United States
Environmental Protection Agency

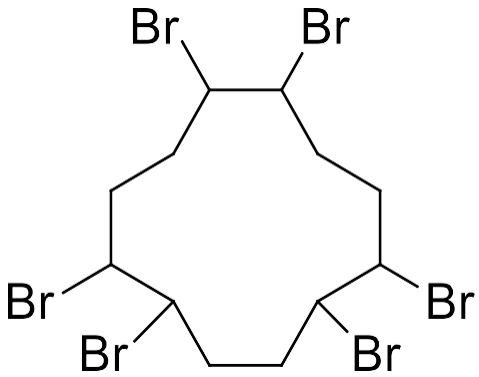
Office of Chemical Safety
and Pollution Prevention

Final Risk Evaluation for Cyclic Aliphatic Bromides Cluster (HBCD)

Systematic Review Supplemental File:

Data Extraction Tables for Human Health Hazard Studies

CASRN: 25637-99-4
CASRN: 3194-55-6
CASRN: 3194-57-8



September 2020

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1 Study Data Extraction

Note: Unacceptable studies not included in data extraction tables

1.1 Key and Supporting Study Data

Table 1. Summary of Key and Supporting Study Data for HBCD

Target Organ/ System	Study Type	Species/ Strain/Sex (Number/ Group)	Exposure Route	Doses/ Concentrations	Duration	Effect Dose/ Concentration/ Result	Effect Measured	Reference	Data Quality Evaluation
Endocrine	Reproductive	Rat, Crl:CD(SD), M/F (n=16-48/group)	Oral, diet	F0 males: 0, 10, 101 or 1008 mg/kg-day; F0 females: 0, 14, 141 or 1363 mg/kg-day; F1 males: 0, 11, 115 or 1142 mg/kg-day; F1 females: 0, 14, 138 or 1363 mg/kg-day	F0: 10 weeks prior to mating F1: post-weaning through necropsy F1/F2 offspring: continuous maternal exposure throughout gestation/ lactation	NOAEL = 101 mg/kg-day (M) LOAEL = 14 mg/kg-day (F)[8]	Increase in TSH in F0 females at low dose; Decreased T4 in F0 males and females at high dose; increased incidence of decreased thyroid follicle size in males in F0 males at mid dose	(Ema et al., 2008)	High
Endocrine	Reproductive	Rat, Wistar, M/F (n=6-10/group)	Oral, diet	0, 0.1, 0.3, 1, 3, 10, 30 or 100 mg/kg-day	F0: exposure started one spermatogenic cycle (males: 70 days) or two estrous cycles (females: 14 days) prior to mating F1: continuous maternal exposure throughout gestation/ lactation; dietary exposure post weaning through postnatal week 11	NOAEL = 100 mg/kg-day (M/F)[8]	No statistically significant effects on T3 or T4 levels, absolute thyroid weight or thyroid histopathology in males or females	(van der Ven et al., 2009)	High

Table 1. Summary of Key and Supporting Study Data for HBCD									
Target Organ/ System	**Study Type**	**Species/ Strain/Sex (Number/ Group)**	**Exposure Route**	**Doses/ Concentrations**	**Duration**	**Effect Dose/ Concentration/ Result**	**Effect Measured**	**Reference**	**Data Quality Evaluation**
Endocrine	Subchronic	Rat, Crl:CD(SD)IGS BR, M/F (n=10-20/group)	Oral, gavage	0, 100, 300 or 1000 mg/kg-day	Exposure started on approximately postnatal week 7 for 90 days followed by a 28-day recovery period	LOAEL = 100 mg/kg-day (M) NOAEL = 100 mg/kg-day (F)[8]	Decreased T4 levels in males at low dose and females at mid dose	(WIL Research, 2001)	High
Endocrine	Short-term	Rat, Wistar, M/F (n=7-10/group)	Oral, gavage	0, 0.3, 1, 3, 10, 30, 100 or 200 mg/kg-day	28 days, starting on postnatal week 11	$BMDL_{10}$ [decreased T4] = 55.5 mg/kg-day (F)[8] $BMDL_{10}$ [increased absolute thyroid weight] = 1.6 mg/kg-day (F)[8]	Significant dose-response trends for decreased T4 levels and increased absolute and relative thyroid weight in females; dose-dependent increases in thyroid activation (*i.e.*, follicle size, epithelial cell height, vacuolation and nuclear size) were reported qualitatively for males and females	(van der Ven et al., 2006)	High

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Target Organ/ System	**Study Type**	**Species/ Strain/Sex (Number/ Group)**	**Exposure Route**	**Doses/ Concentrations**	**Duration**	**Effect Dose/ Concentration/ Result**	**Effect Measured**	**Reference**	**Data Quality Evaluation**
Endocrine	Develop-mental	Rat, Crj:CD(SD)IGS, M/F (n=20/group)	Oral, diet	0, 15, 146 or 1505 mg/kg-day	Maternal exposure from GD 10 to PND 20 followed by 8-week non-exposure period through postnatal week 11	NOAEL = 15 mg/kg-day (M), 146 mg/kg-day (F)[8]	Increased relative thyroid weight and decreased T3 in male offspring at postnatal week 11 at mid dose; increased incidence of thyroid follicular cell hypertrophy in maternal females at high dose	(Saegusa et al., 2009)	High
Endocrine	Short-term	Mouse, BALB/c, F (n=6-8)	Oral, diet	0 or 199 mg/kg-day	28-day exposure starting on PND 26	LOAEL = 199 mg/kg-day (F)[8]	Increased follicle: colloid ratio	(Maranghi et al., 2013)	High
Immune	Short-term and mechanistic	Mouse, BALB/c, F (n=6-7/group)	Oral, diet	Approximately 1700 mg/kg-day, based on average food consumption and body weight (0 or 1% HBCD)	28 days	NOAEL = 1700 mg/kg-day (F)[8]	No changes in functional immune endpoints in respiratory syncytial virus - infected mice (infectivity based on viral titers, lung histology, cytokine levels, numbers of BAL and spleen cell populations)	(Watanabe et al., 2010)	Medium

Table 1. Summary of Key and Supporting Study Data for HBCD									
Target Organ/ System	**Study Type**	**Species/ Strain/Sex (Number/ Group)**	**Exposure Route**	**Doses/ Concentrations**	**Duration**	**Effect Dose/ Concentration/ Result**	**Effect Measured**	**Reference**	**Data Quality Evaluation**
Hepatic	Reproductive	Rat, Crl:CD(SD), M/F (n=26-48/group)	Oral, diet	F0 males: 0, 10, 101 or 1008 mg/kg-day; F0 females: 0, 14, 141 or 1363 mg/kg-day; F1 males: 0, 11, 115 or 1142 mg/kg-day; F1 females: 0, 14, 138 or 1363 mg/kg-day F1 offspring: 0, 17, 168 or 1570 mg/kg-day; F2 offspring: 0, 15, 139 or 1360 mg/kg-day	F0: 10 weeks prior to mating F1: post-weaning through necropsy F1/F2 offspring: continuous maternal exposure throughout gestation/ lactation	NOAEL = 10 mg/kg-day (M), 14 mg/kg-day (F)[8]	Increased relative liver weight in F0, F1 and F2 males and F1 females at mid dose	(Ema et al., 2008)	High
Hepatic	Reproductive	Rat, Wistar, M/F (n=8-10/group)	Oral, diet	0, 0.1, 0.3, 1, 3, 10, 30 or 100 mg/kg-day	F0: exposure started one spermatogenic cycle (males: 70 days) or two estrous cycles (females: 14 days) prior to mating F1: continuous maternal exposure throughout gestation/ lactation; dietary exposure post weaning through postnatal week 11	$BMDL_{10}$ = 8.6 mg/kg-day (F)[8]	Significant dose-response trend for decreased ALP activity in females	(van der Ven et al., 2009)	High

