ATTACHMENT

Comments of the

European Council for Alkylphenols and Derivatives

and the

Alkylphenols & Ethoxylates Research Council

On the REACH Annex XV Report:

Proposal for Identification of a Substance as a CMR Cat. 1A or 1B, PBT or vPvB,

or a Substance of an Equivalent Level of Concern:

4-(1,1,3,3-tetramethylbutyl)phenol

Submitted October 13, 2011

Table A. Aquatic Toxicity Studies with Fish and 17β-Estradiol (E2) and 17α-Ethylylestradiol (EE2) (μg/L)							
Compound (Validity Score)	**Experiment**	**Apical Endpoints**	**Apical Endpoint NOEC (LOEC)**	**Secondary Endpoints**	**Secondary Endpoint NOEC (LOEC)**	**Comments**	**Reference**
Screening or Short Term Reproduction Studies							
E2 (2)	Fathead minnow adults, exposed 19 d	Reproduction (egg production)	EC50 = 0.252	VTG	EC50 = 0.120		Kramer et al. (1998)
E2 (2)	Fathead minnow adults, exposed 14 to 16 d (Exp. 1) or 10 d (Exp. 2), clean water for 16 wk			Exp. 1: HP Exp. 2: HP, SSC	Exp. 1: Males 0.027 (0.136); Females 0.017 (0.027) Exp. 2: (2.724)	In Exp. 2, lesions in male testes occurred but reversed. Changes in SSC also reversed.	Miles-Richardson et al. (1999)
EE2 (2)	Sheepshead minnow sub-adults to adults, exposed 59 d, then breeding trials	Survival, reproductive success, hatching success	Survival: 200(400) Repro: 0.020(0.200) Hatch: 0.020(0.200)	Male fibrosis, male T/O	Male H: 0.0002(0.002) Male T/O: 0.002(0.020)		Zilloux et al. (2001)
EE2 (2)	Zebrafish adults exposed 21 d	Spawning Fertilization	0.005(0.010) (0.005)	GSI (M&F) VTG (M&F)	0.005(0.010) 0.005(0.010)		Van den Belt et al. (2001)
EE2 (1)	Zebrafish exposed 20 to 60 dpf, breeding trials 300 dph, behavior trials 485 dph	F0 sex ratio Egg production Egg viability Female mating behavior	0.00986 0.00986 0.00986 (0.00276)	GHP Male T/O	0.00986 0.00986	Female courting behavior during mating was reduced from the short juvenile exposure	Coe et al. (2010)
Life Cycle Studies							
EE2 (1)	Fathead minnow life-cycle, fertilized eggs to adults, 305 d	F0 hatch F0 E-L survival F0 larval length F0 juv. survival	>0.064 0.016(0.064) 0.004(0.016) 0.016(0.064)	SSC Male T/O F0 GHP F1 GHP	0.001(0.004) 0.001(0.004) 0.001(0.004) 0.001(0.004)	Complete feminization of adult fish exposed from	Lange et al. (2001)

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		F0 juv. length F0 juv. weight F0 Adult survival F0 Adult length F0 Adult weight F0 Sex ratio F0 Eggs/f/d F1 hatch F1 E-L survival F1 larval length F1 larval weight F1 Sex ratio	0.001(0.004) >0.064 >0.001* >0.001* >0.001* >0.001* >0.001* >0.001* >0.001* >0.001* >0.001* (0.0.0002)	VTG	0.004(0.016)	hatch to adult. *0.001 µg/L was highest concentration tested due to lack of males at higher concentrations. Sex ratio in lowest F1 concentrations tested had 69% females.	
EE2 (1)	Zebrafish life cycle, 174 d	F0 E-L survival F0 larval length F0 juv. survival F0 juv. length F0 time to spawn F0 eggs/f/d F0 fertilization F1 E-L survival F1 E-L length F1 juv. survival F1 juv. length F1 time to spawn F1 eggs/f/d F1 fertilization	0.010 0.010 0.0011(0.010) 0.0003(0.0011) 0.0003(0.0011) 0.0003(0.0011) 0.0003(0.0011) 0.002 0.0003(0.002) 0.002 0.0001(0.0003) 0.0003(0.002) 0.0003(0.002) 0.0003(0.002)			96-h LC50 = 1,700 µg/L Ratio of acute LC50 (narcosis) to fertilization NOEC (endocrine modulated) of 0.0003 µg/L = 5.73E+6	Wenzel et al. (2001)
Field Studies							
EE2 (1)	Dosed a natural lake for 3 years	Reproduction of fathead minnow	Complete reproduction			Population collapsed in year	Kidd et al. (2007)

