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Office of Chemical Safety and
Pollution Prevention

TSCA Work Plan Chemical
Technical Supplement – Hazard Assessment of the Brominated Phthalates Cluster (BPC) Chemicals

Brominated Phthalates Cluster
Flame Retardants

CASRN	NAME
26040-51-7	1,2-Benzenedicarboxylic acid, 3,4,5,6-tetrabromo-, 1,2-bis(2-ethylhexyl) ester
183658-27-7	Benzoic acid, 2,3,4,5-tetrabromo-, 2-ethylhexyl ester
20566-35-2	1,2-Benzenedicarboxylic acid, 3,4,5,6-tetrabromo-, 1-[2-(2-hydroxyethoxy)ethyl] 2-(2-hydroxypropyl) ester
77098-07-8	1,2-Benzenedicarboxylic acid, 3,4,5,6-tetrabromo-, mixed esters with diethylene glycol and propylene glycol
7415-86-3	1,2-Benzenedicarboxylic acid, 1,2-bis(2,3-dibromopropyl) ester
*	Confidential A
*	Confidential B

*** Confidential Business Information**

August 2015

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1 HUMAN HEALTH HAZARD

1.1 Toxicokinetics

Limited data are available on the toxicokinetics of the BPC members. Phthalic acid is the common final metabolite of phthalic acid esters in rats; the main route of excretion being in urine (Lim et al., 2007). While information for the structural analogue, bis(2-ethylhexyl)phthalate (DEHP; CASRN 117-81-7) can be used to inform the metabolism and potential hazard of some of the BPC members, it is not appropriate for all members due to the differences in metabolites. The metabolites of DEHP and the cluster members are depicted in Table 1-1.

1,2-Benzenedicarboxylic acid, 1,2-bis(2-ethylhexyl) ester (DEHP; CASRN 117-81-7)

The closest structural analog of the cluster members is 1,2-Benzenedicarboxylic acid, 1,2-bis(2-ethylhexyl) ester (DEHP; CASRN 117-81-7). It is readily absorbed and distributed in the body. Its metabolism involves several pathways and yields a variety of metabolites; more than 30 metabolites have been identified (Lim et al., 2007). The major step in the metabolism of DEHP is hydrolysis by lipases to mono (2-ethylhexyl)phthalate (MEHP; CASRN 4376-20-9) and 2-ethylhexanol (2-EH; CASRN 104-76-7). Phthalic acid (PA; CASRN 88-99-3) is the common final metabolite of phthalic acid esters (Lim *et al*., 2007). DEHP is excreted via the urine, mainly as MEHP-metabolites, but some excretion via bile also occurs in rodents. Additionally, there are animal and human data showing that DEHP is transferred to mothers' milk. The relative extent to which different metabolites are produced and excreted is very complex and may depend upon the species, the age of the animal, sex, inter-individual differences, nutrition state, prior exposure to DEHP, the amount of DEHP administered, and the route of administration (NTP, 2006; OECD, 2005).

1,2-Benzenedicarboxylic acid, 3,4,5,6-tetrabromo-, 1,2-bis(2-ethylhexyl) ester (TBPH; CASRN 26040-51-7)

Limited data are available on the toxicokinetics of 1,2-Benzenedicarboxylic acid, 3,4,5,6-tetrabromo-, 1,2-bis(2-ethylhexyl) ester (**TBPH**; CASRN 26040-51-7). Its primary metabolite is the monoester, mono(2-ethylhexyl) tetrabromophthalate (TBMEHP; CASRN 61776-60-1) which is then ultimately metabolized to tetrabromophthalic acid (CASRN 13810-83-8). When tested *in vitro*, no metabolites of **TBPH** were detected in human or rat subcellular fractions (Roberts *et al*., 2012). However, in the presence of purified porcine carboxylesterase, the formation of TBMEHP was detected. No phase II metabolites of TBMEHP were detected. The metabolism of **TBPH** in humans has not been evaluated (Roberts et al., 2012). No toxicokinetics data were submitted to EPA under the HPV Challenge Program (ACC, 2004) and additional information was not publicly available from the European Chemicals Agency (ECHA) site (ECHA, 2013).

Benzoic acid, 2,3,4,5-tetrabromo-, 2-ethylhexyl ester (TBB; CASRN 183658-27-7)

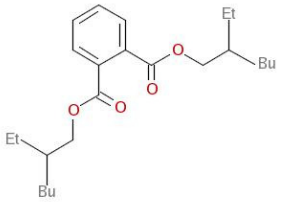
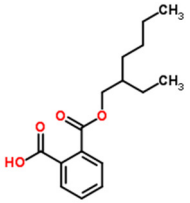
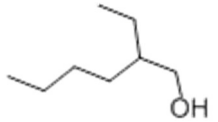
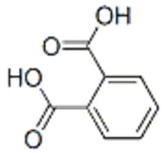
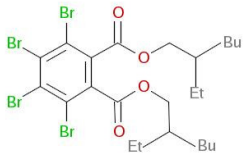
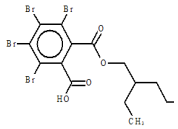
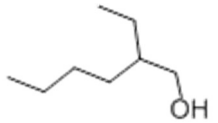
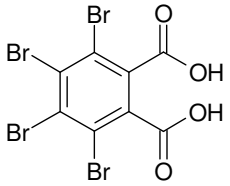
Limited data are available on the toxicokinetics of Benzoic acid, 2,3,4,5-tetrabromo-, 2-ethylhexyl ester (**TBB**; CASRN 183658-27-7). This member of the cluster differs significantly

from the other cluster members in that its final metabolite is not tetrabromophthalic acid (CASRN 13810-83-8) but tetrabromobenzoic acid (TBBA; CASRN 27581-13-1). This was confirmed *in vitro* using liver and intestinal subcellular fractions. In all experiments, TBB was consistently metabolized to 2,3,4,5-tetrabromobenzoic acid (TBBA) via cleavage of the 2-ethylhexyl chain without requiring added cofactors (Roberts et al., 2012). No phase II metabolites of TBBA were detected. The metabolism of **TBB** in humans has not been evaluated (Roberts et al., 2012).