Table 1. Summary of Key and Supporting Study Data for HBCD									
Target Organ/ System	**Study Type**	**Species/ Strain/Sex (Number/ Group)**	**Exposure Route**	**Doses/ Concentrations**	**Duration**	**Effect Dose/ Concentration/ Result**	**Effect Measured**	**Reference**	**Data Quality Evaluation**
Hepatic	Subchronic	Rat, Crl:CD(SD)IGS BR, M/F (n=19-20/group)	Oral, gavage	0, 100, 300 or 1000 mg/kg-day	Exposure started on approximately postnatal week 7 for 90 days followed by a 28-day recovery period	LOAEL = 100 mg/kg-day (M/F)[9]	Increased relative liver weight and hepatocellular vacuolization in males and females at low dose; decreased ALP in females at low dose	(WIL Research, 2001)	High
Hepatic	Short-term	Rat, Wistar, M/F (n=6-10/group)	Oral, gavage	0, 0.3, 1, 3, 10, 30, 100 or 200 mg/kg-day	28 days, starting on postnatal week 11	$BMDL_{10}$ [ALP activity] = 18.9 mg/kg-day (F)[8] $BMDL_{20}$ [absolute liver weight] = 22.9 mg/kg-day (F)[8]	Significant dose-response trend for increased absolute liver weight and decreased ALP activity in females	(van der Ven et al., 2006)	High
Hepatic	Short-term	Rat, Sprague-Dawley, M/F (n=12/group)	Oral, gavage	0, 125, 350 or 1000 mg/kg-day	28-day exposure starting at approximately postnatal week 6 followed by a 14-day recovery period	LOAEL = 125 mg/kg-day (M/F)[8]	Increased relative liver weight in females at low dose; decreased ALT in males at low dose	(WIL Research, 1997)	High
Hepatic	Develop-mental	Rat, Crj:CD(SD)IGS, M/F (n=20/group)	Oral, diet	0, 15, 146 or 1505 mg/kg-day	Maternal exposure from GD 10 to PND 20 followed by 8-week non-exposure period through postnatal week 11	NOAEL = 146 mg/kg-day (M/F)[8]	Increased relative liver weight and increased incidence of hepatocellular vacuolar degeneration in male and female offspring on PND 20 at high dose	(Saegusa et al., 2009)	High

Table 1. Summary of Key and Supporting Study Data for HBCD									
Target Organ/ System	**Study Type**	**Species/ Strain/Sex (Number/ Group)**	**Exposure Route**	**Doses/ Concentrations**	**Duration**	**Effect Dose/ Concentration/ Result**	**Effect Measured**	**Reference**	**Data Quality Evaluation**
Hepatic	Short-term	Mouse, BALB/c, F (n=10-15)	Oral, diet	0 or 199 mg/kg-day	28-day exposure starting on PND 26	LOAEL = 199 mg/kg-day (F)[8]	Increased relative liver weight and increased incidences of periportal lymphatic infiltration, tissue congestion and vacuolation in hepatocytes	(Maranghi et al., 2013)	High
Neurological	Reproductive	Rat, Crl:CD(SD), M,F (n=13-24 litters evaluated for surface righting reflex response time and mid-air righting reflex rate; n=20-46/group evaluated for T-maze swim test trial time and brain weight)	Oral, diet	F1 males: 0, 11, 115 or 1142 mg/kg-day; F1 females: 0, 14, 138 or 1363 mg/kg-day; F1 offspring: 0, 17, 168 or 1570 mg/kg-day; F2 offspring 0, 15, 139 or 1360 mg/kg-day	F0: 10 weeks prior to mating F1: post-weaning through necropsy F1/F2 offspring: continuous maternal exposure throughout gestation/ lactation	NOAEL = 115 mg/kg-day (M), 138 mg/kg-day (F)[8]	Decreased surface righting response time in F1 males at the high dose; decreased mid-air righting reflex completion rate in F2 females at high dose; decreased absolute brain weight in F1 and F2 males and females at high dose	(Ema et al., 2008)	High

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Neurological	Develop-mental	Rat, Long-Evans, M/F (n=8-10 litters evaluated for righting reflex, grip strength and tail pinch response; n=4/group evaluated for go/no-go task and random ratio task)	Oral, gavage	0, 3, 10 or 30 mg/kg-day	F1: continuous maternal exposure from GD 1 throughout gestation until parturition	LOAEL = 3 mg/kg-day (M/F)[8]	Decreased percentage of pups (males and females combined) per litter that did not response to tail pinch on PNDs 1-21 at low dose	(Miller-Rhodes et al., 2014)	Medium
Neurological	Acute	Mouse, NMR1, M (n=10/group)	Oral, gavage	0, 0.9 or 13.5 mg/kg	Single dose on PND 10	LOAEL = 0.9 mg/kg (M)[8]	Decrease in horizontal locomotion and rearing at 0-20 minutes at low dose; increase in Morris water maze time on day 4 at low dose	(Ericksson et al., 2006)	Medium

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Target Organ/ System	**Study Type**	**Species/ Strain/Sex (Number/ Group)**	**Exposure Route**	**Doses/ Concentrations**	**Duration**	**Effect Dose/ Concentration/ Result**	**Effect Measured**	**Reference**	**Data Quality Evaluation**
Neurological	Reproductive	Rat, Wistar, M/F (n=4-6/group)	Oral, diet	0, 0.1, 0.3, 1, 3, 10, 30 or 100 mg/kg-day	F0: exposure started at 10 (males) or 20 (females) weeks prior to mating F1: continuous maternal exposure throughout gestation/ lactation; dietary exposure post weaning until sacrifice (at approximately postnatal week 20)	$BMDL_5$ [BAEP] = 0.9 mg/kg-day (M)[8] $BMDL_{20}$ [catalepsy] = 3.0 mg/kg-day (M), 0.6 mg/kg-day (F)[8]	Significant dose-response trends in brainstem auditory evoked potentials (BAEPs) (increased click threshold) in F1 males and catalepsy (box, foreleg, decreased movement latency) in F1 males and females	(Lilienthal et al., 2009)	High
Neurological	Reproductive	Rat, Wistar, M/F (n=8-10/group)	Oral, diet	0, 0.1, 0.3, 1, 3, 10, 30 or 100 mg/kg-day	F0: exposure started one spermatogenic cycle (males: 70 days) or two estrous cycles (females: 14 days) prior to mating F1: continuous maternal exposure throughout gestation/ lactation; dietary exposure post weaning through postnatal week 11	$BMDL_{10}$ = 108.3 mg/kg-day (M)[8]	Significant dose-response trend in brain weight in F1 males, with most groups showing an increase, relative to controls	(van der Ven et al., 2009)	High

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Target Organ/ System	**Study Type**	**Species/ Strain/Sex (Number/ Group)**	**Exposure Route**	**Doses/ Concentrations**	**Duration**	**Effect Dose/ Concentration/ Result**	**Effect Measured**	**Reference**	**Data Quality Evaluation**
Neurological	Subchronic, Mechanistic (study primarily reports mechanistic endpoints)	Mouse, C57BL/6J, M (n=6/treatment group; n=4 controls)	Oral, gavage	0 or 25 mg/kg-day	1 time/day for 30 days	NOAEL = 25 mg/kg-day (M)[8]	No changes in concentrations of dopamine or its metabolites in striatum tissue	(Genskow et al., 2015)	Medium
Reproductive	Reproductive	Rat, Crl:CD(SD), F (n=8-46/group)	Oral, diet	F0: 0, 14, 141 or 1363 mg/kg-day; F1: 0, 14, 138 or 1363 mg/kg-day; F1 offspring: 0, 17, 168 or 1570 mg/kg-day; F2 offspring 0, 15, 139 or 1360 mg/kg-day	F0: 10 weeks prior to mating F1: post-weaning through necropsy F1/F2 offspring: continuous maternal exposure throughout gestation/ lactation	NOAEL = 14 mg/kg-day (F)[8]	Decreased primordial follicles in F1 females at mid dose	(Ema et al., 2008)	High
Reproductive	Reproductive	Rat, Wistar, F (n=4-10/group)	Oral, diet	0, 0.1, 0.3, 1, 3, 10, 30 or 100 mg/kg-day	F0: exposure started one spermatogenic cycle (males: 70 days) or two estrous cycles (females: 14 days) prior to mating F1: continuous maternal exposure throughout gestation/ lactation; dietary exposure post weaning through postnatal week 11	$BMDL_{10}$ = 82.2 mg/kg-day (F)[8]	Significant dose-response trend for delayed time to vaginal opening in F1 females	(van der Ven et al., 2009)	High

