various studies later in the document. That is, based on studies in rats, TBBPA appears to be well absorbed orally and extensively metabolized prior to elimination in the feces. Metabolites were primarily glucuronide or glucuronide-sulfate ester conjugates. Elimination of a single oral dose in rats was essentially complete with 72 hours.

We would also shorten the acute toxicity section to the first sentence followed by a comment that the oral LD50 in rats was > 5000 mg/kg, the dermal LD50 in rabbits > 2000 mg/kg, and the inhalation LC50 in rats > 10,920 mg/m3. Details on the various studies can be provided later in the document.

We would also shorten the section on short-term or subchronic toxicity. We believe the primary study on which to base a hazard assessment is the 2002 90-day rat (gavage) study (Schroeder R. MPI Research, Mattawan, MI, performed according to current Toxic Substances Control Act (TSCA) guidelines and Good Laboratory Practices. The no-observed-adverse-affect-level (NOAEL) was 1,000 mg/kg, the highest dose tested. No effect on mortality, clinical signs, body or organ weights, histopathology, urinalysis, ophthalmology, functional observational battery, motor activity, serum TSH, serum T3 or serum chemistries were observed. Differences were observed for bilirubin and ALP, but neither of these changes was found to be biologically or toxicologically meaningful or adverse. Serum T4 levels were decreased in treated animals, but the decrease was not of sufficient magnitude to induce adverse effects. We would also mention that additional studies have been performed in rats, mice and rabbits via the dermal, oral and/or inhalation routes, that the results are consistent with those of the 2002 90-day rat study, and demonstrate that TBBPA has a low order of toxicity. We recommend details on these additional studies be provided later in the document, rather than the executive summary.

Under Reproductive and Teratological Effects, reference to the study on Saytex 111 should be deleted. Saytex 111 is a trade name for a former product of Ethyl/Albemarle Corporation. The Saytex 111 product was octabromodiphenyl oxide, not TBBPA, and is no longer manufactured either by Ethyl Corporation or Albemarle Corporation. Information on studies performed on Firemaster PHT4 should also be deleted because that is not a trade name for TBBPA. Further, we believe the primary studies on which to base a hazard assessment with respect to reproduction and developmental effects are the 2001 rat developmental study and the 2002 TBBPA rat two-generation reproduction study which included a neurodevelopmental component. Both of these studies were performed according to current TSCA guidelines and Good Laboratory Practices.

In the 2001 rat developmental study, doses of 0, 100, 300 or 1000 mg/kg were administered by gavage in corn oil to female rats on days 0 – 19 of gestation. No effects of treatment, other than salivation due to the taste of the test article, were seen in clinical examinations, gestational parameters (body weight, body weight gain, or food consumption), uterine implantation data, liver weights, or necropsy findings. Likewise, no effect of treatment was evident from fetal body weights, fetal sex distribution or from fetal external, visceral or skeletal examinations. The NOAEL for maternal and developmental toxicity was 1000 mg/kg/day, the highest dose tested.

In the 2002 rat two-generation study, doses were 0, 10, 100 or 1000 mg/kg/day administered via gavage in corn oil. The NOEL for parental toxicity was 100 mg/kg/day based on lower body weights and body weight gain in males at the 1000 mg/kg/day dose level. The NOEL for effects on thyroid hormone levels was 10 mg/kg/day based on lower T3 and T4 levels at the 100 and 1000 mg/kg/day dose levels. TSH levels were not affected at any of the dose levels in either generation. The NOEL for reproductive performance and pup toxicity was 1000 mg/kg/day, the highest dose tested. In the delayed neurotoxicity-neuropathology component, the NOEL was 100 mg/kg/day based on subtle morphometric changes in the parietal cortex in the brains of the Day 11 F2 pups in the 1000 mg/kg/day group. In this component, no changes at any dose level were seen in the pups for clinical findings, sexual maturation landmarks, growth, or from the various behavioral assessments. Currently, additional sections of the parietal cortex are being cut to determine if the subtle changes observed were artifacts.

MAIN BODY OF THE REVIEW

1.0 Nomination

One reason given for the need for further testing on TBBPA was suspicion of widespread exposure to the general population, which was apparently based on a concern that exposure could occur due to TBBPA's use in printed circuit boards or electronic housings. This appears unlikely given TBBPA's extremely low vapor pressure, and its covalently binding in epoxy resins. Studies demonstrate any emissions from TBBPA flame retarded products are exceedingly low. Measured TBBPA air levels from computer monitors with TBBPA-flame retarded housings were 1 ng/m3 over a 10-day period while no TBBPA was detected in air surrounding a monitor without TBBPA in the housing but presumably using a TBBPA-flame retarded circuit board. In an office setting, TBBPA air concentrations were 0.1-2.3 ng/m3. In comparison to other semi volatiles detectable in indoor air, this level was considered very low *(Ball and Herrmann. Investigation into the emissions of tetrabromobisphenol A from computer monitors. ERGO, Hamburg, Germany. April 2002).*

Another reason given for TBBPA's nomination for testing was thyroid toxicity and possibly thyroid tumors. No further information with respect to these suspicions was provided, but the suspicions may have been based on reports in the literature regarding an effect on circulating T4 levels in rats and *in vitro,* but not *in vivo*, binding to transthyretin (TTR). The 2002 rat 90-day repeated dose study provides the most comprehensive information with respect to TBBPA's potential to affect the thyroid. No histological effects on the thyroid were detected. Thyroid weights in treated and control animals were not statistically different. Mean serum TSH and T3 levels were statistically comparable between control and treated animals at all time points (Day 33, 90-Day and recovery sacrifices). Mean T4 levels in male rats were statistically lower than the control mean in the 100, 300 and 1000 mg/kg dose groups at various times during the study. Statistically lower T4 levels in female rats were detected at Day 33; however, levels were comparable to control at Day 90. Mean T4 levels were comparable to controls in both males and females 30 days after treatment was stopped. The decrease in serum T4 levels was considered a possible effect of test article administration. TBBPA has been shown to competitively displace T4 from TTR, a major serum T4 binding protein in the rat *in vitro* (Meerts el al. 2000). That portion of serum T4 displaced from its binding site would be available for metabolism and elimination, thereby leading to a decrease in serum levels. The half-life of T4 in the rat is short due to its transport by TTR and thus this species is sensitive to perturbations in T4 levels. For example, the plasma T4 half-life is rats is 12-24 hours while T4's half-life in humans is 5-9 days *(Capen C. Chapter 21. Toxic Responses of the Endocrine System. In: Casarett & Doull's Toxicology, The Basic Science of Poisons. Fifth Edition. Ed. Curtis Klassen, McGraw-Hill, New York. 1996).* In humans, circulating T4 is bound primarily to thyroxin binding globulin, but this high affinity binding protein is not present in rodents. This mechanism, displacement of T4 from TTR-binding by TBBPA with subsequent metabolism and elimination in the liver, may account for the decreased mean serum T4 levels in treated rats. Because the decrease in T4 levels was not of sufficient magnitude to alter mean serum TSH or T3 levels, thyroid histopathology, thyroid weight, or other parameters indicative of thyroid pathology (e.g. body weight, etc.), the decrease in serum T4 levels was not considered adverse. The reduction in serum T4 levels was not accompanied by evidence of toxicity or adverse effects, and the animals were clinically normal.

TTR is a major serum binding protein in rats, but it is a minor protein in humans. In human, thyroxin binding globulin (TBG) is the main thyroid hormone binding protein. Thus, a decrease in serum T4 levels due to displacement from TTR and more rapid elimination is less relevant to humans.