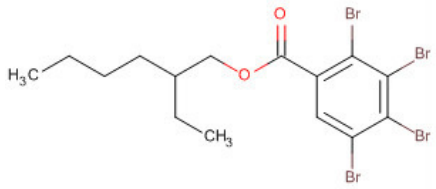
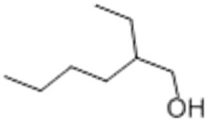
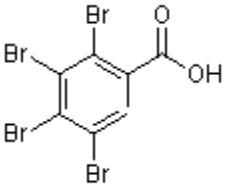
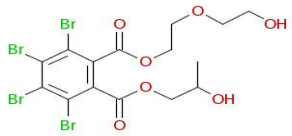
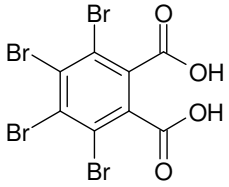
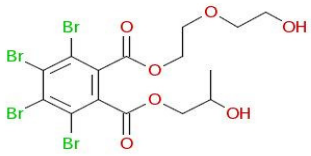
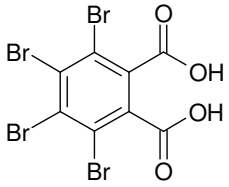
1,2-Benzenedicarboxylic acid, 3,4,5,6-tetrabromo-, 1-[2-(2-hydroxyethoxy)ethyl] 2-(2-hydroxypropyl) ester (CASRN 20566-35-2) and 3,4,5,6 tetrabromo-1,2-benzene dicarboxylic acid, mixed esters with diethylene glycol and propylene glycol (CASRN 77098-07-8)
These two cluster members are mixtures which can be considered together as their composition and metabolites are very similar. No data on the toxicokinetics of these substances are available. Analogous to the other cluster members, the metabolites are expected to be the corresponding alcohols and the tetrabromophthalic acid. No toxicokinetics data were submitted for CASRN 77098-07-8 to EPA under the HPV Challenge Program (Albemarle - GLCC, 2004) and additional information was not publicly available from the European Chemicals Agency (ECHA) site for CASRN 20566-35-2 (ECHA, 2013).

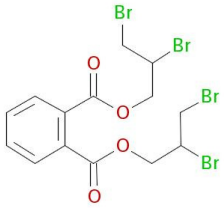
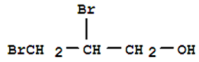
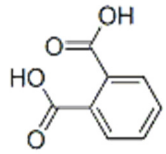
1,2-Benzenedicarboxylic acid, 1,2-bis(2,3-dibromopropyl) ester (CASRN 7415-86-3)
No data are available on the toxicokinetics of this cluster member. It differs from the other cluster members in that the bromines are not attached to the benzene ring but are instead on the side-chains. The metabolites are expected to be 2,3-dibromopropanol (CASRN 96-13-9) and the final metabolite, PA. Two mercapturic acid metabolites of 2,3-dibromopropanol have been identified in the urine of treated rats (IARC, 2000).

Table 1-1: Structure of Brominated Phthalates Cluster and Associated Chemicals

CASRN	NAME	STRUCTURE	Metabolites/Hydrolysis Products	
117-81-7	**DEHP:** ,2-Benzenedicarboxylic acid, ,2-bis(2-ethylhexyl)ester **STRUCTURAL ANALOG** of BPC CLUSTER MEMBERS		 **MEHP** [Mono(2-ethylhexyl) tetrabromophthalate; CASRN 4376-20-9][1]	 2-ethylhexanol (CASRN 104-76-7)  Phthalic acid (CASRN 88-99-3)
26040-51-7	**TBPH**: 1,2-Benzenedicarboxylic acid, 3,4,5,6-tetrabromo-, 1,2-bis(2-ethylhexyl) ester		 **TBMEHP** [Mono(2-ethylhexyl) tetrabromophthalate; CASRN 61776-60-1; not on TSCA inventory]	 2-ethylhexanol (CASRN 104-76-7)  Tetrabromophthalic acid (CASRN 13810-83-8)

[1] CSID:19208, http://www.chemspider.com/Chemical-Structure.19208.html (accessed 15:06, Sep 9, 2013)

CASRN	NAME	STRUCTURE	Metabolites/Hydrolysis Products	
183658-27-7	**TBB**: Benzoic acid, 2,3,4,5-tetrabromo-, 2-ethylhexyl ester		 2-ethylhexanol (CASRN 104-76-7)	 Tetrabromobenzoic acid (**TBBA**: CASRN 27581-13-1)
20566-35-2	**TBPA-Diol**: 1,2-Benzenedicarboxylic acid, 3,4,5,6-tetrabromo-, 1-[2-(2-hydroxyethoxy)ethyl] 2-(2-hydroxypropyl) ester		$HOCH_2CH_2OCH_2CH_2OH$ Diethylene glycol (CASRN 111-46-6) CH_3-$CHOH$-CH_2OH Propylene Glycol (CASRN 57-55-6)	 Tetrabromophthalic acid (CASRN 13810-83-8)
77098-07-8	**TBPA-Diol (Mixed Esters)**: 1,2-Benzenedicarboxylic acid, 3,4,5,6-tetrabromo-, mixed esters with diethylene glycol and propylene glycol		$HOCH_2CH_2OCH_2CH_2OH$ Diethylene glycol (CASRN 111-46-6) CH_3-$CHOH$-CH_2OH Propylene Glycol (CASRN 57-55-6)	 Tetrabromophthalic acid (CASRN 13810-83-8)

