SUPPLEMENTAL FILE 4:
REPORT OF THE CANCER ASSESSMENT REVIEW COMMITTEE (CARC)

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

DATE: September 17, 2014

SUBJECT: **Tetrabromobisphenol-A:** Report of the Cancer Assessment Review Committee

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The Cancer Assessment Review Committee (CARC) met on August 20, 2014 to evaluate the cancer classification of tetrabromobisphenol-A in accordance with the *EPA's Final Guidelines for Carcinogen Risk Assessment* (March, 2005). Attached please find the final Cancer Assessment Document.

CANCER ASSESSMENT DOCUMENT

EVALUATION OF THE CARCINOGENIC POTENTIAL OF

Tetrabromobisphenol A (TBBPA)

For the Office of Pollution Prevention and Toxics

CANCER ASSESSMENT REVIEW COMMITTEE
HEALTH EFFECTS DIVISION
OFFICE OF PESTICIDE PROGRAMS

September 17, 2014

EXECUTIVE SUMMARY

On August 20, 2014, the Cancer Assessment Review Committee (CARC) of the Health Effects Division (HED) of the Office of Pesticide Programs (OPP) evaluated the carcinogenic potential of Tetrabromobisphenol A (TBBPA). Dr. David Lai of the Office of Pollution Prevention and Toxics (OPPT), Risk Assessment Division, presented the results of a cancer bioassay with TBBPA conducted in Wistar Han rats and B6C3F1/N mice by the National Toxicology Program. Toxicology, metabolism, and mutagenicity studies for TBBPA were also discussed, as well as structure-activity relationships.

Groups of 50-60 male and 50-60 female Wistar Han rats and male and female B6C3F1/N mice were administered 0, 250, 500, or 1,000 mg/kg-bw/day of TBBPA in corn oil by gavage, 5 days per week, for up to 105 weeks. Survival of the treated groups was similar to that of the vehicle control group. In rats, the mean body weights of males at 500 and 1000 mg/kg/day were generally at least 10% less than the vehicle control group after study week 25; body weights of females at all dose levels were similar to those of the vehicle control throughout the study. There were no treatment-related clinical signs of toxicity at any dose level in either sex. In mice, survival at the high dose (1,000 mg/kg/day) in both sexes was significantly ($p<0.001$) lower than that of the vehicle control groups. Increased mortality was seen as early as 6 months into the study and coincided with the initial difference of body weight gain in female mice at 1000 mg/kg/day. Histopathology findings suggests that decreased survival may have been due in part to gastrointestinal toxicity, although the various gastrointestinal lesions observed in the high dose groups did not always demonstrate an increase in severity over those in the other treatment groups. After study week 25, the mean body weights of females at 1000 mg/kg/day were decreased (10% to 25%) when compared to the vehicle controls. Body weights of all dosed groups of males and of females in the 250 and 500 mg/kg groups were generally similar to those of the vehicle control groups throughout the study. No clinical findings related to chemical exposure were observed.

Tumors of the testes and uterus were seen in males and female rats, respectively. In males, the incidences of interstitial cell adenoma of the testis were slightly increased at 500 mg/kg/day (2%) and 1000 mg/kg/day (6%) compared to vehicle controls (0%). **The CARC did not consider the testicular tumors to be treatment-related** since no pair-wise statistical significance (high dose) or dose trend were observed and the total incidences (4/200) in this study were comparable to the historical control incidences in two-year studies (4/150). In addition, there were no supportive precursor lesions in the testes. In female rats, the incidence of uterine epithelial tumors (combined adenoma, adenocarcinoma, or malignant mixed Müllerian tumor) were significantly increased at 250 mg/kg/day (12%), 500 mg/kg/day (32%), and 1000 mg/kg/day (38%) when compared to the vehicle control group (12%). **The CARC determined that the uterine tumors were treatment-related** since there was a clear dose response and a dose trend ($p<0.01$) observed, and the tumors were corroborated by the occurrence of precursor lesions (endometrial hyperplasia) at relevant dose levels.