Thyroid tumors have been observed in rats following prolonged stimulation of this gland by TSH. TSH levels were not affected in the TBBPA 90 day study and no evidence of thyroid stimulation was observed

either in terms of organ weight or histopathlogy. Therefore, it appears unlikely that TBBPA would induce thyroid tumors via that mechanism.

Several mutagenicity tests evaluating different end points have shown that TBBPA is not genotoxic. Thus, there does not appear to be adequate justification to suspect a genetic basis for carcinogenicity.

2.1 Chemical Identification and Analysis
Please delete Firemaster PHT and Saytex 111 from the list of synonyms. Neither trade name refers to TBBPA.

2.2. Physical-Chemical Properties
Please include the molecular weight (543.87). TBBPA's vapor pressure has been measured (<1.19 x 10-5 Pa) *(Lezotte, F. and Nixon, W. Project Number 439C-128. 2001. Wildlife International, Ltd, Easton, MD).* TBBPA's octanol-water partition coefficient has also been measured (Log Kow=5.903) *(MacGregor, J. and Nixon, W. Project Number: 439C-129. 2001. Wildlife International, Ltd. Easton, MD).* TBBPA's measured water solubility in pH 5.0, 7.0, and 9.0 buffer solutions was 0.148 mg/L, 1.26 mg/L, and 2.34 mg/L, respectively, at 25 degrees C using the generator column method. The water solubility in non-buffered reagent water was 0.24 mg/L. *(MacGregor J. and Nixon W. Project Number: 439C-132. 2002. Wildlife International, Ltd, Easton, MD).* These studies on vapor pressure, Kow and water solubility were performed according to current TSCA guidelines and Good Laboratory Practices, and should be considered more reliable than the values cited in the review.

We recommend deleting the results of the pyrolysis studies for the reasons given previously, and the Kurtz citation. We recommend inserting: "The composition of the commercial product is typically 98% TBBPA with the remainder composed of other brominated bisphenol A compounds." and "TBBPA has been analyzed for the presence of 15 2,3,7,8-substituted polybrominated-p-dibenzodioxins (PBDD) and dibenzofurans (PBDF). None of the analytes were present at or above the quantitation limits established by the U.S. Environmental Protection Agency *(Ranken et al., Bul. Soc. Chim. Belg., 103/5-6, 1994)."* The potential generation and emission of PBDD/F on incineration of waste plastics was studied in a modern pilot scale municipal waste incinerator (TAMARA) at the Karlsruhe Research Center, Germany over a several year period *(Hardy et al. 2003. Environment International 29: 793-799).* These studies demonstrated that adding excessively large amounts of electrical electronic waste plastic to the incinerator's feedstock did not increase emissions of halogenated dioxins or furans. The added waste plastic actually enhanced combustion because plastic is a good fuel. Other studies at TAMARA showed that recycling the bromine in plastics containing brominated flame retardants is technically feasible. Thus, BFR-containing plastics can be incinerated without increasing halogenated dioxin and furan emission, and have the added benefit of feedstock recycling."

2.3 Commercial Availability
TBBPA is manufactured by Albemarle Corporation, Dead Sea Bromine Group, and Great Lakes Chemical Corporation. Albemarle and GLCC have manufacturing sites in Arkansas. DSBG manufactures TBBPA in Israel. DSBG and GLCC have a joint venture manufacturing TBBPA in Israel. Albemarle has a TBBPA manufacturing plant in Jordan.

4.0 Production and Import Volumes
We are not familiar with the unit "Mg" and recommend that it be defined in the text. Canada and Germany do not export TBBPA to the United States. Manufacture of TBBPA does not take place in Canada or Germany.

5.0 Uses

TBBPA is not used in personal computer acrylonitrile-butadiene-styrene (ABS); rather it is used in ABS housings manufactured for electronics use. TBBPA is "not incorporated into the polymer structure after curing." When used as an additive type flame retardant (a minor use), it is incorporated in a molten polymer mass in a melt extrusion process. This process disperses the TBBPA throughout the polymer matrix, so that when cooled, the TBBPA is encapsulated in plastic. TBBPA is not used in textiles per se; it is used in laminates that fall under the broad "Textiles" Standard Industrial Code. To the best of our knowledge, TBBPA is not used in carpeting or office furniture.

6.0 Environmental Occurrence and Persistence

Delete reference to use in PC-ABS; substitute with ABS. Also, please note that TBBPA is predicted to partition to soil and sediment if released to the environment. Based on a release of 1,000 kg/hr to air, water and soil, the predicted partitioning is: air – 0.0000004%, water - 1.13%, soil - 44.9%, and sediment - 53.9% *(Level III Fugacity Model, EPIWIN V3.04, Syracuse Research Corporation).* The majority would be reacted in sediment and soil (83.9%) with only 16.1% of the total available to undergo advection. TBBPA is expected to be essentially immobile in soil, where it can undergo degradation. Test data shows TBBPA's half-life in a 64-day aerobic and anaerobic soil studies to be approximately 50 days and in a 56-sediment/water degradation study, 48 to 84 days *Fickler 1989, SLS Report 88-11-2848; (Fackler 1989, SLS Report 88-11-2849; Fackler 1989, SLS Report 89-8-3070; All reported in Environmental Health Criteria Document # 172, World Health Organization, Geneva, 1995).*

TBBPA is not expected to volatilize from water based on its air-water partition coefficient and its river and lake volatilization half lives, and is expected to partition to biomass *(EPIWIN V3.04, Syracuse Research Corporation).* Please see Table 1 of these comments for additional information on TBBPA's environmental fate.

Please add with respect to the Eriksson and Jakobsson paper, that the estimated half-life for photodegradation was 33 hours and that total degradation was observed in 5-6 days.

The section on BCFs needs updating; the BCF cited in the International Programme on Chemical Safety document is based on old data. TBBPA's BCF in fish is 307, and its depuration half-life was < 24 hours. Steady state levels were reached in fish in 4 days. This lower BCF is consistent with that reported by CITI (1992) for an 8-week exposure period: BCF= 52-485. TBBPA's BCF in the oyster is 148. Steady state was reached in 5 days, and the depuration half-life was between 3-5 days. Thus, TBBPA's potential for bioconcentration has been shown to be low as expected for a substance with two readily conjugated hydroxyl groups.