CASRN	NAME	STRUCTURE	Metabolites/Hydrolysis Products	
7415-86-3	**Bromo Alkyl Ester**: 1,2-Benzenedicarboxylic acid, 1,2-bis(2,3-dibromopropyl) ester		 2,3-dibromo-1-propanol (CASRN 96-13-9)	 Phthalic acid (CASRN 88-99-3)
CONFIDENTIAL A				
CONFIDENTIAL B				

1.2 Hazard Identification

The available hazard data for the BPC cluster members are summarized in Table 1-3 and Table 2-1. Table 1-3 also shows some hazard data for the structural analog, **DEHP**, for reference. The data are discussed below.

Table 1-2: Availability of human health data for the Brominated Phthalates Cluster

Brominated Phthalates Cluster Members							
Endpoint	**CASRN 26040-51-7[2]**	**CASRN 183658-27-7[3]**	**CASRN 20566-35-2[4]**	**CASRN 77098-07-8[5]**	**CASRN 7415-86-3**	**Confidential A**	**Confidential B**
	TBPH: 1,2-Benzenedicarboxylic acid, 3,4,5,6-tetrabromo-, 1,2-bis(2-ethylhexyl) ester	**TBB**: Benzoic acid, 2,3,4,5-tetrabromo-, 2-ethylhexyl ester	**TBPA-Diol**: 1,2-Benzenedicarboxylic acid, 3,4,5,6-tetrabromo-, 1-[2-(2-hydroxyethoxy) ethyl] 2-(2-hydroxypropyl) ester	**TBPA-Diol**: 1,2-Benzenedicarboxylic acid, 3,4,5,6-tetrabromo-, mixed esters with diethylene glycol and propylene glycol	1,2-Benzenedicarboxylic acid, 1,2-bis(2,3-dibromopropyl) ester		
Acute Oral Toxicity LD_{50} (mg/kg)	X	—	ECHA	X	—	—	—
Acute Dermal Toxicity LD_{50} (mg/kg)	X	—	ECHA	X	—	—	—

[2] Screening-level data available from the HPV Challenge submission: http://www.epa.gov/hpv/pubs/summaries/phthacid/c15484tc.htm
[3] Data available for Firemaster BZ 54 (TBB/TBPH mixture)
[4] Screening-level data are available from ECHA [(European Chemicals Agency): http://apps.echa.europa.eu/registered/data/dossiers/DISS-9ea569d1-072b-18ab-e044-00144f67d031/DISS-9ea569d1-072b-18ab-e044-00144f67d031_DISS-9ea569d1-072b-18ab-e044-00144f67d031.html] For risk assessment, the adequacy of these data is indeterminable without access to the full studies.
[5] Screening-level data available from the HPV Challenge submission: http://www.epa.gov/chemrtk/pubs/summaries/12benznd/c15091tc.htm

Brominated Phthalates Cluster Members							
Endpoint	**CASRN 26040-51-7[2]**	**CASRN 183658-27-7[3]**	**CASRN 20566-35-2[4]**	**CASRN 77098-07-8[5]**	**CASRN 7415-86-3**	**Confidential A**	**Confidential B**
Acute Inhalation Toxicity LC_{50} (mg/L)	—	—	—	X	—	—	—
Repeated-Dose Toxicity Oral NOAEL/ LOAEL (mg/kg-day)	X	—	—	—	—	—	—
Reproductive Toxicity NOAEL/ LOAEL (mg/kg-day)	—	—	—	—	—	—	—
Developmental Toxicity NOAEL/ LOAEL (mg/kg-day)	—	—	—	—	—	—	—
Genetic Toxicity – Gene Mutation *In vitro*	X	—	ECHA	X	—	—	—
Genetic Toxicity – Chromosomal Aberrations *In vitro*	X	—	—	—	—	—	—
Genetic Toxicity – Chromosomal Aberrations *In vivo*	X	—	—	—	—	—	—
Skin Irritation	X	—	—	—	—	—	—

Brominated Phthalates Cluster Members							
Endpoint	**CASRN 26040-51-7[2]**	**CASRN 183658-27-7[3]**	**CASRN 20566-35-2[4]**	**CASRN 77098-07-8[5]**	**CASRN 7415-86-3**	**Confidential A**	**Confidential B**
Eye Irritation	X	—	—	—	—	—	—
Sensitization	X	—	—	—	—	—	—

X denotes available data; - denotes no adequate data

Table 1-3: Human Health Data for Brominated Phthalates Cluster

		Brominated Phthalates Cluster Members				
Endpoint	**CASRN 117-81-7[6]**	**CASRN 26040-51-7[7]**	**CASRN 183658-27-7**	**CASRN 20566-35-2[8]**	**CASRN 77098-07-8[9]**	**CASRN 7415-86-3**
	DEHP: 1,2-Benzendicarboxylic acid, 2-bis(2-ethylhexyl ester)	**TBPH**: 1,2-Benzenedicarboxylic acid, 3,4,5,6-tetrabromo-, 1,2-bis(2-ethylhexyl) ester	**TBB**: Benzoic acid, 2,3,4,5-tetrabromo-, 2-ethylhexyl ester	**TBPA-Diol**: 1,2-Benzenedicarboxylic acid, 3,4,5,6-tetrabromo-, 1-[2-(2-hydroxyethoxy)ethyl] 2-(2-hydroxypropyl) ester	**TBPA-Diol**: 1,2-Benzenedicarboxylic acid, 3,4,5,6-tetrabromo-, mixed esters with diethylene glycol and propylene glycol	1,2-Benzenedicarboxylic acid, 1,2-bis(2,3-dibromopropyl) ester
Acute Oral Toxicity LD_{50} (mg/kg)	>20,000	>5000 (>95%)	—	>2000 (Saytex RB 79 20566-35-2)	>10,000 (PM-PHT-4 Diol)	—
		(Firemaster® BZ-54)[10] >5000				