Tumors of the liver and large intestine as well as hemangiomas/hemangiosarcomas of all organs were seen in male mice. Although the liver adenomas in male mice at the high dose showed statistical significance, the **CARC determined that the tumors of the liver and large intestines were not treatment-related** since the incidences were within the historical control range and there

were no supportive precursor lesions. **The CARC also determined that the hepatoblastomas were not treatment-related** due to lack of statistical significance (pairwise at high dose) or dose trend for hepatoblastomas alone or combined with carcinomas.

The CARC also determined that the adenomas and carcinomas observed in the large intestine (cecum or colon) of male mice were not treatment-related since there was no statistical significance on pairwise (high dose) or dose trend. Additionally, there were no supportive precursor lesions in the stomach.

The incidence of hemangioma or hemangiosarcoma was increased at 250 mg/kg/day (10%) and 500 mg/kg/day (18%) when compared to vehicle controls (6%). These lesions occurred in a variety of organs, such as the bone marrow, liver, lung serosa, lymph nodes, skin, spleen, and vertebra. **The CARC determined that the hemangiomas/hemangiosarcomas observed in male mice were treatment-related** due to the presence of a dose trend and high dose incidence at the upper limit of the historical control range.

There was no evidence of carcinogenicity in female mice. Mode of action data that meets the 2006 International Programme on Chemical Safety (IPCS) Human Relevance Framework were not available for evaluation. There is no concern for mutagenicity.

In accordance with the Agency's 2005 Guideline of Carcinogen Risk Assessment, Tetrabromobisphenol A is classified as **"Likely to be Carcinogenic to Humans"** based on the presence of uterine epithelial tumors (combined adenoma, adenocarcinoma, or malignant mixed Mülllerian) in female Wistar Hans rats and hemangiomas/hemangiosarcomas in male B6C3F1 mice. There was no evidence of carcinogenicity in female mice. There were no mutagenicity concerns.

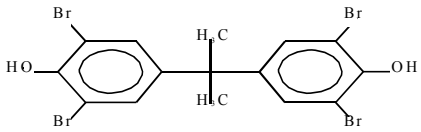
In accordance with the Agency's 2005 Guideline of Carcinogen Risk Assessment, a low dose linear extrapolation model (Q_1*) is appropriate for quantification of human risk.

I. INTRODUCTION

On August 27, 2014, the Cancer Assessment Review Committee (CARC) of the Health Effects Division (HED) of the Office of Pesticide Programs (OPP) evaluated the carcinogenic potential of Tetrabomobisphenol A (TBBPA). Dr. David Lai, Risk Assessment Division, Office of Pollution Prevention and Toxics (OPPT) presented the data on TBBPA.

II. BACKGROUND INFORMATION

Tetrabromobisphenol A (TBBPA) is a crystalline powder with a M.W. of 543.9 g/mole. It has low water solubility (0.063 mg/l at 21°C; 0.24 mg/l at 25°C), low vapor pressure (4.72×10^{-9} at 25°C), and a moderately high log P value (5.9). About 4% of the particles are <15 μm in diameter (EURAR, 2006).



III. EVALUATION OF CARCINOGENICITY STUDIES

Reference: NTP (2013). NTP Technical Report. Toxicological studies of tetrabromobisphenol A (CAS NO.79-94-7) in F344/NT_{AC} rats and B6C3F1/N mice and toxicology and carcinogenesis study of tetrabromobisphenol A in WISTAR HAN [Crl:WI(Han)] rats and B6C3F1/N mice (Gavage studies), NTP TR 587. National Toxicology Program, Research Triangle Park, NC.

1. Carcinogenicity Study in Wistar Han Rats

Groups of 50-60 male and 50-60 female Wistar Han rats were administered 0, 250, 500, or 1,000 mg/kg-bw/day TBBPA in corn oil by gavage, 5 days per week for up to 105 weeks. Survival of the treated groups was similar to that of the vehicle control group. The mean body weights of male rats at 500 and 1000 mg/kg/day group were generally at least 10% less than the vehicle control group after study week 25; body weights of female rats at all dose levels were similar to those of the vehicle control throughout the study. There were no treatment-related clinical signs of toxicity at any dose level in either sex.