Table 1. Summary of Key and Supporting Study Data for HBCD									
Target Organ/ System	**Study Type**	**Species/ Strain/Sex (Number/ Group)**	**Exposure Route**	**Doses/ Concentrations**	**Duration**	**Effect Dose/ Concentration/ Result**	**Effect Measured**	**Reference**	**Data Quality Evaluation**
Reproductive	Develop-mental	Rat, Crj:CD(SD)IGS, F (n=10-14/group)	Oral, diet	0, 15, 146 or 1505 mg/kg-day	Maternal exposure from GD 10 to PND 20 followed by an 8-week non-exposure period through postnatal week 11	NOAEL = 1505 mg/kg-day (F)[8]	No effects on pregnancy outcomes (e.g., number of implantation sites, gestation duration, litter, size) in F0 animals or time to vaginal opening, AGD or relative ovary or uterus weights in F1 offspring	(Saegusa et al., 2009)	High
Reproductive	Short-term	Mouse, BALB/c, F (n=10-15/group)	Oral, diet	0 or 199 mg/kg-day	28-day exposure starting on PND 26	LOAEL = 199 mg/kg-day (F)[8]	Increased testosterone and testosterone/estradiol levels	(Maranghi et al., 2013)	High
Reproductive	Subchronic	Rat, Crl:CD(SD)IGS BR, F (n=10/group)	Oral, gavage	0, 100, 300 or 1000 mg/kg-day	Exposure started on approximately postnatal week 7 for 90 days followed by a 28-day recovery period	NOAEL = 1000 mg/kg-day (F)[8]	No effects on absolute or relative ovary with oviduct weight or uterus with cervix weight	(WIL Research, 2001)	High
Reproductive	Short-term	Rat, Sprague-Dawley, F (n=6/group)	Oral, gavage	0, 125, 350 or 1000 mg/kg-day	28-day exposure starting at approximately postnatal week 6 followed by a 14-day recovery period	NOAEL = 1000 mg/kg-day (F)[8]	No effects on relative ovary with oviduct weight	(WIL Research, 1997)	High

Table 1. Summary of Key and Supporting Study Data for HBCD									
Target Organ/ System	**Study Type**	**Species/ Strain/Sex (Number/ Group)**	**Exposure Route**	**Doses/ Concentrations**	**Duration**	**Effect Dose/ Concentration/ Result**	**Effect Measured**	**Reference**	**Data Quality Evaluation**
Develop-mental	Reproductive	Rat, Crl:CD(SD), M/F (n=, 13-24 litters/group)	Oral, diet	F1 offspring: 0, 17, 168 or 1570 mg/kg-day; F2 offspring 0, 15, 139 or 1360 mg/kg-day	F0: 10 weeks prior to mating F1: post-weaning through necropsy F1/F2 offspring: continuous maternal exposure throughout gestation/ lactation	NOAEL = 139 mg/kg-day (M), 15 mg/kg-day (F)[8]	Decreased pup weight in F1 and F2 males at high dose; decreased F2 pup viability index in litters at high dose on PNDs 4 and 21; delayed eye opening at mid dose in F2 females	(Ema et al., 2008)	High
Develop-mental	Develop-mental	Rat, Crj:CD(SD)IGS, M/F (n=20-28/group)	Oral, diet	0, 15, 146 or 1505 mg/kg-day	Maternal exposure from GD 10 to PND 20 followed by 8-week non-exposure period through postnatal week 11	NOAEL = 1505 mg/kg-day (M), 146 mg/kg-day (F)[8]	Decreased pup weight in F1 females at puberty onset (~PND 35) at high dose	(Saegusa et al., 2009)	High
Develop-mental	Reproductive	Rat, Wistar, M/F (n=9-≥28/group)	Oral, diet	0, 0.1, 0.3, 1, 3, 10, 30 or 100 mg/kg-day	F0: exposure started one spermatogenic cycle (males: 70 days) or two estrous cycles (females: 14 days) prior to mating F1: continuous maternal exposure throughout gestation/ lactation; dietary exposure post weaning through postnatal week 11	$BMDL_{10}$ [pup body weight at necropsy (weaning age)] = 62.7 mg/kg-day (M), 57.9 mg/kg-day (F)[8] $BMDL_{10}$ [tibia trabecular bone mineral density] = 0.056 mg/kg-day (F)[8]	Significant dose-response trends for decreased body weight in F1 male and female pups (PND 4-21) and decreased tibia trabecular bone mineral density in F1 female pups at postnatal week 11	(van der Ven et al., 2009)	High

Table 1. Summary of Key and Supporting Study Data for HBCD									
Target Organ/ System	**Study Type**	**Species/ Strain/Sex (Number/ Group)**	**Exposure Route**	**Doses/ Concentrations**	**Duration**	**Effect Dose/ Concentration/ Result**	**Effect Measured**	**Reference**	**Data Quality Evaluation**
Develop-mental	Develop-mental immuno-toxicity	Rat, Sprague-Dawley, M (n=10/group)	Oral, diet	0, 15, 146 or 1505 mg/kg-day	F1: maternal exposure from GD 10 to postnatal week 3 followed by an 8-week non-exposure period through postnatal week 11	NOAEL = 1505 mg/kg-day (M)[8]	No effects on F1 pup weight	(Hachisuka et al., 2010)	Medium
Develop-mental	Short-term	Mouse, BALB/c, F (n=10-15/group)	Oral, diet	0 or 199 mg/kg-day	28-day exposure starting on PND 26	NOAEL = 199 mg/kg-day (F)[8]	No effects on body weight gain	(Maranghi et al., 2013)	High

1.2 Animal / *In Vivo* Data Identified from OPPT Literature Search

Table 2. Summary of New Animal / *In Vivo* Data for HBCD

Target Organ/ System	Study Type	Species/ Strain/Sex (Number/ group)	Exposure Route	Doses/ Concentrations	Duration	Author Reported Effect Dose/ Concentration/ Result	Reviewer Reported Effect Dose/ Concentration/ Result	Effect Measured	Reference	Data Quality Evaluation
Body Weight	Short-term (1-30 days)	Mouse Balb/c - [mouse] Female (8/group)	Oral	4.6e-05 , 0.107 , 116 mg/kg-bw/day	Not Reported	Not Reported	NOAEL = 0.107 mg/kg - bw/day	Increased body weight gain and relative liver weight; decreased relative spleen, thymus and adipose weight; increased liver triglycerides and serum AST, ALT; microvesicular accumulation of lipids (histo. exam.); decreased serum triglycerides.	Bernhard et al (2016)	High
Body Weight	Subchronic (30-90 days)	Rat Other Female (15/group)	Oral	0 , 100 , 300 , 1000 mg/kg-bw/day	7 days/week for 90 weeks	NOAEL = 0.048	NOAEL = 1000 mg/kg - bw/day	No effects were reported on mortality, neurological/behavior, body weight, hematology, renal, ocular, reproductive, gastrointestinal, cardiovascular, respiratory, or skin endpoints.	ACC (2002)	High
Cardiovascular	Subchronic (30-90 days)	Rat Other Male (15/group)	Oral	0 , 100 , 300 , 1000 mg/kg-bw/day	7 days/week for 90 weeks	NOAEL = 1000 mg/kg - bw/day	Reviewer Agreed with Author	No effects were reported on neurological/behavior, body weight, renal, ocular, gastrointestinal, cardiovascular, respiratory, or skin endpoints.	ACC (2002)	High

Table 2. Summary of New Animal / *In Vivo* Data for HBCD										
Target Organ/ System	**Study Type**	**Species/ Strain/Sex (Number/ group)**	**Exposure Route**	**Doses/ Concentrations**	**Duration**	**Author Reported Effect Dose/ Concentration/ Result**	**Reviewer Reported Effect Dose/ Concentration/ Result**	**Effect Measured**	**Reference**	**Data Quality Evaluation**
Cardiovascular	Subchronic (30-90 days)	Rat Other Female (15/group)	Oral	0 , 100 , 300 , 1000 mg/kg-bw/day	7 days/week for 90 weeks	NOAEL = 0.048	NOAEL = 1000 mg/kg - bw/day	No effects were reported on mortality, neurological/behavior, body weight, hematology, renal, ocular, reproductive, gastrointestinal, cardiovascular, respiratory, or skin endpoints.	ACC (2002)	High
Clinical Chemistry/ Biochemical	Short-term (1-30 days)	Rat Sprague-Dawley - [rat] Both (5/group)	Inhalation	0 , 132 , 545.8 , 2166 mg/kg-bw/day	6 hours/day 7 days/week for 14 days	NOAEL = 2166 mg/m3	Reviewer Agreed with Author	There were no effects of exposure on clinical signs, body weight, hematology and clinical chemistry parameters, organ weights (brain, heart, kidneys, liver, lungs, trachea, ovaries, uterus, testis, and spleen), gross findings, or microscopic findings in the brain, heart, kidneys, liver, lungs trachea, ovaries, uterus, testis, or spleen.	Song et al (2016)	High
Clinical Chemistry/ Biochemical	Subchronic (30-90 days)	Rat Other Male (15/group)	Oral	0 , 100 , 300 , 1000 mg/kg-bw/day	7 days/week for 90 weeks	NOAEL = 0.048	LOAEL = 100 mg/kg - bw/day	Hepatocellular vacuolation, increased liver weight, increased prothrombin time, albumin, and chloride	ACC (2002)	High