[6] ECHA: http://apps.echa.europa.eu/registered/data/dossiers/DISS-9c7eba3b-31b2-3fd1-e044-00144f67d249/DISS-9c7eba3b-31b2-3fd1-e044-00144f67d249_DISS-9c7eba3b-31b2-3fd1-e044-00144f67d249.html

[7] HPV Challenge submission: http://www.epa.gov/hpv/pubs/summaries/phthacid/c15484tc.htm

[8] ECHA: http://apps.echa.europa.eu/registered/data/dossiers/DISS-9ea569d1-072b-18ab-e044-00144f67d031/DISS-9ea569d1-072b-18ab-e044-00144f67d031_DISS-9ea569d1-072b-18ab-e044-00144f67d031.html For risk assessment, the adequacy of these data is indeterminable without access to the full studies.

[9] Screening-level data available from the HPV Challenge submission: http://www.epa.gov/chemrtk/pubs/summaries/12benznd/c15091tc.htm

[10] (NICNAS, 2004)

		Brominated Phthalates Cluster Members				
Endpoint	**CASRN 117-81-7[6]**	**CASRN 26040-51-7[7]**	**CASRN 183658-27-7**	**CASRN 20566-35-2[8]**	**CASRN 77098-07-8[9]**	**CASRN 7415-86-3**
Acute Dermal Toxicity LD_{50} (mg/kg)	19,800	>3090 (>95%)	—	>20,000 (FM-PHT-4 Diol 20566-35-2)	>20,000 (PM-PHT-4 Diol)	—
		(Firemaster® BZ-54)[14] >2000				
Acute Inhalation Toxicity LC_{50} (mg/L)	10,620 [LC_0] (mg/m^3)	—	—	>0.008 (FM-PHT-4 Diol 20566-35-2)	—	—
Repeated-Dose Toxicity Oral NOAEL/ LOAEL (mg/kg-day)	(rat; diet chronic) NOAEL=29-36 LOAEL =146-181	(rat; 28-d diet) NOAEL =223 (2000 ppm) LOAEL = 2331 (20,000 ppm) (>95%)	—	—	—	—
		(Firemaster® BZ-54)[14] Rat (28-d gavage) NOEL = Not established LOEL = 160				
Repeated-Dose Toxicity Inhalation NOAEC/ LOAEC (mg/L-day)	NOAEC= 50 mg/m^3 LOAEC= 1000 mg/m^3	—	—	—	—	—
Reproductive Toxicity Oral NOAEL/ LOAEL (mg/kg-day)	(Rat; 3-gen) NOAEL=46-48 LOAEL=359-391 (parental) NOAEL(off-spring)=1.4 LOAEL(off-spring)=4.8-4.9	(Rat; 2-gen) NOAEL=165 (highest dose tested) NOAEL(parental) = 50 LOAEL(parental) = 165 NOAEL(off-spring)=50 LOAEL(off-spring)=165 (Firemaster® BZ-54)[14]		—	—	—

		Brominated Phthalates Cluster Members				
Endpoint	**CASRN 117-81-7[6]**	**CASRN 26040-51-7[7]**	**CASRN 183658-27-7**	**CASRN 20566-35-2[8]**	**CASRN 77098-07-8[9]**	**CASRN 7415-86-3**
Developmental Toxicity NOAEL/ LOAEL (mg/kg-day) Maternal Toxicity **Developmental Toxicity**	(Rat) NOAEL = 200 LOAEL =1000 NOAEL=200 LOAEL=1000	(Rat) NOAEL = 50 LOAEL =100 NOAEL=50 LOAEL=100 (Firemaster® BZ-54)[14]		—	—	—
Genetic Toxicity – Gene Mutation ***In vitro***	—	Negative (>95%)	—	Negative (Saytex RB 79 20566-35-2)	Negative (Saytex RB 79)	—
Genetic Toxicity – Chromosomal Aberrations ***In vitro***	Negative (SCE)	Positive (>95%)	—	—	—	—
Genetic Toxicity – Chromosomal Aberrations ***In vivo***	Negative	Negative (>95%)	—	—	—	—
Skin Irritation	Slightly irritating	Slightly irritating (>95%)	—	—	—	—
Eye Irritation	—	Slightly irritating (>95%)	—	—	—	—
Sensitization	Not sensitizing (skin or respiratory)	Not sensitizing (>95%)	—	—	—	—
Carcinogenicity	Positive (rat)	—	—	—	—	—

Measured data in bold; NE = Not established; — indicates no data or no reliable data for this endpoint; (%) = % purity or identity of the test substance

1,2-Benzenedicarboxylic acid, 1,2-bis(2-ethylhexyl) ester (DEHP; CASRN 117-81-7)