A. Tumor Data

Tumors of the testes and uterus were seen in males and female rats, respectively (Tables 1 and 2). In male rats, the incidences of interstitial cell adenoma of the testis were slightly increased at 500 (1/50) and 1,000 mg/kg/day (3/50) groups as compared to controls (0/50) (Table 1). In female rats, the incidences of adenocarcinoma and of adenoma, adenocarcinoma, or malignant mixed Müllerian tumor (combined), were significantly increased at 500 and 1,000 mg/kg/day groups (Table 2).

Table 1. Testicular Tumors in Male Wistar Han Rats Following Gavage Dosing of TBBPA

Interstitial Cell, Adenomas	Vehicle Control	250 mg/kg/day	500 mg/kg/day	1000 mg/kg/day
Overall rate	0/50 (0%)	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted rate[a]	0.0%	0.0%	2.2%	6.8%
Terminal rate[b]	0/33 (0%)	0/28 (0%)	1/38 (3%)	3/39 (8%)
First incidence (days)	—[c]	—	727 (T)	727 (T)
Poly-3 test	P=0.023	—	P=0.526	P=0.138

Data obtained from NTP Report TR 587
a Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
b. Observed incidence at termination
c. No neoplasm in animal group
Historical control incidences: 4/150 (2.7%±2.3%; range 0% to 4%)

Table 2. Uterine Tumors in Female Wistar Han Rats Following Gavage Dosing of TBBPA

Interstitial Cell, Adenomas, Adenocarcinomas, or Malignant Mixed Mullerian tumors	Vehicle Control	250 mg/kg/day	500 mg/kg/day	1000 mg/kg/day
Overall rate	6/50 (12%)	11/50 (22%)	16/50 (32%)	19/50 (38%)
Adjusted rate[a]	13.9%	24.2%	38.8%	42.2%
Terminal rate[b]	3/34 9%)	5/34 (15%)	10/29 (35%)	11/33(33%)
First incidence (days)	668	548	321	442
Poly-3 test	P=0.001	P= 0.168	P=0.007	P=0.002

Data obtained from NTP Report TR 587
a Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
b. Observed incidence at termination

B. Non-Neoplastic Lesions

No treatment-related non-neoplastic lesions were seen in the testes at any dose level. In females, endometrial atypical hyperplasia was seen in all dose groups (Table 3).

Table 3. Non-neoplastic Lesion of the Uterus in Female Wistar Han Rats

Lesion	Vehicle Control	250 mg/kg/day	500 mg/kg/day	1000 mg/kg/day
Endometrium, Hyperplasia, Atypical	2	13*	11*	13**P<0.01

C. NTP Conclusion.

The National Toxicology Program (NTP) concluded that under the conditions of the 2-year gavage studies, there was *equivocal evidence of carcinogenic activity* of tetrabromobisphenol A in male Wistar Han rats based on the occurrence of testicular adenoma. There was *clear evidence of carcinogenic activity* of tetrabromobisphenol A in female Wistar Han rats based on increased incidences of uterine epithelial tumors (predominantly uterine adenocarcinoma).

2. Carcinogenicity Study in B6C3F1.N Mice

Groups of 50-60 male and 50-60 female B6C3F1 mice were administered 0, 250, 500, or 1,000

mg/kg-bw/day TBBPA in corn oil by gavage, 5 days per week for up to 105 weeks. Survival at the high dose (1,000 mg/kg/day) in both sexes was significantly ($p<0.001$) lower than that of the vehicle control groups. Increased mortality was seen as early as 6 months into the study and coincided with the initial difference of body weight gain in female mice at 1000 mg/kg/day. Histopathology findings suggests that decreased survival may have been due in part to gastrointestinal toxicity, although the severities of the various gastrointestinal lesions in the high dose groups were not always increased over those in the other dosed groups. After study week 25, the mean body weights of females at 1000 mg/kg/day were decreased (10% to 25%) when compared to the vehicle controls. Body weights of all dosed groups of males and of 250 and 500 mg/kg females were generally similar to those of the vehicle control groups throughout the study. No clinical findings related to chemical exposure were observed.

A. Tumor Data

In the male mice, the incidence of multiple hepatocellular adenoma was significantly ($p<0.05$) increased in males at 500 mg/kg/day. In addition, the incidences of hepatoblastomas were significantly increased in males at 250 mg/kg/day and 500 mg/kg/day when compared to vehicle controls (2/50) (Table 4).