Table 2. Summary of New Animal / *In Vivo* Data for HBCD										
Target Organ/ System	**Study Type**	**Species/ Strain/Sex (Number/ group)**	**Exposure Route**	**Doses/ Concentrations**	**Duration**	**Author Reported Effect Dose/ Concentration/ Result**	**Reviewer Reported Effect Dose/ Concentration/ Result**	**Effect Measured**	**Reference**	**Data Quality Evaluation**
Clinical Chemistry/ Biochemical	Subchronic (30-90 days)	Rat Other Female (15/group)	Oral	0 , 100 , 300 , 1000 mg/kg-bw/day	7 days/week for 90 weeks	NOAEL = 0.048	LOAEL = 100 mg/kg - bw/day	Hepatocellular vacuolation, centrilobular hepatocellular hypertrophy, increased liver weight, increased total protein, decreased alkaline phosphatase	ACC (2002)	High
Gastrointestinal	Subchronic (30-90 days)	Rat Other Male (15/group)	Oral	0 , 100 , 300 , 1000 mg/kg-bw/day	7 days/week for 90 weeks	NOAEL = 1000 mg/kg - bw/day	Reviewer Agreed with Author	No effects were reported on neurological/behavior, body weight, renal, ocular, gastrointestinal, cardiovascular, respiratory, or skin endpoints.	ACC (2002)	High
Gastrointestinal	Subchronic (30-90 days)	Rat Other Female (15/group)	Oral	0 , 100 , 300 , 1000 mg/kg-bw/day	7 days/week for 90 weeks	NOAEL = 0.048	NOAEL = 1000 mg/kg - bw/day	No effects were reported on mortality, neurological/behavior, body weight, hematology, renal, ocular, reproductive, gastrointestinal, cardiovascular, respiratory, or skin endpoints.	ACC (2002)	High

Table 2. Summary of New Animal / *In Vivo* Data for HBCD										
Target Organ/ System	**Study Type**	**Species/ Strain/Sex (Number/ group)**	**Exposure Route**	**Doses/ Concentrations**	**Duration**	**Author Reported Effect Dose/ Concentration/ Result**	**Reviewer Reported Effect Dose/ Concentration/ Result**	**Effect Measured**	**Reference**	**Data Quality Evaluation**
Hematological and Immune	Short-term (1-30 days)	Rat Sprague-Dawley - [rat] Both (5/group)	Inhalation	0 , 132 , 545.8 , 2166 mg/kg-bw/day	6 hours/day 7 days/week for 14 days	NOAEL = 2166 mg/m3	Reviewer Agreed with Author	There were no effects of exposure on clinical signs, body weight, hematology and clinical chemistry parameters, organ weights (brain, heart, kidneys, liver, lungs, trachea, ovaries, uterus, testis, and spleen), gross findings, or microscopic findings in the brain, heart, kidneys, liver, lungs trachea, ovaries, uterus, testis, or spleen.	Song et al (2016)	High
Hematological and Immune	Subchronic (30-90 days)	Rat Other Male (15/group)	Oral	0 , 100 , 300 , 1000 mg/kg-bw/day	7 days/week for 90 weeks	NOAEL = 0.048	LOAEL = 100 mg/kg - bw/day	Hepatocellular vacuolation, increased liver weight, increased prothrombin time, albumin, and chloride	ACC (2002)	High
Hematological and Immune	Subchronic (30-90 days)	Rat Other Female (15/group)	Oral	0 , 100 , 300 , 1000 mg/kg-bw/day	7 days/week for 90 weeks	NOAEL = 0.048	NOAEL = 1000 mg/kg - bw/day	No effects were reported on mortality, neurological/behavior, body weight, hematology, renal, ocular, reproductive, gastrointestinal, cardiovascular, respiratory, or skin endpoints.	ACC (2002)	High

Table 2. Summary of New Animal / *In Vivo* Data for HBCD										
Target Organ/ System	**Study Type**	**Species/ Strain/Sex (Number/ group)**	**Exposure Route**	**Doses/ Concentrations**	**Duration**	**Author Reported Effect Dose/ Concentration/ Result**	**Reviewer Reported Effect Dose/ Concentration/ Result**	**Effect Measured**	**Reference**	**Data Quality Evaluation**
Hepatic	Short-term (1-30 days)	Rat Sprague-Dawley - [rat] Both (5/group)	Inhalation	0 , 132 , 545.8 , 2166 mg/kg-bw/day	6 hours/day 7 days/week for 14 days	NOAEL = 2166 mg/m3	Reviewer Agreed with Author	There were no effects of exposure on clinical signs, body weight, hematology and clinical chemistry parameters, organ weights (brain, heart, kidneys, liver, lungs, trachea, ovaries, uterus, testis, and spleen), gross findings, or microscopic findings in the brain, heart, kidneys, liver, lungs trachea, ovaries, uterus, testis, or spleen.	Song et al (2016)	High
Hepatic	Short-term (1-30 days)	Mouse Balb/c - [mouse] Female (8/group)	Oral	4.6e-05 , 0.107 , 116 mg/kg-bw/day	Not Reported	Not Reported	NOAEL = 0.107 mg/kg - bw/day	Increased body weight gain and relative liver weight; decreased relative spleen, thymus and adipose weight; increased liver triglycerides and serum AST, ALT; microvesicular ACCumulation of lipids (histo. exam.); decreased serum triglycerides.	Bernhard et al (2016)	High
Hepatic	Subchronic (30-90 days)	Rat Other Male (15/group)	Oral	0 , 100 , 300 , 1000 mg/kg-bw/day	7 days/week for 90 weeks	NOAEL = 0.048	LOAEL = 100 mg/kg - bw/day	Hepatocellular vacuolation, increased liver weight, increased prothrombin time, albumin, and chloride	ACC (2002)	High

Table 2. Summary of New Animal / *In Vivo* Data for HBCD										
Target Organ/ System	**Study Type**	**Species/ Strain/Sex (Number/ group)**	**Exposure Route**	**Doses/ Concentrations**	**Duration**	**Author Reported Effect Dose/ Concentration/ Result**	**Reviewer Reported Effect Dose/ Concentration/ Result**	**Effect Measured**	**Reference**	**Data Quality Evaluation**
Hepatic	Subchronic (30-90 days)	Rat Other Female (15/group)	Oral	0 , 100 , 300 , 1000 mg/kg-bw/day	7 days/week for 90 weeks	NOAEL = 0.048	LOAEL = 100 mg/kg - bw/day	Hepatocellular vacuolation, centrilobular hepatocellular hypertrophy, increased liver weight, increased total protein, decreased alkaline phosphatase	ACC (2002)	High
Mortality	Acute/ Short-term	Rat Sprague-Dawley - [rat] Both (5/group)	Inhalation	5312 mg/kg-bw/day	(4hr 1day; 6h/d 14 day)	LC50 = 5312 mg/m3	Reviewer Agreed with Author	No effects were noted in body weight or signs of toxicity.	Song et al (2016)	High
Mortality	Subchronic (30-90 days)	Rat Other Male (15/group)	Oral	0 , 100 , 300 , 1000 mg/kg-bw/day	7 days/week for 90 weeks	NOAEL = 0.048	LOAEL = 1000 mg/kg - bw/day	Follicular cell hypertrophy in thyroid, decreased T4 levels, increased prostate gland weight, decreased survival	ACC (2002)	High
Mortality	Subchronic (30-90 days)	Rat Other Female (15/group)	Oral	0 , 100 , 300 , 1000 mg/kg-bw/day	7 days/week for 90 weeks	NOAEL = 0.048	NOAEL = 1000 mg/kg - bw/day	No effects were reported on mortality, neurological/behavior, body weight, hematology, renal, ocular, reproductive, gastrointestinal, cardiovascular, respiratory, or skin endpoints.	ACC (2002)	High