| Parameter | Estimation Program or Test Result | Result |
|---|---|---|
| Photodegradation | WHO EHC #172, 1992 | Has potential to undergo photodegradation; However, not likely to be a significant route of environmental degradation due to low vapor pressure |
| Hydrolysis | - | Not likely to be a significant route of environmental degradation due to low water solubility |
| Distribution | Estimated (EPI win, V.3.04) | Level III Fugacity Model predicts at 1000 kg/Hr emissions to air, water and soil: Air 0.0000004 %, Water 1.3%, Soil 45%, Sediment 54% |
| Atmospheric Oxidation | Estimated (EPI win, V.3.04) | Overall OH Rate Constant = 2.9 x 10-12 cm3/molecule-sec<br>Half-Life = 3.6 Days (12-hr day; 1.56 x 10+6 OH/cm3)<br>Half-Life = 43.4 Hrs |
| Henry's Law Constant | Estimated (EPI win, V.3.04) | 2.31 x 10-13 atm-m3/mole at 25 □C<br>9.43 X 10-12 unitless at 25 □ C |
| Soil Koc | Estimated (EPI win, V.3.04) | 5.6 x 10+6 |
| Octanol-Water Partition Coefficient | Estimated (EPI win, V.3.04) | 1.6 x 10+7 |
| Air-Water Partition coefficient | Estimated (EPI win, V.3.04) | 9.4 x 10-12 |
| Biomass to Water Partition Coefficient | Estimated (EPI win, V.3.04) | 3.1 x 10+6 |
| Volatization from Water | Estimated (EPI win, V.3.04) | Half life: 6.7 x 10+5 years (River);7.3 x 10+6 years (Lake) |
| Sewage Treatment Plant Fugacity Model | Estimated (EPI win, V.3.04) | Total Removal: 94%, Total Biodegradation: 0.78%, Primary Sludge: 59.8%, Waste Sludge: 33.3%, Final Water Effluent: 6% |
| Level III Fugacity Model | Estimated (EPI win, V.3.04) | At Emissions to Air, Water, Soil and Sediment of 1,000, 1,000, 1,000 and 0 kg/hr, respectively:<br><br>Fugacity (atm): Air 4.3 x 10-17, Water 4.5 x 10-20, Soil 1.5 x 10-21, Sediment 8 x 10–20<br><br>Reaction (kg/hr): Air 0.0007, Water 48, Soil 1.9 x10+3, Sediment 570<br><br>Advection (kg/hr): Air 0.0009, Water 247, Soil 0, Sediment 237<br><br>Reaction (%): Air 2.5 x 10-5, Water 2, Soil 63, Sediment 19<br><br>Advection (%): Air 3 x 10-5, Water 8, Soil 0, Sediment 8 |
| Biodegradation | CITI-Japan, 1992 | Not readily biodegradable |
| | Fackler P., 1989 | Aerobic Soil (64 D): Degradable, Half-life ~50 D |
| | Fackler P., 1989 | Anaerobic Soil (64 D): Degradable, Half-life ~50 D |
| | Fackler P., 1989 | Sediment/Water (56 D): Degradable, Half-life 67 D |

TBBPA was first listed for TRI reporting in 2000. The latest publicly available data are from 2001. In 2001, total on-site releases and off-site releases for disposal of TBBPA in the U.S. were 876,171 pounds. Of this, 625,482 pounds were sent off-site for disposal. On-site land releases, predominantly to one manufacturer's on-site landfill built to hazardous waste standards, were 196,675 pounds. On-site air discharges were 54,005 pounds, while surface water discharges were 9 pounds. The majority of the on-site releases were associated with TBBPA's manufacture. Total off-site transfers for further waste management were 47,300 pounds; of this, 44,299 pounds went to treatment and 2,979 to energy recovery. Discharges to publicly owned sewage treatment works were 9 pounds. Forty-eight facilities reported TBBPA releases in 2001.

7.0 Human Exposure

This section states that exposure to TBBPA in the general population is possible from inhalation of ambient air and dermal contact with the compound in products from polymers incorporating TBBPA. It seems unrealistic to assume that the public will be exposed to TBBPA in circuit boards where it is covalently bound or by electronics housings where TBBPA is encapsulated in the resin. Thus, while exposure is theoretically possible, a more practical view indicates it is highly improbable.

The reference regarding TBBPA's detection in air at the ng/m3 concentration around Arkansas manufacturing sites and at the low ppb concentration in hair collected from floor sweepings in an Arkansas barbershop was based on a study from 1976. The levels reported may or may not be representative of current exposures.

The references regarding dust samples were from European, not U.S., buildings. The content of TBBPA in waste electrical appliances, PCs or circuit boards is not applicable to or representative of human exposure. We recommend this be deleted.

The summation of a study on water stored in reusable polycarbonate containers and containing trace levels of TBBPA should include that the levels did not derive from its use as a flame retardant. Rather, TBBPA was apparently present as a result of *de novo* synthesis from leached BPA (from the container walls) and subsequent bromination by substances used to sanitize the containers.

The section on occupational exposure should include that the blood was collected in Norway and Sweden, and is not representative of the U.S. Also, the sample size in each case was small; typically 5-6 persons. While the Thomson et al. 2002 paper does make the statement that there is an "ongoing increase" in human exposure to brominated flame retardants, the TBBPA review document did not appear to review the literature to determine if this was fact or the authors' opinion. As manufacturers of brominated flame retardants, we follow these issues closely. The data is far from as clear as stated by Thomson et al. There is little actual time trend data, the existing data is largely from samples collected in Europe, the numbers of individuals included in each of the studies are very small, the analytical methodology is only briefly described, only a few brominated flame retardants have been included in the analyses, and the values reported are often so small as to make definite determinations that the compounds reported were actually present in the samples exceedingly difficult. Thus, we suggest that the review document not categorically state that human exposure to brominated flame retardants is an "ongoing increase".

Additional studies are available on the PBDD/F content of TBBPA and its resins and on the potential for TBBPA to form PBDD/Fs during processing. Please see Hardy et al. 2003. Environment International 29:793-799.

8.0 Regulatory Status

This section should mention that the BFRIP volunteered to sponsor TBBPA under the HPV Challenge Program and that robust summaries and a data summary and test plan are available on EPA's web site. The BFRIP submission does not appear to have been consulted when the TBBPA review was prepared. TBBPA's manufacturers have extensive knowledge regarding TBBPA's toxicology and potential for exposure. Please note that BFRIP is in the process of updating TBBPA's HPV data summary.

9.0 Toxicology Data

9.1 General Toxicology

9.1.1 Human Data

The study on Firemaster PHT4 should be deleted. As mentioned earlier, Firemaster PHT4 is not a trade name for TBBPA. Firemaster PHT4 is tetrabromophthalic anhydride.

9.1.2 Chemical Disposition, Metabolism, and Toxicokinetics

An introductory paragraph would be helpful. We suggest:

> "Pharmacokinetic studies demonstrate TBBPA has a short half-life and is readily metabolized and excreted, as would be expected of a chemical possessing two hydroxyl groups suitable for metabolic conjugation."

In our opinion, the definitive study on TBBPA's pharmacokinetics is Hakk et al., 2000. We suggest relegating the Brady 1979 study to perhaps one sentence, e.g. that TBBPA was first thought to be poorly absorbed due to rapid and near complete elimination of a single oral dose in the feces as the parent molecule. Hakk et al., however, using conventional and bile-cannulated rats found that the rapid fecal elimination was due to rapid absorption, metabolism and excretion in the bile as conjugates that were subsequently deconjugated by intestinal bacteria. We believe the Haak et al. study is better described as follows:

> In the rat, TBBPA was readily absorbed, metabolized and eliminated within 72 hours after oral dosing. Recovery of $^{14}$C-activity in the conventional and bile-cannulated rat administered a single oral dose of $^{14}$C-TBBPA was 92 and 98.5% of the dose, respectively, by 72 hours post-dosing. Owing to the extensive elimination, total tissue retention at 72 hours was limited. In the conventional rat, 2% of the dose was retained in the tissues, but <1% in the cannulated rat at 72 hours. Essentially no deposition of TBBPA was detected in adipose tissue, heart, spleen, testis or thymus (<0.0005% of dose). The primary route of elimination was the feces; only negligible amounts were detected in urine. Glucuronic acid and sulphate ester conjugates were detected in bile; however the parent molecule was the predominant form found in species due to deconjugation by intestinal bacteria *(Haak et al., Xenobiotica, 2000, 30,9,881-890; Larsen, G. et al, Organohalogen Compounds, 31, 413-416, 199).*

A description of the 1979 Brady study is:

> Earlier work concluded that in rats, after oral dosing, approximately 95 percent of the administered material was found in the feces and less than 1.1 percent in the urine within 72 hours. Blood and tissue levels were extremely low at all time points measured. The half-life in the blood was about 20 hours; the maximum half-life in any tissue was less than 3 days. Because of the short half-life, the small amounts of TBBPA absorbed would have relatively little persistence or accumulation in mammalian systems. *(Environmental Health Criteria Document # 172, World Health Organization, Geneva, 1995)*

We suggest adding the information obtained from the repeated dose studies on levels in adipose tissues. Liver and adipose bromine levels were similar in rats of the control and high dose groups (1000 ppm TBBPA in the diet) sacrificed at the end of the 28-day treatment period. *(Goldenthal and Geil, 1972; reported in Environmental Health Criteria Document # 172, World Health Organization, Geneva, 1995).* The total bromine content in liver, kidney, skeletal muscle, fat and serum of rats fed 3 mg TBBPA/kg diet for 90 days did not differ from that of the controls. (The 3 mg/kg group was the only group tested for total bromine content.) *(Quast et al. 1975; reported in Environmental Health Criteria Document # 172, World Health Organization, Geneva, 1995).*

9.1.3 Acute Exposure

An introductory paragraph would be helpful. We suggest:

> "TBBPA was not acutely toxic or irritating to the skin or eye. The oral LD50 in the rat is >5,000 mg/kg and the dermal LD50 in rabbits is > 2,000 mg/kg. TBBPA was also not acutely toxic by inhalation; the inhalation LC50 in rats is >2550 mg/m$^3$ for a 2 hour exposure. TBBPA did not induce chloracne on skin exposure and did not induce skin sensitization in guinea pigs. Testing in human volunteers showed no evidence of irritation or induction of skin sensitization."

The study on Firemaster PHT4 should be deleted. As mentioned earlier, Firemaster PHT4 is not a trade name for TBBPA. Firemaster PHT4 is tetrabromophthalic anhydride.

Eye Application, page 9. The study on Firemaster PHT4 should be deleted. As mentioned earlier, Firemaster PHT4 is not a trade name for TBBPA. Firemaster PHT4 is tetrabromophthalic anhydride.

9.1.4. Short-term and Subchronic Exposure

A short introductory section would be helpful. We suggest:

> "TBBPA produced minimal effects in mammals when tested in subchronic studies. The repeated dose studies include a 14-day inhalation in rats, a 21-day dermal in rabbits, a 28-day oral study in rats, 2 90-day oral studies in rats, and a 90-day oral study in mice. The most recent of these studies was performed in 2001 in which a 90-day NOAEL of 1000 mg/kg/d (gavage) was determined. Results from the other repeated dose studies are consistent with the 2001 90-day study."

We believe the following summaries best describes the results of these studies:

14-Day Rat Inhalation

In a 14-day inhalation study, no systemic toxicity was observed in rats treated with up to 18 mg/L. Rats were exposed to an atmosphere of 0, 2, 6 or 18 mg micronized TBBPA/L air (0, 2000, 6000, or 18,000 mg/m3) for 4 h daily, 5 days/week for 2 weeks. Mortality, body weight gain, food consumption, hematological, biochemical or urinary parameters were not affected by treatment. No gross or microscopic lesions were detected in any dose level. *(Goldenthal et al. 1975; reported in Environmental Health Criteria Document # 172, World Health Organization, Geneva, 1995)*

21-Day Rabbit Dermal

In a 21-day dermal study, no systemic toxicity was observed in rabbits treated with 0, 100, 500, or 2,500 mg TBBPA/kg body weight for 6 hours/day, 5 days/week for 3 weeks. No mortality or overt signs of toxicity were observed. Body weight gain, hematological parameters, urinalysis, organ weights, and gross and microscopic examinations did not reveal any compound-related changes.

*(Goldenthal et al., 1979; reported in Environmental Health Criteria Document # 172, World Health Organization, Geneva, 1995)*

28-Day Rat Oral

In a 28-day oral study, no toxicity was observed in rats treated with up to 1,000 ppm TBBPA in the diet. Rats were fed at dietary dose levels of 0, 1, 10, 100 or 1000 ppm TBBPA for 28 days after which one group was sacrificed and the remaining rats placed on untreated diets for 2, 6 or 12 weeks. No effects on general appearance, behavior, body weight, food consumption or mortality were observed. No compound related gross or microscopic lesions or variations in organ weights were observed at any dose level. Liver and adipose bromine levels were similar in rats of the control and high dose groups sacrificed at the end of the 28-day treatment period. *(Goldenthal and Geil, 1972; reported in Environmental Health Criteria Document # 172, World Health Organization, Geneva, 1995)*

90-Day Rat Oral (2002)

In a 90-day oral toxicity study with TBBPA, the NOAL was 1000 mg/kg/day, the highest dose tested. Rats were administered TBBPA by gavage in corn oil for 13 weeks at dose levels of 0, 100, 300 and 1000 mg/kg/d. No effect on morality, clinical signs, body or organ weights, histopathology, urinalysis, ophthalmology, functional observational battery, motor activity, serum TSH, serum T3 or serum chemistries was observed. Differences were observed for bilirubin and ALP, but neither of these changes were found to be biologically or toxicologically meaningful or adverse. Serum T4 levels were decreased in treated animal, but the decrease was not of sufficient magnitude to induce adverse effects. This study was performed using a composite of 3 manufacturer's commercial product, and according to current EPA guidelines and Good Laboratory Practices. *(Schroeder R. A 90-day oral toxicity study of tetrabromobisphenol A in rats with a recovery group. MPI Research, Inc. Mattawan, MI. Aug 2002.)*

[NOTE: The abstract of the 2002 90-day study is attached]

90-Day Rat Oral (1975)
In a 90-day oral study, no toxicity was found in rats treated with up to 100 mg/kg in the feed. Rats were fed a diet supplying 0, 0.3, 3, 30 or 100 mg TBBPA/kg body weight for 90 days. No toxicological effects were detected at any dose level for appearance, demeanor, body weight gain, food consumption, hematology, clinical chemistry values, urinalysis, organ weights, and gross and microscopic examinations. The total bromine content in liver, kidney, skeletal muscle, fat and serum of rats in the 3 mg/kg dose group did not differ from that of the controls. (The 3 mg/kg group was the only group tested for total bromine content.) *(Quast et al. 1975; reported in Environmental Health Criteria Document # 172, World Health Organization, Geneva, 1995).*

90-Day Mouse Oral

In another 90-day study, a no adverse effect level of 4,900 mg/kg diet (~700 mg/kg body weight) was determined in mice *(Tobe et al., 1986; reported in Environmental Health Criteria Document # 172, World Health Organization, Geneva, 1995)."*

Table 2., Page 11. We suggest the following corrections:

- Add the 2001 90-Day study.
- Indicate that the 28-Day Goldenthal and Geil (1972) study was conducted via dietary administration. The TBBPA doses in this study were 0, 1, 10, 100 or 1000 mg/kg diet.

- Indicate that the 90-Day Dow Chemical study (Quast et al, 1975) was conducted via dietary administration. The TBBPA dose in this study were 0, 0.3, 3, 30 or 100 mg/kg diet.
- Delete the 28-Day oral study in rabbits (IRDC 1975). This study was performed with tetrabromophthalic anhydride, not TBBPA.
- Add the 14-Day mouse inhalation study (Goldenthal 1975).
- Add the 90-Day mouse oral study (Tobe et al. 1986).

9.1 Reproductive and Teratological Effects

An introductory paragraph would be helpful. We suggest:

> "TBBPA did not induce developmental or reproductive toxicity in rats. A NOEL of 1000 mg/kg/d, administered on Days 0-19 of gestation, was determined for maternal and fetal effects. TBBPA did not affect reproduction in a rat 2-generation study at doses up to 1000 mg/kg."