Table 4. Liver Tumors in Male B6C3F1/N Mice Following Gavage Dosing of TBBPA

	Vehicle Control	**250 mg/kg/day**	**500 mg/kg/day**
Hepatocellular adenoma, multiple	12 (24%)	20 (40%)	28* (56%) ($p<0.05$)
Hepatocellular carcinoma, multiple	2	4	5
Hepatoblastomas			
Overall rate	2/50 (4%)	11/50 (22%)	8/50 (16%)
Adjusted rate[a]	4.6%	25.6%	17.6%
Terminal rate[b]	1/33 (3%)	7/25 (28%)	7/39 (18%)
First incidence (days)	619	535	727
Poly-3 test	p=0.065	p=0.006	p=0.052

Data obtained from NTP Report TR 587
a Number of animals with neoplasm per number with live examined microscopically
b. Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
c. No neoplasm in animal group
Historical control incidences for adenomas: 145/250 (58% ± 5.1%; range 52% to 64%
Historical control incidences for hepatoblastomas: 9/250 (3.6%±2.6%; range 0% to 6%

As shown in Table 5, the incidences of adenoma or carcinoma (combined) of the large intestine (cecum or colon) were seen in male mice. As shown in Table 6, hemangioma or hemangio-sarcomas (all organs) occurred with significant positive trends in male mice. These lesions occurred in a variety of organs such as the bone marrow, liver, lung serosa, lymph nodes, skin, spleen, and vertebra. No evidence of carcinogenicity was found in female mice.

Table 5. Large Intestine Tumors in Male B6C3F1/N Mice Following Gavage Dosing of TBBPA

Cecum or Colon: Adenoma or Carcinoma	Vehicle Control	250 mg/kg/day	500 mg/kg/day
Overall rate	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted rate[a]	0.0%	0.0%	6.5%
Terminal rate[b]	0/33 (3%)	0/25 (28%)	3/39 (5%)
First incidence (days)[c]	-	-	513
Poly-3 test	p=0.039	-	p=0.131

Data obtained from NTP Report TR 587
a Number of animals with neoplasm per number with live examined microscopically
b. Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
c. No neoplasm in animal group
Historical control incidences: 0/250

Table 6. Hemangioma/Hemangiosarcomas (All Organs) in Male B6C3F1/N Mice Following Gavage Dosing of TBBPA

All organs: Hemangioma or Hemangiosarcoma	Vehicle Control	250 mg/kg/day	500 mg/kg/day
Overall rate	3/50 (6%)	5/50 (10%)	9/50 (18%)
Adjusted rate[a]	6.9%	11.9%	19.8%
Terminal rate[b]	2/33 (6%)	3/25 (12%)	9/39 (23%)
First incidence (days)	645	602	730 (terminal)
Poly-3 test	p=0.047	p=0.338	p=0.069

Data obtained from NTP Report TR 587
a Number of animals with neoplasm per number with live examined microscopically
b. Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
Historical control incidences: 32/250 (12.8%±5.4%; range 6% to 18%)

B. Non-Neoplastic Lesions

No treatment-related neoplastic lesions were see in the liver or the intestine at any dose level.

C. NTP Conclusion

NTP concluded that under the conditions of the bioassay, there was *some evidence of carcinogenic activity* of tetrabromobisphenol A in male B6C3F1/N mice based on increased incidences of hepatoblastoma. The increased incidences of large intestine neoplasms and hemangiosarcoma (all organs) may have been related to chemical administration. There was *no evidence of carcinogenic activity* of TBBPA in female B6C3F1/N mice.

III. TOXICOLOGY

a. Mutagenicity

TBBPA was tested for bacterial mutagenicity in two independent assays and results were negative

in both assays. In the first assay, tetrabromobisphenol A (100 to 10,000 µg/plate) showed no evidence of mutagenicity in *S. typhimurium* strains TA98, TA100, TA1535, or TA1537, with or without exogenous metabolic activation from induced hamster or rat liver S9. In the second assay, conducted with the same lot of tetrabromobisphenol A that was used in the 2-year studies, no mutagenic activity was detected in *S. typhimurium* strains TA98 or TA100 or in *E. coli* strain WP2 *uvrA*; all tests were conducted with and without rat liver S9, and the highest concentration tested was 6,000 µg/plate. *In vivo*, no increases in micronucleated NCEs were observed in male or female B6C3F1/N mice following 3 months of administration of tetrabromobisphenol A by gavage over a dose range of 10 to 1,000 mg/kg (NTP 2103).