Table 2. Summary of New Animal / *In Vivo* Data for HBCD										
Target Organ/ System	**Study Type**	**Species/ Strain/Sex (Number/ group)**	**Exposure Route**	**Doses/ Concentrations**	**Duration**	**Author Reported Effect Dose/ Concentration/ Result**	**Reviewer Reported Effect Dose/ Concentration/ Result**	**Effect Measured**	**Reference**	**Data Quality Evaluation**
Neurological/ Behavior	Subchronic (30-90 days)	Rat Other Male (15/group)	Oral	0 , 100 , 300 , 1000 mg/kg-bw/day	7 days/week for 90 weeks	NOAEL = 1000 mg/kg - bw/day	Reviewer Agreed with Author	No effects were reported on neurological/behavior, body weight, renal, ocular, gastrointestinal, cardiovascular, respiratory, or skin endpoints.	ACC (2002)	High
Neurological/ Behavior	Subchronic (30-90 days)	Rat Other Female (15/group)	Oral	0 , 100 , 300 , 1000 mg/kg-bw/day	7 days/week for 90 weeks	NOAEL = 0.048	NOAEL = 1000 mg/kg - bw/day	No effects were reported on mortality, neurological/behavior, body weight, hematology, renal, ocular, reproductive, gastrointestinal, cardiovascular, respiratory, or skin endpoints.	ACC (2002)	High
Not Reported	Short-term (1-30 days)	Rat Sprague-Dawley - [rat] Both (5/group)	Inhalation	0 , 132 , 545.8 , 2166 mg/kg-bw/day	6 hours/day 7 days/week for 14 days	NOAEL = 2166 mg/m3	Reviewer Agreed with Author	There were no effects of exposure on clinical signs, body weight, hematology and clinical chemistry parameters, organ weights (brain, heart, kidneys, liver, lungs, trachea, ovaries, uterus, testis, and spleen), gross findings, or microscopic findings in the brain, heart, kidneys, liver, lungs trachea, ovaries, uterus, testis, or spleen.	Song et al (2016)	High

Table 2. Summary of New Animal / *In Vivo* Data for HBCD										
Target Organ/ System	**Study Type**	**Species/ Strain/Sex (Number/ group)**	**Exposure Route**	**Doses/ Concentrations**	**Duration**	**Author Reported Effect Dose/ Concentration/ Result**	**Reviewer Reported Effect Dose/ Concentration/ Result**	**Effect Measured**	**Reference**	**Data Quality Evaluation**
Not Reported	Short-term (1-30 days)	Rat Sprague-Dawley - [rat] Both (5)	Inhalation	0 , 132 , 545.8 , 2166 mg/kg-bw/day	6 hours/day 7 days/week for 14 days	NOAEL = 2166 mg/m^3	Reviewer Agreed with Author	There were no effects of exposure on clinical signs, body weight, hematology and clinical chemistry parameters, organ weights (brain, heart, kidneys, liver, lungs, trachea, ovaries, uterus, testis, and spleen), gross findings, or microscopic findings in the brain, heart, kidneys, liver, lungs trachea, ovaries, uterus, testis, or spleen.	Song et al (2016)	High
Not Reported	Subchronic (30-90 days)	Rat Other Male (15/group)	Oral	0 , 100 , 300 , 1000 mg/kg-bw/day	7 days/week for 90 weeks	NOAEL = 0.048	LOAEL = 100 mg/kg - bw/day	Hepatocellular vacuolation, increased liver weight, increased prothrombin time, albumin, and chloride	ACC (2002)	High
Not Reported	Subchronic (30-90 days)	Rat Other Male (15/group)	Oral	0 , 100 , 300 , 1000 mg/kg-bw/day	7 days/week for 90 weeks	NOAEL = 0.048	LOAEL = 100 mg/kg - bw/day	Hepatocellular vacuolation, increased liver weight, increased prothrombin time, albumin, and chloride	ACC (2002)	High
Not Reported	Subchronic (30-90 days)	Rat Other Female (15/group)	Oral	0 , 100 , 300 , 1000 mg/kg-bw/day	7 days/week for 90 weeks	NOAEL = 0.048	LOAEL = 100 mg/kg - bw/day	Hepatocellular vacuolation, centrilobular hepatocellular hypertrophy, increased liver weight, increased total protein, decreased alkaline phosphatase	ACC (2002)	High

Table 2. Summary of New Animal / *In Vivo* Data for HBCD										
Target Organ/ System	**Study Type**	**Species/ Strain/Sex (Number/ group)**	**Exposure Route**	**Doses/ Concentrations**	**Duration**	**Author Reported Effect Dose/ Concentration/ Result**	**Reviewer Reported Effect Dose/ Concentration/ Result**	**Effect Measured**	**Reference**	**Data Quality Evaluation**
Not Reported	Subchronic (30-90 days)	Rat Other Female (15/group)	Oral	0 , 100 , 300 , 1000 mg/kg-bw/day	7 days/week for 90 weeks	NOAEL = 0.048	LOAEL = 100 mg/kg - bw/day	Hepatocellular vacuolation, centrilobular hepatocellular hypertrophy, increased liver weight, increased total protein, decreased alkaline phosphatase	ACC (2002)	High
Nutrition and Metabolic/Adult Exposure Body Weight	Subchronic (30-90 days)	Rat Other Male (15/group)	Oral	0 , 100 , 300 , 1000 mg/kg-bw/day	7 days/week for 90 weeks	NOAEL = 1000 mg/kg - bw/day	Reviewer Agreed with Author	No effects were reported on neurological/behavior, body weight, renal, ocular, gastrointestinal, cardiovascular, respiratory, or skin endpoints.	ACC (2002)	High
Ocular and Sensory	Subchronic (30-90 days)	Rat Other Male (15/group)	Oral	0 , 100 , 300 , 1000 mg/kg-bw/day	7 days/week for 90 weeks	NOAEL = 1000 mg/kg - bw/day	Reviewer Agreed with Author	No effects were reported on neurological/behavior, body weight, renal, ocular, gastrointestinal, cardiovascular, respiratory, or skin endpoints.	ACC (2002)	High
Ocular and Sensory	Subchronic (30-90 days)	Rat Other Female (15/group)	Oral	0 , 100 , 300 , 1000 mg/kg-bw/day	7 days/week for 90 weeks	NOAEL = 0.048	NOAEL = 1000 mg/kg - bw/day	No effects were reported on mortality, neurological/behavior, body weight, hematology, renal, ocular, reproductive, gastrointestinal, cardiovascular, respiratory, or skin endpoints.	ACC (2002)	High

Table 2. Summary of New Animal / *In Vivo* Data for HBCD										
Target Organ/ System	**Study Type**	**Species/ Strain/Sex (Number/ group)**	**Exposure Route**	**Doses/ Concentrations**	**Duration**	**Author Reported Effect Dose/ Concentration/ Result**	**Reviewer Reported Effect Dose/ Concentration/ Result**	**Effect Measured**	**Reference**	**Data Quality Evaluation**
Renal	Short-term (1-30 days)	Rat Sprague-Dawley - [rat] Both (5/group)	Inhalation	0 , 132 , 545.8 , 2166 mg/kg-bw/day	6 hours/day 7 days/week for 14 days	NOAEL = 2166 mg/m3	Reviewer Agreed with Author	There were no effects of exposure on clinical signs, body weight, hematology and clinical chemistry parameters, organ weights (brain, heart, kidneys, liver, lungs, trachea, ovaries, uterus, testis, and spleen), gross findings, or microscopic findings in the brain, heart, kidneys, liver, lungs trachea, ovaries, uterus, testis, or spleen.	Song et al (2016)	High
Renal	Subchronic (30-90 days)	Rat Other Male (15/group)	Oral	0 , 100 , 300 , 1000 mg/kg-bw/day	7 days/week for 90 weeks	NOAEL = 1000 mg/kg - bw/day	Reviewer Agreed with Author	No effects were reported on neurological/behavior, body weight, renal, ocular, gastrointestinal, cardiovascular, respiratory, or skin endpoints.	ACC (2002)	High
Renal	Subchronic (30-90 days)	Rat Other Female (15/group)	Oral	0 , 100 , 300 , 1000 mg/kg-bw/day	7 days/week for 90 weeks	NOAEL = 0.048	NOAEL = 1000 mg/kg - bw/day	No effects were reported on mortality, neurological/behavior, body weight, hematology, renal, ocular, reproductive, gastrointestinal, cardiovascular, respiratory, or skin endpoints.	ACC (2002)	High