The information on the Saytex 111 study should be deleted. Saytex 111 was the trade name for the octabromodiphenyl oxide product formerly manufactured by Ethyl/Albemarle Corporation. Saytex 111 is not TBBPA.

We suggest the following changes in Table 3.

- Indicate that the 2001 BFRIP study utilized 25 mated female CD(SD)IGS BR rats/group. The females were 10 weeks old at initiation of pairing with male rats. The test article was 98.91% TBBPA, 0.05% o,p'-tetrabromobisphenol A, <0.01% 2,4,6-tribromophenol, and 1.04% tribromobisphenol A. This study was performed according to current EPA guidelines and Good Laboratory Practices. The abstract from the final report on this study is attached as a PDF file.
- Delete the 1975 study on Saytex 111.
- Delete the 1978 Velsicol study on Firemaster PHT-4.

We suggest deleting the Brouwer 1998 reference. The only information in the Brower paper with respect to developmental effects is one sentence: "Recently Meerts (personal communication) also found very high accumulation of radiolabel in fetal brain, following maternal exposure to the hydroxy-metabolites 4-OH-2,3,3',4',5-PeCB or TBrBPA." This is insufficient information to reach the conclusions expressed in the TBBPA review document. In fact, the Meerts 1999 4-page abstract where the results referred to by Brouwer were reported states "There is *no* [emphasis added] selective accumulation of TBBPA-related radioactivity in the fetal brain." Further, accumulation is inconsistent with the data reported in Section 9.1.2 Chemical Disposition, Metabolism and Toxicokinetics and attributed to Meerts et al., 1999. As reported in Section 9.1.2, only 0.34% of the dose was detected in fetal tissues after oral administration to dams on days 10-16 of gestation. Finally, TBBPA is readily metabolized and eliminated and therefore accumulation is unlikely.

We suggest including the following on the two-generation rat reproduction study:

> "The potential effects of TBBPA were studied over the course of two generations (P and F1) and the growth and development of the offspring (F1 and F2). A developmental neurotoxicity/neuropathology assessment was also conducted on the F2 offspring. The doses were 0, 10, 100 and 1000 mg/kg administered as a gavage in corn oil. In a rat two-generation reproduction study with TBBPA the NOEL for parental toxicity was 100 mg/kg/day, based on lower body weights and body weight gains in males a the 1000 mg/kg/d dose level. The NOEL for effects of TBBPA on thyroid hormone levels was 10 mg/kg/d based on lower T3 and T4 levels at the 100 and 1000 mg/kg/d dose levels. THS levels, however, were not affected at any of the doses in either generation. The NOEL for reproductive performance and pup toxicity was 1000 mg/kg/d, the highest dose level

evaluated. In the delayed neurotoxicity/neuropathology component, the NOEL was 100 mg/kg/d based on subtle morphometric changes in the parietal cortex in the brains of the Day 11 F2 pups in the 1000 mg/kg/d group. In this component, no changes at any dose level were seen in the pups in terms of clinical findings, sexual maturation landmarks, growth or from the various behavioral assessments. This study was performed according to current EPA guidelines and Good Laboratory Practices using test article that was a composite of 3 manufacturers commercial products. (*Schroeder, R. An oral two generation reproductive, fertility, and developmental neurobehavioral study of tetrabromobisphenol A in rats. MPI Research, Inc, Mattawan, MI. December 2002.*"

[NOTE: The abstract from the final report on the 2-generation study is attached.]

9.6 Genotoxicity
We suggest adding an introductory statement to the effect that "TBBPA was negative in the Ames Salmonella mutagenicity test and in the *in vitro* chromosome aberration test."

We suggest adding the following to this section:

Chromosome Aberration.
TBBPA was tested in the *in vitro* mammalian chromosome aberration test using human peripheral lymphocytes (HPBL) in both the absence and presence of an Arochlor-induced S9 activation system. Dose levels in the definitive assay in absence of exogenous metabolic activation (4 hr treatment, 20 hr harvest) were 6.25, 25, 100 μg/ml, and for a 20 hr treatment, 20 hr harvest were 6.25, 25, 75 μg/ml. In the presence of metabolic activation (4 hr treatment, 20 hr harvest), test article concentrations were 3.125, 12.5, 50 μg/ml.

The test article was soluble in treatment medium at all concentrations tested. Toxicity (mitotic inhibition) was appr. 54 and 59% at the highest dose level evaluated for chromosome aberrations, 100 μg/ml and 75 μg/ml in the non-activated 4 hr and 20 hr exposure groups, respectively. Toxicity (mitotic inhibition) was 58% at the highest dose level evaluated for chromosome aberrations, 50 μg/ml, in the S9 activated study.

No statistically significant increases in structural and numerical chromosome aberrations were observed in the non-activated or the S9 activated 4 hr exposure groups relative to the solvent control group, regardless of dose level ($p>0.05$, Fisher's exact test). In the absence of a positive response in the non-activated 4 hr exposure group, the non-activated 20 hr continuous exposure group was evaluated for structural and numerical chromosome aberrations. No statistically significant increases in structural and numerical chromosome aberrations were observed in the non-activated 20 hr continuous exposure group relative to the solvent control group, regardless of dose level ($p>0.05$, Fisher's exact test). The positive controls performed as expected.

TBBPA was negative for the induction of structural and numerical chromosome aberrations in the in vitro chromosome aberration test using human peripheral lymphocytes *(Gudi, R. and Brown, C. In vitro chromosome aberration test. Test Article: Tetrabromobisphenol A (TBBPA). Study Number: AA47PV.341.BTL. 2001. BioReliance, Rockville, MD).*

Intragenic Recombination.
The Sp5 and SPD8 cell lines were developed by the paper's authors. The clones used in this study exhibit spontaneous partial duplication of the hprt gene, resulting in a non-functional hgprt protein. These mutants revert spontaneously to a functional hprt gene phenotype by recombination with a frequency of 1 x $10^5$ reversions/cell generation. This reversion frequency is said to increase by exposure to chemical or physical agents. Treatment with the test substance was for 24 hr.

In the SPD8 cells, TBBPA concentrations of 0, 5, 10, 20, 30, and 40 μg/ml resulted in a reversion frequency of 1.0, 1.1, 1.4, 1.3, 1.3, and 1.0, respectively. Cytoxicity was not observed at the doses tested. In the Sp5 cells, TBBPA concentrations of 0, 10, 20, 40, 70 μg/ml resulted in a reversion frequency of 1.0, 0.8, 0.8, 1.0 and 0.7, respectively. Cytotoxicity was observed at 70 μg/ml. None of these reversion frequencies were statistically different from the control (Student's t test, $p<0.05$). Thus, TBBPA had no effect in either the SPD8 or Sp5 recombination assay *(Helleday et al. Brominated flame retardants induce intragenic recombination in mammalian cells. Mutation Research 439 (1999) 137-147).*

9.10 Other Data

Effects on Thyroid Hormones

We believe this Brower reference should be deleted. That reference does not report original research, and is a short 4-page paper. The Meerts *et al.* 2000 paper is the full publication on the work purportedly covered in Brouwer's paper. With respect to TBBPA, Meerts *et al.* (2000) stated regarding her *in vitro* results "We were able to show very potent competition binding for TBBPA and PBP (10.6- and 7.1 fold stronger than the natural ligand T4, respectively." In 1999, Meerts *et al.* reported on her study in pregnant and fetal rats and concluded "these results indicate that there is an apparent lack of TBBPA binding to TTR *in vivo*, and explain the normal levels in total and free T4. In conclusion, these results indicate that despite a very high *in vitro* potency of TBBPA to compete with thyroxine for binding to TTR, this can not be observed *in vivo*. This most likely can be explained by the high faecal elimination of TBBPA via oral exposure. Of the administered dose, only 0.83% can be detected in maternal and 0.34% in fetal tissues."