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	to 0.005 μg/L EE2		inhibition			2 due to loss of young.	
EE2 (1)	Dosed a natural lake for 3 years	Reproduction of pearl dace fish	Abundance not different between years, but trending to smaller fish	VTG Edema in ovaries Testes dev. Intersex Kidney lesions	(0.005) (0.005) (0.005) (0.005) (0.005)	Pearl dace have different life history than fathead minnow, so collapse may come if dosing continued.	Palace et al. (2006)

Exp. = experiment, HP = histopathology, GHP = gonadal histopathology, SSC = secondary sex characteristics, GSI, TSI, OSI – gonadal, testes, or ovarian somatic indices, T/O – testis ova, L, W – apical endpoints of growth, length or weight, VTG = vitellogenin, d = days, wk = weeks, E-L = embryo-larval, dpf = days post fertilization, M&F = male and female, eggs/f/d = production of eggs per female per reproductive day,

Table B. Aquatic Toxicity with Fish and Octylphenol (OP) (μg/L)							
Compound and Validity Score	Experiment	Apical Endpoints	Apical Endpoint NOEC (LOEC)	Secondary Endpoints	Secondary Endpoint NOEC (LOEC)	Comments	Reference
Screening or Short Term Reproduction Studies							
OP (2)	Rainbow trout, adult males exposed 21 d, Exp. 1 30 μg/L only, Exp. 2 dose-response			GHP VTG	Exp. 1: GHP, VTG (30) Exp. 2: GHP: No effects at 43.9 VTG 1.6(4.8)	Contradictory results on GHP	Jobling et al. (1996)
OP (2)	Rainbow trout & roach, adult males exposed 21 d			VTG	Trout: 1(10) Roach: 10(100)		Routledge et al. (1998)
OP (2)	Eelpout males exposed 21 d	Survival	No effects at 100	HSI GHP GSI VTG	50(100) (10) (10) (10)	Exposure to an antiestrogen reduced effects	Rasmussen et al. (2005)
OP (2)	Japanese medaka exposed from fertilization to swim-up 17 d	Time to hatch Hatch success	No effects at 1000 250(500)				Gray and Metcalfe (1999c)
OP (1)	Japanese medaka, adult males exposed 21 d, breeding trials	Egg production Fertilization E-L survival	(20) No effects at 230 No effects at 230	Abnormal embryos	(20) (1.5 to 4% incidence)	Fertilization success and E-L survival were not different from controls but significant downward trends were observed	Gronen et al. (1999)
OP (1)	Zebrafish adults exposed 21 d	Survival (F, M) Spawning (F) Fertilization (M)	No effects at 100 No effects at 100 No effects at 100	TSI OSI GHP (F) VTG	No effects at 100 12.5(25) No effects at 100 No effects at 100	VTG apparently not different from controls	Van den Belt et al. (2001)
OP (1)	Sheepshead minnow adult males exposed 24 d, breeding trials	%viable eggs	11.5 (33.6)	VTG GHP	(11.5) 11.5(33.6)	72-LC50 = 720 μg/L. Ratio of acute	Karels et al. (2003)