b. Structure-Activity Relationship

Based on the chemical structure, there is no structural alert of genotoxicity potential; this is supported by the available, predominantly negative genotoxicity data. With respect to carcinogenicity potential, there are very few suitable structural analogs available for SAR consideration. Bisphenol A (BPA) and 3,3',4,4',5,5'-hexabromobiphenyl (PBB 169) are two of the most frequently cited analogs for TBBPA. In a 1982 NTP cancer bioassay of BPA, there was "no convincing evidence" that BPA was carcinogenic for F344 rats or B6C3F1 mice of either sex. BPA has been suspected to contribute to increase in breast and prostate cancer in exposed humans because of its endocrine disruptor activity but convincing evidence remains to be developed. The ring substitution of four bromine atom the rings to BPA is expected to significantly affect the physicochemical properties, toxicokinetics and adverse health effects. A recent detailed review of TBBPA concluded that it should not be considered as an "endocrine disruptor" (Colnot et al., 2014). The analogy between TBBPA and PBB 169 is not valid. The substitution of bromine at the 4,4'-position is expected to abolish the biopersistence of PBB. TBBPA also cannot bind to AhR receptor because it is nonplanar.

c. Toxicity

Acute oral, dermal, and inhalation studies have been performed on TBBPA. These studies show that TBBPA has low acute toxicity by all routes of exposure (oral LD_{50} > 5,000 mg/kg-bw in rats; dermal LD_{50} > 10,000 mg/kg-bw in rabbits, and inhalation LC_{50} > 10,000 mg/m^3 in rats and mice) (EURAR, 2006; Canada 2012; ECHA 2014). Available data show that TBBPA is not a skin, eye or respiratory irritant, and not a skin or respiratory sensitizer in animals or humans (EURAR, 2006, Canada, 2012).

The chronic/subchronic toxicity of TBBPA was investigated in a number of repeated-dose studies and has been reviewed in the European Union Risk Assessment Report (EURAR, 2006). Overall, the repeated-dose toxicity studies show that TBBPA has a low hazard concern.

In a 14-day inhalation study in rats, the EU concluded that no adverse effects were reported up to the limit dose of 18 mg/L, with the exception of signs of mechanical irritation in all treatment groups due to the high dust levels. In a 21-day dermal study, TBBPA was administered to rabbits at dose levels up to 2,500 mg/kg/day for 6 hours/day, 5 days/week. No toxicologically significant effects were identified. In a 90-day oral gavage study, rats were administered TBBPA at dose levels of 0, 100, 300, or 1,000 mg/kg/day. No neurobehavioral effects were observed during the weekly functional observational battery evaluations. Slight changes in hematological evaluations and clinical chemistry were reported; however, the EU concluded that these effects were not

toxicologically significant. Statistically significant decreases in serum T4 were reported in males and females, but no accompanying change in serum T3, thyroid stimulating hormone (TSH), or histopathology of the liver, thyroid, parathyroid, and pituitary was reported. The EU concluded that the decreases in serum T4 were not considered to be adverse. Absolute spleen weight was decreased in males in the top two dose groups; no histopathological findings were noted. An increase in relative epididymis weight was reported in the middle dose group; however, no changes in relative epididymis weight or histopathology were identified in the high dose group. The EU concluded that these findings were of no toxicological significance.

In a study of newborn rats dosed from day 4 to day 21 after birth by gavage, an effect on the kidneys (polycystic lesions associated with the dilation of tubules) was noted at 200 or 600 mg/kg-bw/day but not at 40 mg/kg/day (NOAEL). No similar effect was found in 5-week old rats dosed at 2,000 or 6,000 mg/kg-bw/day for 18 days (Fukuda et al., 2004). The EU (EURAR) suggested that the kidney effects observed in the newborn rats are likely due to the immature metabolic capability and/or immature kidneys of such young animals.