We suggest deleting the Berg *et al.* 2001 reference. That publication did not include TBBPA. Halldin *et al.* 2001 reported that when injected into quail eggs, TBBPA (15 μg/g egg) did not cause any significant estrogen-like effects on the variables studied. TBBPA appear to be absorbed into the embryo after the yolk sac injection, and to be metabolized and excreted, based on $^{14}$C-activity in bile and allantoic fluid. $^{14}$C-TBBPA administered to laying quail was largely excreted via the bile and 9 days after oral dosing, only small amounts of the label remained within the hen. Maternal transfer of $^{14}$C-TBBPA to the egg was low.

MPI RESEARCH

# A 90-DAY ORAL TOXICITY STUDY OF TETRABROMOBISPHENOL A IN RATS WITH A RECOVERY GROUP

**TEST ARTICLE:** Tetrabromobisphenol A

**TESTING FACILITY:** MPI Research, Inc.
54943 North Main Street
Mattawan, Michigan 49071-9399

**STUDY NUMBER:** 474-006

**STUDY DIRECTOR:** Raymond E. Schroeder, M.S., D.A.B.T.

**SPONSOR ADDRESS:** American Chemistry Council
Brominated Flame Retardant
Industry Panel (BFRIP)
1300 Wilson Blvd.
Arlington, Virginia 22209

**SPONSOR REPRESENTATIVE:** Wendy K. Sherman

**DATE OF STUDY COMPLETION:** August 22, 2002

## 2. SUMMARY

This study was conducted for American Chemistry Council-Brominated Flame Retardant Industry Panel (BFRIP) to evaluate the subchronic toxicity of Tetrabromobisphenol A (TBBPA) in CD® [Crl: CD® (SD) IGS BR] rats. This study consisted of three treatment groups and one vehicle (corn oil) control group (ten rats/sex/group). Recovery animals (five rats/sex) were included in the control and high-dose group and evaluated over a 6-week posttreatment period. The TBBPA was administered orally by gavage daily for 13 weeks at dose levels of 0, 100, 300, and 1000 mg/kg/day at a constant volume of 5 mL/kg/day. The control animals received the vehicle at the same volume and dosing regimen as the treated groups. Animals were observed daily cageside for survivability, injury, and availability of feed and water. Other observations conducted weekly during the study included detailed physical and neurobehavioral evaluations, and measurements of body weights and food consumption. A Functional Observational Battery (FOB) was conducted pretest and at Week 12. Motor activity (MA) was also evaluated during Week 12. Ophthalmoscopic examinations were conducted pretest, study termination, and following recovery. Other evaluations conducted at termination and following recovery included: hematology, clinical chemistry, urinalysis, organ weights, and pathological examinations (macroscopic and microscopic). Thyroid hormone levels [Thyroid Stimulating Hormone (TSH), $T_3$ (3,5,3′ - triiodothyronine), and $T_4$ (thyroxine or 3,5,3′5′-tetraiodothyronine)] were evaluated of animals at 33 days and at termination. These same hormone levels were evaluated following recovery.

Homogeneity of the dosing suspensions at the low and high concentration levels was determined on mixes used the first week of study. Mean concentration recoveries from the periodic analyses of dosing suspensions used on study were 102.5%, 110.2%, and 106.8% of nominal for the 100, 300, and 1000 mg/kg/day groups, respectively.

A total of six females (two control and four in the 1000 mg/kg/day group) died or were euthanized *in extremis*. The mortality/moribundity seen in these groups was considered related to dosing injury and not treatment related.

No effect of treatment was seen in clinical or neurobehavioral evaluations, body weights, food consumption, ophthalmological examinations, MA, FOB evaluations, hematology or urinalysis evaluations. Likewise, no effect of treatment was evident from organ weights, or from the macroscopic or microscopic examinations.

After 90 days of dosing, total bilirubin values were statistically higher than the control means (males: 0.14 ± 0.05; females: 0.13 ± 0.05) in males in the 1000 mg/kg/day dose (0.34 ± 0.024) ($p<0.01$) group and in females in the 300 (0.19 ± 0.03) ($p<0.05$) and 1000 mg/kg/day (0.2 ± 0.06) groups ($p<0.01$). Mean serum alkaline phosphatase (ALP) levels after 90 days of dosing in the female 1000 mg/kg/day (98.9 ± 49.47) group was statistically higher than that of the control mean (58.4 ± 28.46) ($p<0.05$). A slight increase, but non-statistically different, was also observed in males. Although these differences were considered possibly due to test article administration, neither of these changes was of a magnitude that were found to be biologically or toxicologically meaningful or adverse. Serum bilirubin and ALP levels in control and treated groups of both sexes were comparable after the end of the recovery period.

With respect to serum hormone levels, mean TSH and T3 levels were statistically comparable between control and treated animals at all time points (Day 33, terminal and recovery euthanasia). Mean T4 levels were statistically lower than the control mean (Day 33: 4.96 ± 0.84; terminal: 5.09 ± 0.80) in the 100 (Day 33: 3.66 ± 0.88; terminal: 3.27 ± 0.67), 300 (Day 33: 3.42 ± 0.71; terminal: 2.61 ± 0.87) and 1000 (Day 33: 3.39 ± 0.55; terminal: 3.09 ± 0.91) mg/kg/day male dose groups at days 33 and 90 ($p<0.01$). Mean T4 levels were also statistically lower than the control mean (4.27 ± 0.96) in females in the 100 (3.31 ± 1.08), 300 (3.24 ± 0.85) and 1000 (3.33 ± 0.84) mg/kg/day dose groups at Day 33 ($p<0.05$). Mean T4 levels in all female dose groups were statistically comparable to the control mean at Day 90. At the recovery euthanasia, mean T4 levels were comparable in the control and 1000 mg/kg/day male and female groups. The change in T4 levels seen in the 1000 mg/kg/day group was reversible and levels comparable to control were seen following recovery.

The decrease in serum T4 levels was considered a possible effect of test article administration. TBBPA has been shown to competitively displace T4 from transthyretin (TTR), a major serum T4-binding protein in the rat, *in vitro* (Meerts et al. 2000)[1]. That portion of serum T4 displaced from its binding site would be available for metabolism and elimination, thereby leading to a decrease in serum levels. The half-life of T4 in the rat is short due to its transport by TTR, and thus this species is sensitive to perturbations in T4 levels. For example, the plasma T4 half-life in rats is 12-24 hours while T4's half-life in humans is 5-9 days (Capen, C. 1996)[2]. In humans circulating T4 is bound primarily to thyroxin binding globulin, but this high affinity binding protein is not present in rodents. This mechanism, displacement of T4 from TTR-binding by TBBPA with subsequent metabolism and elimination in the liver, may account for the decreased mean serum T4 levels in treated animals. Because the decrease in T4 levels was not of sufficient magnitude to alter mean serum TSH or T3 levels, thyroid histopathology, thyroid weight, or other parameters indicative of thyroid pathology (e.g. body weight, etc.), the decrease in serum T4 levels was not considered adverse. The reduction in serum T4 levels was not accompanied by evidence of toxicity or adverse effects, and the animals were clinically normal.