Table 2. Summary of New Animal / *In Vivo* Data for HBCD										
Target Organ/ System	**Study Type**	**Species/ Strain/Sex (Number/ group)**	**Exposure Route**	**Doses/ Concentrations**	**Duration**	**Author Reported Effect Dose/ Concentration/ Result**	**Reviewer Reported Effect Dose/ Concentration/ Result**	**Effect Measured**	**Reference**	**Data Quality Evaluation**
Thyroid	Short-term (1-30 days)	Rat Other Female (6/group)	Oral	0, 3, 30 mg/kg-bw/day	7 days	Not Reported	NOAEL = 30 mg/kg - bw/day	Liver weight	Miller et al (2016)	Medium
Reproductive	Short-term (1-30 days)	Rat Sprague-Dawley - [rat] Both (5/group)	Inhalation	0 , 132 , 545.8 , 2166 mg/kg-bw/day	6 hours/day 7 days/week for 14 days	NOAEL = 2166 mg/m3	Reviewer Agreed with Author	There were no effects of exposure on clinical signs, body weight, hematology and clinical chemistry parameters, organ weights (brain, heart, kidneys, liver, lungs, trachea, ovaries, uterus, testis, and spleen), gross findings, or microscopic findings in the brain, heart, kidneys, liver, lungs trachea, ovaries, uterus, testis, or spleen.	Song et al (2016)	High
Reproductive	Subchronic (30-90 days)	Rat Other Male (15/group)	Oral	0 , 100 , 300 , 1000 mg/kg-bw/day	7 days/week for 90 weeks	NOAEL = 0.048	LOAEL = 1000 mg/kg - bw/day	Follicular cell hypertrophy in thyroid, decreased T4 levels, increased prostate gland weight, decreased survival	ACC (2002)	High

Table 2. Summary of New Animal / *In Vivo* Data for HBCD										
Target Organ/ System	**Study Type**	**Species/ Strain/Sex (Number/ group)**	**Exposure Route**	**Doses/ Concentrations**	**Duration**	**Author Reported Effect Dose/ Concentration/ Result**	**Reviewer Reported Effect Dose/ Concentration/ Result**	**Effect Measured**	**Reference**	**Data Quality Evaluation**
Reproductive	Subchronic (30-90 days)	Rat Other Female (15/group)	Oral	0 , 100 , 300 , 1000 mg/kg-bw/day	7 days/week for 90 weeks	NOAEL = 0.048	NOAEL = 1000 mg/kg - bw/day	No effects were reported on mortality, neurological/behavior, body weight, hematology, renal, ocular, reproductive, gastrointestinal, cardiovascular, respiratory, or skin endpoints.	ACC (2002)	High
Respiratory	Subchronic (30-90 days)	Rat Other Male (15/group)	Oral	0 , 100 , 300 , 1000 mg/kg-bw/day	7 days/week for 90 weeks	NOAEL = 1000 mg/kg - bw/day	Reviewer Agreed with Author	No effects were reported on neurological/behavior, body weight, renal, ocular, gastrointestinal, cardiovascular, respiratory, or skin endpoints.	ACC (2002)	High
Respiratory	Subchronic (30-90 days)	Rat Other Female (15/group)	Oral	0 , 100 , 300 , 1000 mg/kg-bw/day	7 days/week for 90 weeks	NOAEL = 0.048	NOAEL = 1000 mg/kg - bw/day	No effects were reported on mortality, neurological/behavior, body weight, hematology, renal, ocular, reproductive, gastrointestinal, cardiovascular, respiratory, or skin endpoints.	ACC (2002)	High

Table 2. Summary of New Animal / *In Vivo* Data for HBCD										
Target Organ/ System	**Study Type**	**Species/ Strain/Sex (Number/ group)**	**Exposure Route**	**Doses/ Concentrations**	**Duration**	**Author Reported Effect Dose/ Concentration/ Result**	**Reviewer Reported Effect Dose/ Concentration/ Result**	**Effect Measured**	**Reference**	**Data Quality Evaluation**
Skin and Connective Tissue	Subchronic (30-90 days)	Rat Other Male (15/group)	Oral	0 , 100 , 300 , 1000 mg/kg-bw/day	7 days/week for 90 weeks	NOAEL = 1000 mg/kg - bw/day	Reviewer Agreed with Author	No effects were reported on neurological/behavior, body weight, renal, ocular, gastrointestinal, cardiovascular, respiratory, or skin endpoints.	ACC (2002)	High
Skin and Connective Tissue	Subchronic (30-90 days)	Rat Other Female (15/group)	Oral	0 , 100 , 300 , 1000 mg/kg-bw/day	7 days/week for 90 weeks	NOAEL = 0.048	NOAEL = 1000 mg/kg - bw/day	No effects were reported on mortality, neurological/behavior, body weight, hematology, renal, ocular, reproductive, gastrointestinal, cardiovascular, respiratory, or skin endpoints.	ACC (2002)	High
Thyroid	Short-term (1-30 days)	Rat Other Female (6/group)	Oral	0, 3, 30 mg/kg-bw/day	7 days	Not Reported	NOAEL = 30 mg/kg - bw/day	TSH, T3, LH, FSH, Leptin, and Cortocosterone levels	Miller et al (2016)	Medium
Thyroid	Subchronic (30-90 days)	Rat Other Male (15/group)	Oral	0 , 100 , 300 , 1000 mg/kg-bw/day	7 days/week for 90 weeks	NOAEL = 0.048	LOAEL = 1000 mg/kg - bw/day	Follicular cell hypertrophy in thyroid, decreased T4 levels, increased prostate gland weight, decreased survival	ACC (2002)	High
Thyroid	Subchronic (30-90 days)	Rat Other Female (15/group)	Oral	0 , 100 , 300 , 1000 mg/kg-bw/day	7 days/week for 90 weeks	NOAEL = 0.048	LOAEL = 300 mg/kg - bw/day	Follicular cell hypertrophy in thyroid, decreased T4 levels	ACC (2002)	High

1.3 Mechanistic / *In Vitro* Data Identified from OPPT Literature Search

Table 3. Summary of New Mechanistic / *In Vitro* Data for HBCD

Target Organ/ System	Study Type	Species/ Strain/Cell type (Number/ Group)	Exposure Route	Doses/ Concentrations	Duration	Effect Dose/ Concentration/ Result	Effect Measured	Reference	Data Quality Evaluation
Immune	Short-term	Human peripheral blood mononuclear cells (PBMCs), monocyte-depleted peripheral blood mononuclear cells (MD-PBMCs), and natural killer (NK) cells (4-6 donors, n ≥ 4 replicates)	*In vitro*	0, 0.05, 0.1, 0.25, 0.5, 1, 2.5, 5 µM	24 h, 48 h and 6 days	No effect up to 5 µM	Cell viability with or without inhibitors of NFκB (BAY11-7085), MEK ½ (PD98059), p38 (SB202190), and JNK (JNK B178D3)	(Almughamsi and Whalen, 2016) (Data not shown in report, but provided in a supplementary document available at https://link.springer.com/article/10.1007%2Fs00204-015-1586-6)	High
Immune	Short-term	Human PBMCs, MD-PBMCs and NK cells (4-6 donors, 3 replicates)	*In vitro*	0, 0.05, 0.1, 0.25, 0.5, 1, 2.5, 5 µM	24 h, 48 h and 6 days	LOEC PBMCs and MD-PBMCs: 0.05 µM LOEC NK cells: 0.1 µM (results varied among donors; LOEC based on a significant effect occurring in at least one donor at all durations)	Increased IFN-γ secretion	(Almughamsi and Whalen, 2016)	High
Immune	Short-term	Human MD-PBMCs (4 donors, 3 replicates)	*In vitro*	0, 0.5, 1, 2.5 µM	24 h	Inhibitors of NF-κB and MEK ½ diminished the ability of HBCD to increase IFN-γ secretion; inhibitors of p38	Increased IFN-γ secretion: effect of inhibitors of NFκB (BAY11-7085), MEK ½ (PD98059), p38 (SB202190), and JNK (JNK B178D3)	(Almughamsi and Whalen, 2016)	High