In a recent subchronic toxicity study, groups of 10 male and 10 female F344/NTac rats and B6C3F1 mice were administered 0, 10, 50, 100, 500, or 1,000 mg/kg-bw/day TBBPA in corn oil by gavage, 5 days per week for up to 14 weeks (NTP, 2013). In the rats, dose-related decreases in serum T4 levels occurred on day 4 and at week 14 in 500 and 1,000 mg/kg- bw/day males and females. Significant increases occurred in liver weights of 500 and 1,000 mg/kg-bw/day rats and significant decreases occurred in spleen weights of 500 and 1,000 mg/kg-bw/day males. In the mice, liver weights of 500 mg/kg males and 1,000 mg/kg males and females were significantly greater than those of the vehicle controls.

No effects on reproduction, fertility, or developmental toxicity including neurobehavioural abnormalities (*e.g.*, motor activity, learning and memory) were observed in an OECD-compliant two-generation study in Sprague Dawley rats at doses of 0., 10, 100 or 1,000 mg/kg-bw/day. The NOAEL for these effects was determined to be 1,000 mg/kg. In this study, there was a significant decrease in serum T4 levels in F0 and F1 offspring at doses of 100 and 1,000 mg/kg-bw/day. Mean serum T3 levels were also significantly lower in F0 males at the highest dose (1,000 mg/kg-bw/day), but no changes were found in the F0 females or in the male or female F1 offspring. There were also no effects on the TSH levels or microscopic changes in the list or pituitary gland. Furthermore, there is no dose-response relationship and following the 30-day recovery period, serum T4 levels returned to control levels. The EU concluded that the thyroxine effects were not toxicologically significant (EURAR, 2006).

TBBPA did not alter brain development and there were no significant dose-related effects on T4, T3 or TSH at postnatal day (PND) 20 or postnatal week 11 after pregnant Sprague Dawley rats were fed TBBPA at dietary levels of 0, 100, 1,000, or 10,000 ppm from gestation day (GD) 10 to PND 20. In a pilot range-finding study (Velsicol Chemical Corporation, 1978c) and two standard developmental toxicity studies, no developmental effects were observed at doses up to 10,000 mg/kg-bw/day (Saegusa et al., 2009).

Van der Ven et al (2008) reported the results of a one-generation reproduction study in Wistar rats. In this study, dietary exposure was for 70 days (male) and 14 days (female) prior to mating, during mating and throughout gestation and lactation at 0, 3, 10, 30, 100, 300, 1,000, or 3,000

mg/kg-bw/day. There were no effects of all reproduction parameters examined including sperm count or morphology. The main adverse effects were decreased plasma T4 levels (both sexes), increased T3 levels (females), and increased weight of testis and pituitary gland in the males of the F1 generation. However, there were no clear dose response relationships of these endpoints and some of the changes reported are not statistically significantly different from the controls; no histopathological changes were observed in any of the assessed organs including the testes, pituitary gland and thyroid gland to explain the increased organ weights or hormones changes. Concerns have been expressed regarding the use of modeling software, methodology and conduct of this study (Banasik et al., 2009). These effects were not considered critical endpoints by the Health and Environment Canada (Canada, 2012).

Neurobehavioral effects in offspring from the above one-generation reproduction study were also investigated. Auditory response with brainstem auditory evoked potential (BAEP), an electrophysiological response elicited by auditory stimuli and recorded from the scalp or brain surface as waveform with a series of positive and negative peaks, was examined. The authors reported that BAEP thresholds and wave IV latency were increased in exposed female offspring in the low frequency range. In the males, absolute latency of wave IV and interpeak latencies II-IV were also reported at low frequencies (Lilienthal et al., 2008). However, as pointed out by Strain et al., (2009), there was no consistent pattern of the BAEP alterations reported and a number of methodological confounding factors (e.g., animal age, body temperature) have been identified. In addition, there are a number of other limitations/deficiencies in the study of Lilienthal et al., (2008) which are not in compliance with the OPPTS Test Guidelines on Neurophysiology: Sensory Evoked Potential (OPPTS 870.6855, August 1998). According to the EPA test guidelines, a pigmented strain of rat is the preferred animal species to be tested since albino strains of animals have abnormalities of the visual and auditory systems. Furthermore, at least 10 nulliparous and nonpregnant rats per group should be used, and positive control groups exhibiting functional changes in the sensory systems to be tested are required. Instead, the study of Lilienthal et al., (2008) used groups of 5-6 pregnant Wistar rats which are albino rats, and did not include positive controls.