Thus, in this rat 90-day oral toxicity study with TBBPA, the No Observed Adverse Effect Level (NOAEL) was 1000 mg/kg/day, the highest dose tested. No effect on mortality, clinical signs, body or organ weights, histopathology, urinalysis, ophthalmology, FOB, MA, serum TSH, serum T3 or serum chemistries was observed. Differences were observed for bilirubin and ALP, but neither of these changes were found to be biologically or toxicologically meaningful or adverse. Serum T4 levels were decreased in treated animals, but the decrease was not of sufficient magnitude to induce adverse effects.

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[1] Meerts (2000) Potent competitive interactions of some brominated flame retardants and related compounds with human transthyretin *in vitro*. Toxicological Sciences, 56, 95-104.

[2] Capen, C. Chapter 21. Toxic Responses of the Endocrine System. In: Casarett & Doull's Toxicology, The Basic Science of Poisons. Fifth Edition. Ed. Curtis Klaassen. McGraw-Hill, New York. 1996.

MPI RESEARCH

# AN ORAL TWO GENERATION REPRODUCTIVE, FERTILITY, AND DEVELOPMENTAL NEUROBEHAVIORAL STUDY OF TETRABROMOBISPHENOL A IN RATS

| | |
|---|---|
| **DATA REQUIREMENT:** | US EPA OPPTS 870.3800 |
| **TEST ARTICLE:** | Tetrabromobisphenol A |
| **PERFORMING LABORATORY:** | MPI Research, Inc.<br>54943 North Main Street<br>Mattawan, MI 49071-9399 |
| **LABORATORY STUDY IDENTIFICATION:** | 474-004 |
| **STUDY DIRECTOR:** | Raymond E. Schroeder, M.S., D.A.B.T. |
| **SPONSOR ADDRESS:** | Brominated Flame Retardant Industry Panel<br>American Chemistry Council<br>1300 Wilson Blvd.<br>Arlington, Virginia 22209 |
| **SPONSOR REPRESENTATIVE:** | Wendy K. Sherman |
| **DATE OF STUDY COMPLETION:** | December 11, 2002 |

## 2. SUMMARY

The objective of this reproduction study was to provide general information concerning the effects of Tetrabromobisphenol A (TBBPA) over the course of two generations (P and $F_1$) and the growth and development of the offspring ($F_1$ and $F_2$). A developmental neurotoxicity/neuropathology assessment was also conducted on the $F_2$ offspring. The study consisted of three treatment groups (10, 100 and 1000 mg/kg/day) and a vehicle (corn oil)-treated control group (30 CD® Sprague-Dawley rats/sex/group/generation). TBBPA was administered orally via gastric intubation. Animals were treated seven days a week throughout the study. Dosing suspensions were prepared fresh weekly. Parental animals were treated for at least 10 weeks prior to mating (premating treatment period) to produce the $F_1$ and $F_2$ litters. In the developmental neurotoxicity/neuropathology (DNT/NP) component, $F_2$ pups were randomly selected to continue on study for the following evaluations (unique sets of animals [10 pups/sex/group] were randomly selected for each assessment): PND 60 brain weights, PND 60 perfusion and neuropathology, special detailed clinical examinations (PND 4, 11, 21, 35, 45, and 60), motor activity [MA] (PND 13, 17, 21, and 60), auditory startle habituation [ASH] (PND 22 and 60), and learning and memory [L&M] (PND 22, 60 and 110). Additionally, 10 $F_2$ pups/sex/group were selected randomly on PND 11 for collecting, weighing, and preserving of the brains.

For breeding of the P and $F_1$ generations, one male was paired with one female from the same treatment group continuously until mating occurred or for 14 consecutive days. The day of mating evidence was considered Day 0 of gestation. During mating of the $F_1$ generation, cohabitation of littermates was avoided. Females delivered and nursed litters over a 21-day lactation period. On Day 4 of lactation all litters were culled if necessary to 8 pups ($F_1$) or 10 pups ($F_2$) with sex distribution equalized, when possible. Litters with fewer pups than required at culling were not adjusted.

At weaning of each $F_1$ litter, at least one pup/sex/litter was selected to continue on study as the $F_1$ parental generation (30 pups/sex/group). These pups started treatment on PND 22. The premating period formally initiated after the last litter weaned. Thus, there was a maximum of two weeks difference in age for the $F_1$ animals within each treatment group at initiation of the premating growth period.

Detailed clinical examinations, body weights, and food consumption were recorded periodically throughout the study for the P and $F_1$ parental animals. Estrous cyclicity was evaluated in the P and $F_1$ females the last three weeks of the premating period, and these evaluations continued until the female was confirmed mated or to the end of the mating period. Females were allowed to deliver and nurse the litter to weaning. Litters were evaluated at birth and throughout the lactation period. Each pup was individually identified at birth (paw tattoo), sexed, examined externally for defects, and weighed. All pups were monitored for appearance, growth, and survival throughout the lactation period. Clinical examinations, body weights, food consumption, and occurrence of maturation landmarks (vaginal opening [VO] and preputial separation [PS]) were recorded for $F_1$ parental animals.

Several days before terminal euthanasia of the P and $F_1$ animals, blood was collected from 10 randomly selected animals/sex/group and analyzed for thyroid hormone levels (TSH, $T_3$ and $T_4$). At necropsy, P and $F_1$ animals received a macroscopic examination and reproductive tissues and other designated tissues were taken, weighed, and preserved. Reproductive tissues were evaluated microscopically for all P and $F_1$ animals in the control and 1000 mg/kg/day groups. Microscopic examinations were also performed for reproductive tissues of the few low- and mid-dose P and $F_1$ animals that failed to mate, conceive or sire. Gross lesions were also examined microscopically for all parental animals. Sperm evaluations (motility, caudal epididymal sperm counts, homogenization-resistant testicular sperm head counts, and morphology) for P and $F_1$ males and a count of primordial follicles were conducted for P and $F_1$ females. The latter evaluations were conducted only in the control and 1000 mg/kg/day groups. At weaning, the unselected $F_1$ pups and one $F_2$ pup/sex/litter were euthanized, necropsied, specific organs weighed (brain, spleen, and thymus), and gross lesions preserved.

In the DNT/NP component, $F_2$ pups euthanized on PND 11 (10/sex/group) had the brains taken, weighed, and preserved in fixative for neuropathological evaluation and morphometric measurements. These examinations were initially conducted in the control and high-dose animals and were expanded to include the lower dose groups. $F_2$ pups retained postweaning were observed twice daily cageside for mortality and were weighed and given detailed clinical examinations periodically during the study. Sexual maturation (VO and PS) was evaluated for the 40 animals/sex/group retained for the neurobehavioral assessments (i.e., special clinical examinations, MA, L&M, and ASH). These animals were euthanized after all the behavioral tests had been completed. At termination, all $F_2$ animals were weighed, given a detailed clinical examination and necropsied. The $F_2$ animals euthanized on PND 60 for neuropathological evaluation were anesthetized with sodium pentobarbital and perfused with 3% paraformaldehyde and 3% glutaraldehyde. The whole brain, sections of the spinal cord, and selected peripheral nerves were collected and processed for neuropathological examination in the control and 1000 mg/kg/day groups.

Dosing formulations were homogeneous at the batch size prepared and stable when refrigerated to 14 days. Mean recoveries from the periodic analyses of dosing suspensions used on study were 101%, 99%, and 105% of nominal for the 10, 100, and 1000 mg/kg/day groups, respectively.

No effect of treatment was seen for mortality in the P and $F_1$ generations. The low incidence of mortality seen in these animals was considered incidental and unrelated to treatment with TBBPA.