Table 3. Summary of New Mechanistic / *In Vitro* Data for HBCD									
Target Organ/ System	**Study Type**	**Species/ Strain/Cell type (Number/ Group)**	**Exposure Route**	**Doses/ Concentrations**	**Duration**	**Effect Dose/ Concentration/ Result**	**Effect Measured**	**Reference**	**Data Quality Evaluation**
						and JNK had no effect			
Immune	Short-term	Human PBMCs, MD-PBMCs and NK cells (3-9 donors, number of replicates was not specified)	*In vitro*	0, 0.05, 0.1, 0.25, 0.5, 1, 2.5, 5 µM	24 h, 48 h and 6 days	LOEC MD-PBMCs: 5 µM (~13% of control cell viability at 6 days); No effect up to 5 µM in PBMCs and NK cells; pathway inhibitors did not affect cell viability	Cell viability with or without inhibitors of Caspase 1 (Caspace 1-inhibitor II), NFκB (BAY11-7085), MEK ½ (PD98059), p38 (SB202190), and JNK (JNK B178D3)	(Almughamsi and Whalen, 2016)	High
Immune	Short-term	Human PBMCs, MD-PBMCs and NK cells (3-9 donors, 3 replicates)	*In vitro*	0, 0.05, 0.1, 0.25, 0.5, 1, 2.5, 5 µM	24 h, 48 h and 6 days	LOEC 0.05 µM for all cell types (results varied among donors; LOEC based on a significant effect occurring in at least one donor at all durations)	Increased IL-1β secretion	(Anisuzzaman and Whalen, 2016)	High
Immune	Short-term	Human MD-PBMCs (4-9 donors, 3 replicates)	*In vitro*	0, 0.5, 1, 2.5 µM	24 h	Inhibitors of MEK ½ and p38 reproducibly diminished the ability of HBCD to increase IL-1β secretion (i.e., across donors); inhibitors of Caspace 1, NFκB and JNK had no	Increased IL-1β secretion: effect of inhibitors of Caspace 1 (Caspace 1-inhibitor II), NFκB (BAY11-7085), MEK ½ (PD98059), p38 (SB202190), and JNK (JNK B178D3)	(Anisuzzaman and Whalen, 2016)	High

Table 3. Summary of New Mechanistic / *In Vitro* Data for HBCD									
Target Organ/ System	**Study Type**	**Species/ Strain/Cell type (Number/ Group)**	**Exposure Route**	**Doses/ Concentrations**	**Duration**	**Effect Dose/ Concentration/ Result**	**Effect Measured**	**Reference**	**Data Quality Evaluation**
						reproducible effect on IL-1β secretion			
Immune	Short-term	Human monocyte-derived dendritic cells (7 volunteers, 3 replicates)	*In vitro*	0, 0.1, 1, 10, 20 µM	24 h	No effect up to 20 µM	Cell viability	(Canbaz et al., 2016)	High
Immune	Short-term	Human monocyte-derived dendritic cells (5 volunteers, 3 replicates)	*In vitro*	0, 0.1, 1, 10, 20 µM	24 h	Increased IL-8 LOEC:10 µM IL-6 and TNFα: no effect up to 20 µM	Cytokine production (IL-6, IL-8, TNFα)	(Canbaz et al., 2016)	High
Immune	Short-term	Human monocyte-derived dendritic cells (7 volunteers, 3 replicates)	*In vitro*	0, 0.1, 1, 10, 20 µM	24 h	Increased CD86 LOEC: 10 µM All other phenotypes: no effect up to 20 µM	Expression of phenotypic cell markers (CD86, CD80, CD83, CD40, HLA-DR, $CD80^+$, $CD83^+$, $CD40^+$)	(Canbaz et al., 2016)	High
Hepatic	Short-term	Human heptatoma HepG2 cells (10 replicates)	*In vitro*	0, 0.05, 0.5, 1, 5, 10 mg/L	24, 48, and 72 h	LOEC: 0.05 mg/L at 24 and 72 h (decreased)	Cell viability	(Wang et al., 2016)	High
Hepatic	Short-term	Human heptatoma HepG2 cells (6 replicates)	*In vitro*	0, 0.05, 1, 10 mg/L	24 h	LOEC: 0.05 mg/L for increased reactive oxygen species (ROS); increased catalase; decreased long-chain acyl-CoA dehydrogenase, lactate dehydrogenase, adenosine-triphosphate (ATP), $Ca2^+$-	ROS; oxidative stress markers (glutathione, malondialdehyde, total protein, superoxide dismutase, catalase); activity of metabolic enzymes (metabolomics analysis)	(Wang et al., 2016)	High

Table 3. Summary of New Mechanistic / *In Vitro* Data for HBCD									
Target Organ/ System	**Study Type**	**Species/ Strain/Cell type (Number/ Group)**	**Exposure Route**	**Doses/ Concentrations**	**Duration**	**Effect Dose/ Concentration/ Result**	**Effect Measured**	**Reference**	**Data Quality Evaluation**
						ATPase, Na^+/K^+-ATPase			
Hepatic	Short-term	Human hepatocytes LO2 (6 replicates, experiments repeated 3 times)	*In vitro*	0, 10^{-13}, 10^{-11} M	48 h	LOEC: 10^{-13} for ROS; no effect up to 10^{-11} M for cell viability and DNA single strand breaks; CYP2B6 induction (tested at 10^{-13} M only)	Cell survival, ROS and DNA single strand breaks (comet assay); expression of metabolic enzymes (CYP1A1, CYP1B1, CYP2B6)	(An et al., 2016)	High
Hepatic	Short-term	Human hepatocytes LO2 (6 replicates, experiments repeated 3 times)	*In vitro*	0, 50 µM	48 h	Decreased cell survival and increased ROS and DNA single strand breaks	Cell survival, ROS and DNA single strand breaks (comet assay)	(An et al., 2016)	High
Hepatic	Short-term	Human hepatocytes LO2 (6 replicates, experiments repeated 3 times)	*In vitro*	0, 50 µM with 48h of pretreatment with 10^{-13}, 10^{-11} M	48 h	Pretreatment with low concentrations of HBCD produced an adaptive response for cell survival, ROS and DNA single-strand breaks	Cell survival, ROS, DNA single-strand breaks (comet assay)	(An et al., 2016)	High
Hepatic	Short-term	Human hepatocytes LO2 (6 replicates, experiments repeated 3 times)	*In vitro*	0, 50 µM with 48h of pretreatment with 10^{-13}, 10^{-11} M followed by a 1-hour treatment with PI3K inhibitors LY294002 (10 µM), wortmannin	48 h	The adaptive response for cell survival, ROS and DNA single-strand breaks was eliminated by pretreatment with inhibitors of PI3K and p38	Cell survival, ROS, DNA single-strand breaks (comet assay)	(An et al., 2016)	High

Table 3. Summary of New Mechanistic / *In Vitro* Data for HBCD									
Target Organ/ System	**Study Type**	**Species/ Strain/Cell type (Number/ Group)**	**Exposure Route**	**Doses/ Concentrations**	**Duration**	**Effect Dose/ Concentration/ Result**	**Effect Measured**	**Reference**	**Data Quality Evaluation**
				(100 µM), MK-2206 (10 µM) or p38 inhibitor SB203580 (10 µM)					
Hepatic	Short-term	Human liver cells LO2 cells (3 replicates, experiments repeated 3 times)	*In vitro*	0, 10^{-7}, 10^{-6}, 10^{-5} M	24 and 48 h	LOEC: 10^{-5} M for β- and γ-HBCD at 48 h No effect up to 10^{-5} M for β- and γ-HBCD at 24 h and α-HBCD at 24 or 48 h	Cell viability	(Huang et al., 2016)	Low
Hepatic	Short-term	Human hepatoma cells HepG2 (3 replicates, experiments repeated 3 times)	*In vitro*	0, 10^{-7}, 10^{-6}, 10^{-5} M	24 and 48 h	LOEC: 10^{-5} M for β- and γ-HBCD at 24 and 48 h and α-HBCD at 48 h No effect up to 10^{-5} M for α-HBCD at 24 h	Cell viability	(Huang et al., 2016)	Low
Hepatic	Short-term	Human liver cells LO2 cells (3 replicates, experiments repeated 3 times)	*In vitro*	0, 10^{-7}, 10^{-6}, 10^{-5} M	24 hours	LOEC β- and γ-HBCD: 10^{-5} M No effect up to 10^{-5} M for α-HBCD	ROS	(Huang et al., 2016)	Low
Hepatic	Short-term	Human hepatoma cells HepG2 (3 replicates, experiments repeated 3 times)	*In vitro*	0, 10^{-7}, 10^{-6}, 10^{-5} M	24 hours	LOEC β- and γ-HBCD: 10^{-6} M LOEC for α-HBCD: 10^{-5} M	ROS	(Huang et al., 2016)	Low
Hepatic	Short-term	Human liver cells LO2 cells (3 replicates, experiments repeated 3 times)	*In vitro*	0, 10^{-7}, 10^{-6}, 10^{-5} M	24 hours	LOEC α- and β-HBCD: 10^{-6} M LOEC γ-HBCD: 10^{-5} M	DNA single-strand breaks (comet assay)	(Huang et al., 2016)	Low