Table B. Aquatic Toxicity with Fish and Octylphenol (OP) (μg/L)							
Compound and Validity Score	Experiment	Apical Endpoints	Apical Endpoint NOEC (LOEC)	Secondary Endpoints	Secondary Endpoint NOEC (LOEC)	Comments	Reference
	w/ unexposed females					LC50 to %viable eggs NOEC of 11.5 μg/L = 63	
OP (2)	Guppy adults exposed 28 d (M), 26-36 d (F) until birth, 26 μg/L only, offspring held in clean water 70 d	Adult Survival Brood size Brood interval Larval length Larval weight Gonopodium length Gonadal development Sex ratio	No effects at 26 No effects at 26 No effects at 26 No effects at 26 No effects at 26 No effects at 26 No effects at 26 (both sexes) No effects at 26	Male GSI Female GSI GHP SSC Liver histology	No effects at 26 No effects at 26 No effects at 26 (26)	Increased liver vacuoles	Kinnberg et al. (2003)
OP (1)	Guppy males exposed 30 d	Survival Breeding success Gonopodium length	300(900) 300(900) No effects at 900	Sperm count Coloration GSI	(100) (increase) (100) (decrease) (100)		Toft & Baatrup (2001)
OP (3)	Guppy adult males exposed 4 wk					Not valid due to 40% control mortality. Any reported effects could be narcotic-induced. No replication.	Bayley et al. (1999)
OP (2)	Eelpout, pregnant females exposed 35 d	E-L survival E-L length E-L weight	(14) (14) (14)	ER-binding VTG OST HSI GHP	(14) (14) (14) (14) 14(65)		Rasmussen et al. (2002)
OP (1)	Japanese medaka fertilized eggs exposed to 60 dph	Survival Hatch success Length Weight Sex ratio	No effects at 94 No effects at 94 No effects at 94 No effects at 94 23.7(48.1)	VTG (M) VTG (F)	6.94(11.4) 23.7(48.1)	Males began reverting to females in clean water	Seki et al. (2003)
OP (2)	Guppy males exposed 60 d	Survival	300(900)	H	(100)		Kinnberg & Toft (2003)
OP (1)	Guppy embryos	Survival	10(100)	Coloration	100(200)	Sexual behavior	Toft & Baatrup

Table B. Aquatic Toxicity with Fish and Octylphenol (OP) (µg/L)							
Compound and Validity Score	Experiment	Apical Endpoints	Apical Endpoint NOEC (LOEC)	Secondary Endpoints	Secondary Endpoint NOEC (LOEC)	Comments	Reference
	exposed 90 d	Sex ratio Male length Gonopodium length Sexual behavior	No effects at 200 100(200) 10(100) (increase) No effects at 200	Male GSI Female GSI Sperm count	No effects at 200 No effects at 200 10(100) (increase)	highly variable parameter 96-h LC50 = 495 µg/L. Ratio of acute LC50 to gonopodium length NOEC of 10 µg/L = 49.5. Ratio to sex ratio NOEC of 200 = 2.5.	(2003)
OP (3)	Japanese medaka exposed 1 to 180 dph					Not valid. Mortality ≥42% in controls	Gray et al. (1999a)
OP (2)	Japanese medaka Exp. 1: exposed to 100 µg/L 1 to 35 dph until 100 dph Exp. 2: exposed to 100 µg/L 1 dph to 1, 2 or 3 months dph Exp. 3: exposed adult males to 200-300 µg/L	Exp.1: Sex ratio Growth Exp. 2: Sex ratio Growth Exp. 3: Sex ratio Male length Male weight	No effects at 100 (100) No effects at 100 (100) No effects at 300 200(300) 200(300)	Exp.1: T/O Exp. 2: T/O Exp. 3: T/O GHP	No effects at 100 No effects at 100 200(300) (200)	No T/O in males exposed to 100 µg/L E2	Gray et al. (1999b)
Life Cycle Studies							
OP (4)	Japanese medaka fertilized eggs, lifecycle study	Survival Fecundity Fertilization Hatch success Time to hatch F0 growth F1 growth	No effects at 82.3 30.4(82.3) 30.4(82.3) No effects at 82.3 No effects at 82.3 No effects at 82.3 No effects at 82.3	T/O VTG	9.9(30.4) (9.9)	Report not available. Results taken from Annex XV report.	Japan Ministry of Environment (2002)
OP (1)	Zebrafish life	F0 E-L survival	No effects at 35			96-h LC50 = 370	Wenzel et al.

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Compound and Validity Score	Experiment	Apical Endpoints	Apical Endpoint NOEC (LOEC)	Secondary Endpoints	Secondary Endpoint NOEC (LOEC)	Comments	Reference
	cycle, 174 d	F0 larval length F0 juv. survival F0 juv. length F0 time to spawn F0 eggs/f/d F0 fertilization F0 sex ratio F1 E-L survival F1 E-L length	No effects at 35 No effects at 35 12(35) 12(35) 12(35) 12(35) 12(35) No effects at 35 No effects at 35			µg/L Ratio of acute LC50 (narcosis) to fertilization NOEC (endocrine modulated) of 12 µg/L = 31	(2001)
OP (3)	Japanese medaka fertilized eggs to maturity, breeding trials					Not valid. Statistical analysis results not given for many key endpoints including mortality, sex ratio, fertilization rate, and reproductive success.	Knorr and Braunbeck (2002)