In the parental generations, the only effect of treatment with TBBPA was seen in the $F_1$ males at 1000 mg/kg/day and involved lower body weights for several weekly intervals during the study and lower weight gain over the entire Week 1-11 premating period. No effect of treatment in either generation was evident from the clinical examinations, estrous cyclicity, reproductive performance, gestation/lactation body weights or food consumption, gestation length, litter data, or from the macroscopic and microscopic evaluations, organ weights, sperm evaluations, and primordial follicle counts. No effect on body weights or body weight

gain was seen in the P animals or $F_1$ parental females. Likewise, no adverse effect on food consumption was seen in the treated groups for either generation.

No effect of treatment with TBBPA was evident in the $F_1$ and $F_2$ pups in regard to body weights, clinical findings, sex ratios, survival to weaning, macroscopic findings, or organ weight data (Day 21).

No effects on thyroid hormone levels (TSH, $T_3$ and $T_4$) were observed at the 10 mg/kg/day dose level in either generation. At 100 and 1000 mg/kg/day, some treatment-related effects on some thyroid hormone parameters ($T_3$ and $T_4$) were seen. TSH levels were unaffected, however, in either generation. Treatment with TBBPA demonstrated an increased incidence and magnitude of lower $T_4$ values in the 100 and 1000 mg/kg/day groups. P males given 1000 mg/kg/day, and $F_1$ males given 100 or 1000 mg/kg/day also had mild reductions in $T_3$ values. In the absence of increases in TSH hormone levels, moderate reductions in circulating serum $T_4$ levels, with only mild decreases in $T_3$ for a few 1000 mg/kg/day P males, and 100 and 1000 mg/kg/day $F_1$ males, are suggestive of induction of hepatic $T_4$-uridine diphosphate glucuronyl transferase (UDP-GT) enzymes that increase the removal of thyroxine. TBBPA has been shown *in vitro* to competively displace $T_4$ from human transthyretin, a serum carrier protein. The decreases in $T_4$ and $T_3$ observed in this study did not exceed the threshold for stimulation of TSH production. Thus, repeat daily dosing with TBBPA at doses of 100 or 1000 mg/kg/day to P and $F_1$ generation rats resulted in effects on thyroid function, probably secondary to enzyme induction, without alteration in TSH activity. The 10 mg/kg/day dose was determined to be a no observed effect level (NOEL) for TBBPA and its response on thyroid function.

In the DNT/NP component, the only suggestion of a treatment-related effect was a reduction in the thickness of the parietal cortex of the Day 11 pups at the 1000 mg/kg/day dose level. It was not accompanied by any histologic changes in the parietal cortex, such as degeneration, necrosis, cell loss, demyelination, proliferative changes, or changes in neuronal cell density. A likely explanation for the decreased thickness of parietal cortex would be a decreased number of cells without changes in cell density. The brain weights of the 11-day-old rats were virtually equal across groups. However, it is possible that other regions of the brain were enlarged and compensated for the decrease in the thickness of parietal cortex in the affected groups. The thickness of the parietal cortex for the animals at the 10 and 100 mg/kg/day dose levels was comparable to the control. No microscopic alterations were observed in brain, spinal cord, nerves, and ganglia in the 60-day-old rats. Therefore, this apparent test-article related effect in the Day 11 $F_2$ pup brains must be interpreted with caution, given the limitations of morphometric analysis. No effect of treatment was evident from the other parameters evaluated in the DNT/NP component. This would include the special detailed clinical observations, developmental maturation landmarks (VO and PS), neurobehavioral evaluations (MA, L&M, ASH), or Day 60 brain weights.

Thus, in this 2-generation reproduction study with TBBPA the No Observed Effect Level (NOEL) for parental toxicity was 100 mg/kg/day based on lower body weights and body weight gain in males at the 1000 mg/kg/day dose level. The NOEL for effects of TBBPA on thyroid hormone levels was 10 mg/kg/day based on lower $T_3$ and $T_4$ levels at the 100 and

1000 mg/kg/day dose levels. TSH levels, however, were not affected at any of the dose levels in either generation. The NOEL for reproductive performance and pup toxicity was 1000 mg/kg/day, the highest dose level evaluated. In the DNT/NP component, the NOEL was 100 mg/kg/day based on subtle morphometric changes in the parietal cortex in the brains of the Day 11 $F_2$ pups in the 1000 mg/kg/day group. In this component no changes at any dose levels were seen in the pups from clinical findings, sexual maturation landmarks, growth, or from the various behavioral assessments.

Attachment 2
Studies of TBBPA Not Available
At the Time of the US HPV Challenge Program Submission

| Study Title | Holder |
|---|---|
| A 90 day Subchronic Toxicology Study | BFRIP |
| A 2-generation Developmental Study with Neurobehavioral Assessment | BFRIP |
| Water Solubility | BFRIP |
| Other Environmental Toxicity Studies | BFRIP |

Attachment 3
Studies of TBBPA-DBPE

| Study Title | Holder |
|---|---|
| Unscheduled DNA Synthesis Rat Hepatocyte Assay | Great Lakes Chemical Corp. |
| In Vitro Sister Chromatid Exchange in Chinese Hamster Ovary Cells | Great Lakes Chemical Corp |
| Mutagenicity Evaluation in the Ames Salmonella/Microsome Plate Test (Multiple) | Great Lakes Chemical Corp. |
| Fish Bioaccumulation (Killfish) | Great Lakes Chemical Corp |
| Acute Toxicity Studies in Rabbits and Rats | Great Lakes Chemical Corp. |
| Acute Inhalation Toxicity Study in Rats | Great Lakes Chemical Corp |
| Mutagenicity Evaluation | Great Lakes Chemical Corp. |
| Adsorption/Desorption Characteristics in Representative Soils | Great Lakes Chemical Corp |
| An Evaluation of Hydrolysis as a Function of pH | Great Lakes Chemical Corp. |
| Determination of the n-Octanol/Water Parition Coefficient by the Shake Flask Method | Great Lakes Chemical Corp |
| Determination of the Water Solubility | Dead Sea Bromine Group |
| Determination of the Vapor Pressure | Dead Sea Bromine Group |
| Determination of the Ready Biodegradability | Dead Sea Bromine Group |
| The Estimation of the Adsorption Coefficient | Dead Sea Bromine Group |
| The Toxicity to *Daphnia magna* | Dead Sea Bromine Group |
| The toxicity to Rainbow trout (*Oncorhynchus mykiss)* | Dead Sea Bromine Group |
| The Growth Inhibition of the Alga *Selenastrum capricornutum* | Dead Sea Bromine Group |
| An Evaluation of the Effect of FR-720 on the Inhibition of Activated Sludge Respiration | Dead Sea Bromine Group |
| Slow Stirring Method for the Determination of the Partition Coefficient | Dead Sea Bromine Group |
| Evaluation of the Mutagenic Activity (AMES) in Salmonella and E. coli (Multiple) | Dead Sea Bromine Group |
| Evaluation of the Mutagenic Activity in an *in vitro M*ammalian Cell Gene Mutation Test with Mouse Lymphoma Cells | Dead Sea Bromine Group |
| Eye Irritation Test in the Rabbit | Dead Sea Bromine Group |
| Magnusson & Kligman Maximisation study in the guinea pig | Dead Sea Bromine Group |
| Oral Toxicity in the Rat | Dead Sea Bromine Group |
| Dermal Irritation Test in the Rabbit | Dead Sea Bromine Group |
| Polybrominated Dibenzodioxins and dibenzofurans Contamination | Dead Sea Bromine Group |