Table 3. Summary of New Mechanistic / *In Vitro* Data for HBCD									
Target Organ/ System	**Study Type**	**Species/ Strain/Cell type (Number/ Group)**	**Exposure Route**	**Doses/ Concentrations**	**Duration**	**Effect Dose/ Concentration/ Result**	**Effect Measured**	**Reference**	**Data Quality Evaluation**
Hepatic	Short-term	Human hepatoma cells HepG2 (3 replicates, experiments repeated 3 times)	*In vitro*	0, 10^{-7}, 10^{-6}, 10^{-5} M	24 hours	LOEC β- and γ-HBCD: 10^{-5} M No effect up to 10^{-5} M for α-HBCD	DNA single-strand breaks (comet assay)	(Huang et al., 2016)	Low
Cancer and Endocrine	Short-term	Human LNCaP prostate cancer cells (3 replicates)	*In vitro*	0, 10^{-8}, 10^{-7}, 10^{-6}, 10^{-5} M	4 days	Increased cell growth at 10^{-8} M only	Cell viability/proliferation	(Kim et al., 2016)	High
Cancer and Endocrine	Short-term	Human LNCaP prostate cancer cells (3 replicates)	*In vitro*	10^{-8} M (co-treated with Casodex, a non-steroidal anit-androgen 10^{-9}M)	6 days	Increased cell growth blocked by anti-androgen	Cell viability/proliferation	(Kim et al., 2016)	High
Cancer and Endocrine	Short-term	Human LNCaP prostate cancer cells (3 replicates)	*In vitro*	10^{-8} M	3 and 5 days	Enhanced cell migration	Cell mobility/migration	(Kim et al., 2016)	High
Cancer and Endocrine	Short-term	Human LNCaP prostate cancer cells (3 replicates)	*In vitro*	10^{-8} M	24 and 48 h	Increased mRNA and protein expression of cyclin D1; increased protein expression of cyclin E; decreased mRNA and protein expression of p27; decreased protein levels of bax	mRNA and protein expression of cell cycle (cyclin D1, cyclin E, p21, p27), apoptosis (BCL-2, bax) and metastasis (cathepsin D) related genes	(Kim et al., 2016)	High
Respiratory	Short-term	Human bronchial epithelial cells (BEAS-2B) (3 replicates)	*In vitro*	0, 0.01, 0.1, 1, 10 µg/mL	24 h	Increased cell number at 0.1 and 1 µg/mL; decreased cell number at 10 µg/mL	Cell viability/ proliferation	(Kim et al., 2016)	High

Table 3. Summary of New Mechanistic / *In Vitro* Data for HBCD									
Target Organ/ System	**Study Type**	**Species/ Strain/Cell type (Number/ Group)**	**Exposure Route**	**Doses/ Concentrations**	**Duration**	**Effect Dose/ Concentration/ Result**	**Effect Measured**	**Reference**	**Data Quality Evaluation**
Respiratory and Immune	Short-term	Human bronchial epithelial cells (BEAS-2B) (3 replicates)	*In vitro*	0, 0.01, 1, 10 µg/mL	24 h	LOEC: 10 µg/mL for increased expression of ICAM-1, IL-6 and IL-8	Expression of proinflammatory proteins (ICAM-1, IL-6 and IL-8)	(Koike et al., 2016)	High
Respiratory and Immune	Short-term	Human bronchial epithelial cells (BEAS-2B) (3 replicates)	*In vitro*	0, 3 µg/mL in the presence of protein kinase inhibitors (10 µM) following 1h pretreatment	24 h	Protein kinase inhibitors eliminated the HBCD increases in IL-6 and IL-8	Change in IL-6 and IL-8 expression by inhibitors of p38 (SB203580), MEK (PD98059) and EGF receptor-selective tyrosine kinase (AG1478)	(Koike et al., 2016)	High
Respiratory and Immune	Acute	Human bronchial epithelial cells (BEAS-2B) (3 replicates)	*In vitro*	0, 1, 3, 10 µg/mL	24 h	LOAEL: 3 µg/mL (increased)	EGF production	(Koike et al., 2016)	High
Respiratory and Immune	Acute	Human bronchial epithelial cells (BEAS-2B) (3 replicates)	*In vitro*	0, 10 µg/mL	15 minutes	Increased	EGF receptor phosphorylation	(Koike et al., 2016)	High
Respiratory	Acute	Human bronchial epithelial cells (BEAS-2B) (3 replicates)	*In vitro*	0, 10 µg/mL	1-24 hours	Increased activation of NFκB and AP-1; no change in STAT	Activation of nuclear transcription factors NFκB, AP-1, and STAT	(Koike et al., 2016)	High

1.4 Epidemiological Study Data

Table 4. Summary of Epidemiological Study Data for HBCD

Target Organ/ System	Outcome/ Endpoint	Study Population	Exposure	Results	Reference	Data Quality Evaluation
Neurological/ Behavior	Reaction time, errors of omission, errors of commission, digit symbol total latency, forward digit span, backward digit span, and finger tapping	High school students (n=515), 13.6-17 years of age from two industrial areas or from the general Flemish population	Serum HBCD (median <level of quantification, range below quantification to 234 ng/L)	HBCD was not significantly associated with any of the neurobehavioral tests.	(Kicinski et al. 2012)	Medium
Neurological/ Behavior	Movement ABC, coordination, fine manipulative abilities, tremors, sensory integration, choreiform dyskinesia, and DCD-Q	5-6 year old boys and girls (n=62) from the Groningen-infant-compare (GIC) cohort (2001-2002)	Maternal serum HBCD at 35 weeks gestation	There was a significant correlation between HBCD and coordination, but there was no significant association with any other motor outcome.	(Roze et al. 2009)	Medium
Reproductive	Testosterone, sex hormone-binding globulin, LH, FSH, E2, and inhibin measured in serum at 3 months of age (only testosterone data was provided for HBCD)	Infant boys (n=55) from the Groningen-infant-compare (GIC) cohort in the Netherlands	Maternal serum HBCD at 35 weeks of gestation	Trend toward significant correlation between HBCD and free testosterone ($p<0.10$), but no significant correlation noted for other hormones.	(Meijer et al. 2012)	Medium
Thyroid	Thyroid-stimulating hormone (TSH) in neonates	Norwegian Human Milk Study, 2003-2006: Multi-center cohort of mothers (n=193 babies with maternal breast milk HBCD samples) recruited from six counties in Norway.	HBCD measured in breast milk; exposure stratified by quintile < 0.13, 0.13–0.52, 0.53–0.79, 0.8–1.24, and 1.29–31.2 ng/g lipid with 62 subject in the lowest quintile and 31-34 subjects in higher quintile	HBCD was not significantly associated with thyroid stimulating hormone (TSH) levels in neonates.	(Eggesbø et al., 2011)	High

Table 4. Summary of Epidemiological Study Data for HBCD						
Target Organ/ System	**Outcome/ Endpoint**	**Study Population**	**Exposure**	**Results**	**Reference**	**Data Quality Evaluation**
Thyroid	Free T3, free T4, TSH	High school students (n=515) age 13.6-17 years of age from two industrial areas (163 from Genk, 178 from Menen) or from the general Flemish population (n=174)	Serum HBCD (median <level of quantification, range below quantification to 234 ng/L)	HBCD was not significantly associated with free T3, free T4, or TSH.	(Kicinski et al. 2012)	Medium
Thyroid	Serum triiodothyronine (T3), free thyroxine (FT4), and thyroid stimulating hormone (TSH)	Mother-infant pairs of infants with hypothyroidism (n=12), Seoul, Korea, Nov 2009-May 2010, 23-37 years	Serum beta-HBCD (mean 0.461 ng/g lipid)	Mother's T3 was negatively associated with beta-HBCD concentration. Non-significant associations with all other thyroid hormone-HBCD diastereomer combinations.	(Kim and Oh 2014)	Medium

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