Several assessments are available on the toxicity and risks of phthalates. EPA has published a screening-level hazard characterization for phthalate esters (EPA, 2010a) and has revised the action plan for phthalates (EPA, 2012d); both of which use data for bis(2-ethylhexyl)phthalate (DEHP; CASRN 117-81-7) to ascribe hazard. DEHP is metabolized by esterases to mono (2-ethylhexyl)phthalate (MEHP; CASRN 4376-20-9), its toxicologically active monoester (Springer et al., 2012). DEHP is a known peroxisome proliferator and male reproductive toxicant in rodents. It induces hepatotoxicity in rodents, most likely as a result of MEHP-induce activation of peroxisome proliferator activated receptor alpha (PPARα) (Ward *et al*., 1998 cited in Springer *et al*., 2012). The developing male reproductive system in rats is highly sensitive to the effects of these phthalates, which decrease fetal male testosterone levels (Parks *et al*., 2000 cited in Springer *et al*., 2012). In 2006, the National Toxicology Program (NTP) deliberated on the reproductive toxicity of DEHP and concluded the following: there is serious concern that certain intensive medical treatments of male infants may result in DEHP exposure levels that adversely affect development of the male reproductive tract, there is concern for adverse effects on development of the reproductive tract in male offspring of pregnant and breastfeeding women undergoing certain medical procedures involving high DEHP exposures, there is concern for the effects of DEHP exposure on the development of the male reproductive tract for infants less than one year old and less so for male children older than one year old and there is concern for adverse effects of DEHP exposure on development of the male reproductive tract in male offspring of pregnant women not medically exposed to DEHP and some concern for reproductive toxicity in adults exposed to DEHP at 1-30 µg/kg bw/day (NTP, 2006). It is this toxicity to the male reproductive system from DEHP exposure, a phthalate ester, that is of specific concern for this cluster of brominated phthalate esters.

1,2-Benzenedicarboxylic acid, 3,4,5,6-tetrabromo-, 1,2-bis(2-ethylhexyl) ester (TBPH; CASRN 26040-51-7)

bis(2-Ethylhexyl)-3,4,5,6-tetrabromophthalate (**TBPH)** exhibits low acute toxicity to rats and rabbits via the oral and dermal routes, respectively. It is slightly irritating to the skin and eyes in rabbits and was not a skin sensitizer in guinea pigs. In a dietary repeat-dose study in rats, there was a slight body weight decrease in females and clinical biochemistry perturbations (decreased alanine aminotransferase activity, decreased calcium and decreased phosphorus levels) at the highest concentration tested (2331 mg/kg-day). The NOAEL was designated as 223 mg/kg-day. **TBPH** was not mutagenic in bacteria *in vitro* but did induce chromosomal aberrations in mammalian cells *in vitro*. **TBPH** did not induce micronuclei in mice *in vivo*. No data are available for the reproductive/developmental toxicity endpoint.

In a non-guideline study, Springer *et al*., (2012) compared the toxicity of the primary metabolite of **TBPH** [mono(2-ethylhexyl) tetrabromophthalate (TBMEHP; CASRN 61776-60-1)] with that of DEHP [mono (2-ethylhexyl)phthalate (MEHP; CASRN 4376-20-9)]. Dust collected from homes, offices, and cars was measured for **TBPH** by gas chromatography followed by mass spectrometry. Pregnant rats were gavaged with TBMEHP (200 or 500 mg/kg) or corn oil on gestational days 18 and 19, and dams and fetuses were evaluated histologically for toxicity. TBMEHP was also evaluated for deiodinase inhibition using rat liver microsomes and for

peroxisome proliferator-activated receptor (PPAR) α and γ activation using murine FAO cells and NIH 3T3 L1 cells. They found that in contrast to DEHP, TBMEHP did not exhibit anti-androgenic activity. However, it did exhibit liver toxicity attributable to a PPAR α mode of action which is similar to that observed for DEHP/MEHP.

Benzoic acid, 2,3,4,5-tetrabromo-, 2-ethylhexyl ester (TBB; CASRN 183658-27-7)

Limited toxicity data are available for Benzoic acid, 2,3,4,5-tetrabromo-, 2-ethylhexyl ester (**TBB**; CASRN 183658-27-7). The available data (Chemtura, 2012a, 2013a; NICNAS, 2004) are for the commercial product, Firemaster® BZ-54. This commercial product is a mixture of **TBB** and 2-ethylhexyl tetrabromophthalate (**TBPH**; CASRN 26040-51-7) (Chemtura, 2010). Firemaster® BZ-54 exhibits low acute toxicity via the oral and dermal routes of exposure. In a 28-day repeated dose study in rats, kidney effects (cortical tubular epithelial regeneration) and increased levels of mean serum chloride were observed at all dose levels. The females appeared more sensitive to the test substance (significant differences in organ weights, changes in clinical chemistry parameters, decreased in mean body weight gain); the no observed adverse effect level was not determined. The lowest observed effect level was 160 mg/kg-day. The effects observed in parental animals in the two-generation reproductive toxicity study with Firemaster® BZ-54 were lower body weights and body weight gains during the premating periods in the parental and first generation females at the highest dose tested. First generation males also had lower body weights in the premating period but body weight gain was unaffected by treatment. At the highest dose tested, both generations of offspring had lower body weights at birth and throughout lactation which resulted in the lower premating body weights of the first female generation. Another effect of treatment was lower spleen weights at lactation day 21 in the first generation male pups and both pup sexes of the second generation. There were no adverse effects on reproductive performance or fertility in rats in this study up to the highest dose tested (165 mg/kg-day). Based on these observations, the NOAEL for parental and neonatal toxicity was designated 50 mg/kg-day; the NOAEL for reproductive toxicity was 165 mg/kg-day (highest dose tested).