No differences in performance were observed in a study assessing developmental neurotoxicity of TBBPA in NMRI mice administered 0.75 and 11.5 mg/kg orally on day PND 10 (Eriksson et al., 1998, 2001). As different from pentabromo-diphenyl ethers (PBDE), TBBPA did not affect neonatal development of the brain and neural behavior, learning and memory of adult mice (Viberg et al., 2002, 2004). Changes in several proteins involved in maturation of the brain, neuronal growth and synaptogenesis in the neonatal brains were observed in mice exposed to PBDE but not in those exposed to TBBPA (Viberg and Eriksson, 2011). The results of these studies appear to be consistent with the findings in a recent cross-sectional study on 515 adolescents in Belgium, which showed that PBDE exposure, but not TBBPA, was associated with changes in the neurobehavioral function in humans (Kiciriski et al., 2012).

No reproductive effects were reported in a study feeding a diet containing 0%, 01%, 0.1%, or 1% TBBPA to pregnant ICR mice from the first day of gestation to weaning at postnatal day 27. Based on enlargement of hepatocytes and very slight focal necrosis of hepatocytes in female offspring, a LOAEL of 140 mg/kg-bw/day was determined (Tada et al., 2006).

IV. COMMITTEES ASSESSMENT OF WEIGHT-OF-EVIDENCE

a. Testicular tumors: The CARC did not consider the testicular tumors to be treatment-related since there was no dose trend nor pair-wise statistical significance compared to high dose group, and the total all-group incidence (4/200) in the study was within the historical control range (0-4%). In addition, there were no supportive precursor lesions in the testes.

b. Uterine tumors: The CARC determined that the uterine epithelial tumors (combined adenoma, adenocarcinoma, malignant mixed Müllerian) observed in female rats at the high dose were treatment-related based on the increased incidences at all dose levels (12% at 250 mg/kg/day, 32% at 500 mg/kg/day and 38% at 1000 mg/kg/day) when compared to controls (12%), a statistically significant dose trend ($p<0.01$), and the presence of supportive precursor lesions.

c. Liver tumors: Although the liver adenomas in male mice at the high dose showed statistical significance, the CARC determined that they were not treatment-related since the incidences were within the historical control range and there were no supportive precursor lesions. The CARC determined that the hepatoblastomas were not treatment-related due to lack of statistical significance (pairwise at high dose) or dose trend for hepatoblastomas alone or combined with carcinomas.

d. Large Intestine tumors: The CARC determined that the adenoma or carcinoma observed in the large intestine (cecum or colon) of male mice were not treatment-related given lack of statistical significance on pairwise (high dose) or dose trend and no supportive precursor lesions in the intestines.

e. Hemangioma/hemangiosarcomas (all organs): These lesions occurred in a variety of organs such as the bone marrow, liver, lung serosa, lymph nodes, skin, spleen and vertebra. The incidence was increased at 250 mg/kg/day (10%) and 500 mg/kg/day (18%) when compared to vehicle controls (6%). The CARC determined that the hemangiomas/ hemangiosarcomas observed in male mice were treatment-related due to the presence of a dose trend and mortality-adjusted incidence in the high dose group at the upper limit of the historical control range (18%).

There was no evidence of carcinogenicity in female mice. Mode of action data that meets the 2006 IPCS Human Relevance Framework were not available for evaluation. There is no concern for mutagenicity.

V. CLASSIFICTION OF CARCINOGENIC POTENIAL

In accordance with the Agency's 2005 Guideline of Carcinogen Risk Assessment, Tetrabromobisphenol A is classified as "Likely to be Carcinogenic to Humans" based on the presence of uterine tumors (adenoma, adenocarcinoma, malignant mixed mullerian) in female Wistar Hans rats and hemangiomas/hemangiosarcomas in male B6C3F1/N mice. There was no evidence of carcinogenicity in female mice. There were no mutagenicity concerns.

VI. QUANTIFICATION

In accordance with the Agency's 2005 Guideline of Carcinogen Risk Assessment, a low dose linear extrapolation model (Q_1*) will be used for quantification of human risk.

VII. REFERENCES

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