In the prenatal developmental toxicity study with Firemaster®BZ-54 in rats, maternal toxicity included clinical findings (increased incidence of animals with sparse hair in the abdominal region), lower gestation body weights and body weight gain, and lower gestation food consumption at doses greater than or equal to 100 mg/kg-day. Fetal body weights were lower than controls at these doses. At 300 mg/kg-day, examination of the fetuses indicated fused cervical vertebral neural arches which were considered treatment-related (litter incidence of 8%). In addition, there was also an increased litter incidence for fetal ossification variations involving additional ossification centers to the cervical vertebral neural arches, incomplete ossified skull bones (jugal, parietal, and squamosal), and unossified sternebrae. Based on these observations, the NOAEL for maternal and developmental toxicity were designated 50 mg/kg-day.

1,2-Benzenedicarboxylic acid, 3,4,5,6-tetrabromo-, 1-[2-(2-hydroxyethoxy)ethyl] 2-(2-hydroxypropyl) ester (CASRN 20566-35-2) and 3,4,5,6 tetrabromo-1,2-benzene dicarboxylic acid, mixed esters with diethylene glycol and propylene glycol (CASRN 77098-07-8)
CASRNs 20566 and 77098-07-8 exhibit low acute toxicity to rats and rabbits via the oral and dermal routes, respectively. They are not mutagenic to bacteria *in vitro*. No additional data are available on these cluster members.

1,2-Benzenedicarboxylic acid, 1,2-bis(2,3-dibromopropyl) ester (CASRN 7415-86-3)
No data are available for this cluster member.

Confidential A** and **Confidential B.
Confidential A is subject to a consent order whose testing is triggered by production volume. No data are available for this cluster member or Confidential B.

Commercial Products (Firemaster® 550 and Firemaster® BZ-54)
The commercial product cited in the literature (Firemaster® 550) is comprised of a mixture of two of the members of the brominated phthalates cluster (**TBPH** and **TBB**) as well as two phosphates: triphenyl phosphate (**TPP**; CASRN 115-86-6) and isopropylated triphenyl phosphate (**ITPP**; CASRN 68937-41-7) (Chemtura, 2012b). Available screening-level data on these phosphates (ECHA, 2013; EPA, 2010b; OECD, 2002) suggest that these constituents pose a hazard to human health and the environment. Firemaster® BZ-54 does not have phosphates in its formulation (Chemtura, 2010, 2013a).

Triphenyl phosphate (TPP; CASRN 115-86-6)
Triphenyl phosphate (**TPP**) exhibits low acute toxicity via the oral (rats, mice, rabbits and guinea pigs) and dermal (rabbits) routes. TPP is not irritating to the skin and is slightly irritating to the eyes. There is evidence (case reports) of skin sensitization in humans. Oral repeat dose studies in rats showed a slight depression in body weight gain and an increase in liver weights at 350 mg/kg-day; the NOAEL was 70 mg/kg-day. **TPP** did not induce immediate or delayed neuropathy in hens and cats. **TPP** was not mutagenic in bacteria or mammalian cells *in vitro*. No adverse effects on fertility or development were found in rats fed up to 700 mg/kg-day **TPP** during gametogenesis prior to mating and throughout mating and gestation. **TPP** did not show carcinogenic potential in a mouse lung adenoma assay (OECD, 2002).

Isopropylated triphenyl phosphate (ITPP; CASRN 68937-41-7)
The acute oral and dermal toxicity of isopropylated triphenyl phosphate (**ITPP)** in rats is low. **ITPP** is not irritating to rabbit skin but is irritating to rabbit eyes. **ITPP** was neurotoxic to hens. No additional data were available or considered reliable for the EPA hazard characterization (EPA, 2010b). In the submission to the European Chemicals Agency (ECHA, 2013), data for several commercial products suggest that ITPP exhibits chronic toxicity. In addition, data from an oral gavage reproductive/developmental toxicity screening test showed that rats treated with Reofos 65 exhibited poor reproductive performance at 400 mg/kg-day (only dose tested) (ECHA, 2013). In a combined repeated-dose/reproductive/developmental toxicity screening test with the same compound, rats exhibited increased ovary/oviduct, adrenal gland (males and

females) and liver (males only) weights and decreased epididymal weights with corresponding macroscopic and/or microscopic changes in these tissues at 25 mg/kg-day. The NOAEL for systemic toxicity was not established. Male and female reproductive performance was also adversely affected at dose levels of 100 and 400 mg/kg-day, manifested by significant reductions in fertility and copulation/conception indices. Early postnatal development was also affected at dose levels of 100 and 400 mg/kg/day. The number of pups born and live litter size were decreased in these groups, while the numbers of pups found dead or euthanized in extremis were increased; all pups from five of six litters in the 400 mg/kg-day group were either found dead or euthanized in extremis prior to PND 4. The NOAEL for reproductive/developmental toxicity was 25 mg/kg-day.

1.3 Data Needs Assessment

The potential for exposure to the brominated phthalates cluster (BPC) members during chemical manufacture is not clearly understood. Similarly, there is evidence for potential exposure to some of the cluster members during occupational use of products containing some of the cluster members. There is also evidence to suggest potential consumer exposure to the BPC members during the use of some of the products containing some of the BPC members.

An overview of the data for the structural analog, bis(2-ethylhexyl)phthalate (DEHP; CASRN 117-81-7), was presented. It could be argued that conservatively, these data could be used to characterize the hazard for the brominated phthalates cluster (BPC) members. However, available data suggest that the mode of action of DEHP that elicits chronic (specifically reproductive and developmental) toxicity is not the same as that of the BPC members. In addition, the available data support this hypothesis. There is uncertainty characterizing the hazard for the BPC members because the chronic (including reproductive/developmental) toxicity observed in animal studies with the BPC members is via a mode of action not considered relevant to humans or at concentrations that either do not raise immediate concerns, or which are difficult to attribute to a particular chemical because the data were obtained using a commercial mixture.

Based on the available data for **TBPH**, there is a low hazard for acute toxicity. In the screening-level dietary study in rats with **TBPH** (described above), the potential for liver toxicity was observed by perturbations in clinical chemistry values. However, some liver effects have been attributed to a mode of action, peroxisome proliferation (peroxisome proliferator activated receptor; PPARα), not considered relevant to humans (Springer et al., 2012). The repeated-dose study with the commercial product Firemaster® BZ-54 showed the potential for kidney effects at the lowest dose tested, indicating that the kidney may be a potential target organ (NICNAS, 2004). In the two-generation reproductive toxicity study and a prenatal developmental toxicity study with the commercial product Firemaster® BZ-54 (**TBPH/TBB** mixture), showed the potential to affect fetal development at high doses. The uncertainty of using the data for the commercial product to characterize the hazard for **TBPH** or **TBB** lies in the attribution of the toxicity observed to either mixture component. No toxicity studies with **TBB** alone are available;

however, given that the metabolites of **TBPH** and **TBB** are different, it is expected that any toxicity observed would not be by the same mode of action or attributable to the same chemical. Springer et al., (Springer et al., 2012) observed the potential for endocrine disruption with the metabolites of **TBPH** and **TBB** suggesting that the potential for reproductive/developmental toxicity needs to be explored further. It would also be useful to identify the targets organs of toxicity for **TBB**, if any. Screening level data do not suggest a concern for carcinogenicity and the potential for a mode of action not relevant to humans (PPARα) further lowers the potential concern and the need for data for this chronic toxicity endpoint.

No data are available for CASRN 7415-86-3. The acute toxicity of CASRNs 20566-35-2 and 77098-07-8 is considered low. No data for repeated-dose or reproductive/developmental toxicity are available for CASRNs 20566-35-2 and 77098-07-8. The need for human health data for these chemicals is dependent on the potential exposure during manufacture and the potential for at least CASRNs 20566-35-2 and 77098-07-8 to be released from the polymer backbone.

2 ECOLOGICAL HAZARD

2.1 Hazard Identification

The environmental hazard of brominated phthalates reviewed and summarized in this section is based on studies located and reviewed from EPA's TSCATS databases (public), public literature searches, and other confidential sources; information from confidential sources not already public were excluded from this assessment. Full study reports were not located for all identified studies. Available hazard data are summarized in Table 2-1 and described below.

Table 2-1: Environmental Effects Data for Brominated Phthalates Cluster

Test Substance	Composition	Test Organism	Species	Test Guideline	Duration	Endpoint	Value (mg/L)	Reference
Firemaster® BZ-54	**TBB/TBPH**	Fish	*Oncorhynchus mykiss*	OECD TG 203	96-h	LC50	NES	Chemtura (2013a)
		Daphnid	*Daphnia magna*	OECD TG 202	48-h	EC50	0.42	Chemtura (2013a)
		Daphnid	*Daphnia carinata*		15-d	ChV	0.022	Access: UTS Pty Ltd (2003) as cited in NICNAS, 2004
		Algae	*Selenastrum capricornutum*	OECD TG 201	96-h	EC50 ChV	NES NES	Chemtura (2013a)
TBPH:1,2-Benzenedicarboxylic acid, 3,4,5,6-tetrabromo-, 1,2-bis(2-ethylhexyl) ester	>95% **TBPH**	Fish	*Oncorhynchus mykiss*	OECD TG 203	96-h	EC50	NES	ECHA (accessed 9/2013)
		Daphnid	*Daphnia magna*	OECD TG 202	48-h	EC50	0.3	IUCLID, 2004 as submitted to the HPV Challenge Program
		Daphnid	*Daphnia magna*	OECD TG 202	48-h	EC50	NES	ECHA (accessed 9/2013)
		Algae	*Desmodesmus subspicatus*	OECD TG 201	72-h	EC50 ChV	NES NES	ECHA (accessed 9/2013)
PM-PHT-4 Diol: 2-(2-hydroxyethoxy) ethyl 2-hydroxy propyl 3,4,5,6 tetrabromobenzene dicarboxylate	Not Stated	Fish	*Lepomis macrochirus*	EPA-660/3-75-009, April, 1975.	96-h	LC50	12	ECHA (under CASRN 20566-35-2 accessed 11/2013)

In general, insufficient experimental data are available to characterize hazard that would result from chronic exposure to wildlife populations. Currently, information from experimental studies that address standard aquatic toxicity endpoints are limited to two chronic invertebrate studies conducted on two different species and two different flame retardant formulations (BZ-54 and pure **TBPH**) that present conflicting conclusions. Additional studies are available that attempt to address population level effects using approaches that would not be sufficient to support a full risk assessment, but can be used to support qualitative hazard concerns for the brominated phthalates. One such study, a long term mesocosm study (de Jourdan et al., 2014; de Jourdan et al., 2012), demonstrates that the benthic community composition exhibited significantly lower diversity and greater abundance of Chironomids in cosms treated with 500 ng BZ-54/g sediment compared to the controls and suggests aquatic and/or sediment dwelling invertebrate populations may be impacted by chronic exposure.

Acute aquatic base-set toxicity data were available for **TBPH/TBB** that also suggest aquatic invertebrates as the most sensitive species; however, given the low water solubility and high Log K_{ow} of **TBPH/TBB** and the use of solvents and/or test concentrations above the limit of solubility, there is concern that these effects do not represent environmental conditions. A single acute fish toxicity study was available for cluster members with a Log Kow of less than 5 that suggests moderate toxicity; however, given results from **TBPH/TBB**, aquatic invertebrates are likely more sensitive than fish. Acute experimental data are not available for Confidential A and Confidential B, but Confidential A is subject to a consent order whose testing is triggered by production volume.

Commercial products cited in the literature as containing brominated phthalates (*i.e.*, Firemaster® 550 and Firemaster® BZ-54) are considered to be known mixtures of the brominated phthalates/esters **TBPH** and **TBB** (Firemaster® BZ-54) (Chemtura, 2013a) or mixtures of the brominated phthalates/esters **TBPH** and **TBB** in addition to triphenyl phosphate (TPP; CASRN 115-86-6) and isopropylated triphenyl phosphate (ITPP; CASRN 68937-41-7) (Firemaster® 550) (Chemtura, 2012b). These latter aryl phosphates are considered to have a mode of action unlike the brominated phthalates cluster and may exert toxic effects on exposed organisms different than those noted for the brominated phthalates. However, insufficient experimental data are available to characterize ecotoxicity of the Firemaster® 550 formulation and, thus, a comparison of the more homogenous brominated phthalate formulations to the more heterogeneous aryl phosphate and brominated phthalate formulations cannot be made. Risk determination of aryl phosphates is outside the scope of the brominated phthalates data needs assessment. Screening-level data on these phosphates are available in (ECHA, 2013; EPA, 2010b; OECD, 2002).

2.2 Data Needs Assessment

The goal of this data needs assessment is to identify information that is currently needed to characterize environmental risk. In order to determine whether there are risks to the aquatic,

benthic, and terrestrial environment, both hazard and exposure data are needed to address the following key questions:

1. How do levels of brominated phthalates measured in effluent and surface water compare to levels that produce adverse effects in aquatic invertebrates, fish, or plants?
2. How do levels of brominated phthalates measured in sediment compare to levels that produce adverse effects in sediment invertebrates?
3. How do levels of brominated phthalates measured in soil compare to levels that produce adverse effects in soil invertebrates and plants?
4. Given the levels of brominated phthalates detected in avian species during biomonitoring, what is the likely exposure route and at what level are adverse population level effects expected?
5. Are there persistent or bioaccumulative degradates that may result in a hazard concern?

Based on current knowledge of the class, the additives, i.e. **TBPH, TBB** and 1,2-Benzenedicarboxylic acid, 1,2-bis(2,3-dibromopropyl) ester (CASRN 7415-86-3) are likely to exhibit differences in environmental mobility and bioavailability than the remaining cluster members (reactives) [*i.e* **TBPA-Diol**: 1,2-Benzenedicarboxylic acid, 3,4,5,6-tetrabromo-, 1-[2-(2-hydroxyethoxy)ethyl] 2-(2-hydroxypropyl) ester (CASRN 20566-35-2) and **TBPA-Diol**: 1,2-Benzenedicarboxylic acid, 3,4,5,6-tetrabromo-, mixed esters with diethylene glycol and propylene glycol (CASRN 77098-07-8)]. Data needs are being assessed for the brominated phthalate ester clusters separately for **TBPH/TBB** and the remaining cluster members based on this perceived difference in transport and bioavailability that will affect testing recommendations.

Insufficient experimental data are available to assess chronic aquatic, sediment, and terrestrial hazard across the brominated phthalates cluster. This includes the fish, aquatic invertebrates, aquatic plants, sediment dwelling organisms, terrestrial invertebrates, terrestrial plants, and avian taxa. Experimental data to assess all acute aquatic hazard endpoints are limited to chemicals with a Log K_{ow} of > 5. These data suggest increased sensitivity to aquatic invertebrates with high hazard concerns even though physicochemical properties suggest limited bioavailability following acute exposure. Most studies reviewed used a solvent or emulsifier to solubilize the test substance over time in solution. Use of a solvent may confound the results when effects are observed, but in all cases a solvent control was included for comparison.

Given the low water solubility and high log K_{ow} of **TBPH** and **TBB**, these cluster members are expected to be found in the sediment, sludge and soil. Monitoring data are available that support predicted partitioning to sediment, soil, and sludge and suggest likely chronic exposure. Organisms likely exposed for which no experimental data are available include sediment invertebrates and terrestrial organisms (e.g., plants, invertebrates and birds). Based on the likely long-term exposure, chronic hazard data should be provided. Due to difficulties interpreting studies of mixtures, experimental data should be conducted on pure substances (*e.g.*, ≥ 90 % purity).

Likely exposure pathways based on predictive and experimental physicochemical and fate parameters and reported release information for **TBPH** and **TBB** suggests minimal persistence in the water column and limited/no processing or manufacturing releases to water due to regulatory action. No monitoring data are available to suggest the presences of brominated phthalates in surface water, but monitoring of biota in water bodies has identified **TBB**/**TBPH** in aquatic organisms suggesting chronic exposure ecotoxicity data for water column organisms are limited to two chronic aquatic invertebrate studies on **TBPH** and Firemaster® BZ-54 (**TBB/TBPH**) that report conflicting results. Since data suggest high chronic hazard to aquatic invertebrates, data from additional independent chronic aquatic invertebrate studies on **TBPH** and **TBB** are needed to verify chronic aquatic invertebrate toxicity.

The two remaining brominated phthalates cluster members (*i.e.*, CASRNs 20566-35-2 and 77098-07-8) have no monitoring data, little hazard data, and represent the more soluble and bioavailable members of the cluster. These reactive cluster members are physically incorporated into end-use products and, thus, less likely to be released to the environment from their end-use products. Release from manufacturing and processing prior to reactive incorporation into the end-use product represents a potential pathway of exposure to the environment. Thus, further characterization of exposure pathways is needed to determine ecotoxicity data needs for these cluster members.

No data are available for CASRN 7415-86-3.

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