Exp. = experiment, HP = histopathology, GHP = gonadal histopathology, SSC = secondary sex characteristics, GSI, TSI, OSI – gonadal, testes, or ovarian somatic indices, T/O – testis ova, L, W – apical endpoints of growth, length or weight, VTG = vitellogenin, d = days, wk = weeks, E-L = embryo-larval, dpf = days post fertilization, M&F = male and female, eggs/f/d = production of eggs per female per reproductive day, WWTP = wastewater treatment plant, ER-binding = estrogen receptor binding,

Table C. Aquatic Toxicity Studies with Amphibians and Invertebrates Exposed to Octylphenol (OP) (μg/L)					
Compound and Validity Score	**Experiment**	**Endpoints**	**NOEC (LOEC)**	**Validity Score / Comments**	**Reference**
Amphibians					
African clawed frog Xenopus laevis	Exposed 2 to 3 dph larvae for 12 wk			(3) Not valid Temperature varied, not well controlled, no analytical, improper statistics	Kloas et al. (1999)
African clawed frog Xenopus laevis	Embryos exposed up to stage of hind limb development (10.5 to 37), 2 to 2000 μg/L OP	Body length Developmental abnormalities	20(100) 100(1000)	(2) Use with care Lack of statistics for mortality data, nominal concentrations only	Bevan et al. (2003)
African clawed frog Xenopus laevis	Males dosed using intraperitoneal injection			(3) Not valid Dosing method not relevant to aquatic hazard assessment	Van Wyk et al. (2003)
Northern leopard frog Rana pipiens	Newly hatched tadpoles (stage 21) exposed for 10 days, 0.2 and 200 μg/L OP	Body weight Development Hind limb emergence	No effects at 200 No effects at 200 No effects at 200 7-d LC50 = 577	(2) Use with care Only two widely separated concentrations tested, nominal concentrations only	Crump et al. (2002)
Northern leopard frog Rana pipiens	Tadpoles (stage 25) exposed for 8 months, 0.002 and 2.0 μg/L (0.01 and 10 nM)	Body weight Development	Transient increase in body weight and development at stage 29, but not stage 34. No effects at 2 μg/L (stage 34, latest stage examined). No linkage possible of a thyroid receptor activation to body weight or development	(2) Use with care Attempted testing at 0.01 nM or 0.002 μg/L, no confirmation of test concentrations	Croteau et al. (2009)
Northern leopard frog Rana pipiens Wood frog Rana sylvatica	Tadpoles exposed from stage 26 to 36 (hind limb development), 50 to 2000 μg/L	Survival Body weight	Stage 26: LC50 = 293 Stage 36: LC50 = 578 Stage 26: LC50 = 153 Body weight data not	(2) Use with care Nominal concentrations only, overcrowding potentially causing stress related effects noted	Hogan et al. (2006)

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Compound and Validity Score	**Experiment**	**Endpoints**	**NOEC (LOEC)**	**Validity Score / Comments**	**Reference**
			usable due to very high density of developing frogs leading to high stress conditions, known to affect growth.		
North American bullfrog Rana catesbeiana	Tadpoles at stages 32-36 exposed for 24 h, 0.2 to 20 μg/L	Sex differentiation Sex ratio	Transient earlier sex differentiation at stages 32 to 34 (all treatments) that disappeared by stage 35 No effects on sex ratio (all treatments)	(2) Use with care Nominal concentrations only	Mayer et al. (2003)
Streamside salamander Ambystoma barbouri	Eggs/larvae exposed for 37 days, 5 to 500 μg/L OP	Time to hatch Survival Growth	50(500) 50(500) 50(500)	(2) Use with care Nominal concentrations only	Rohr et al. (2003)
Invertebrates					
Water flea Daphnia magna	First instar neonates exposed for 5 days, 10 to 40 μg/L OP	Molting	No effects at 40 μg/L 48-h LC50 = 90 μg/L	(2) Use with care Nominal concentrations only	Zou and Fingerman (1997)
Water flea Daphnia magna	Life-cycle, 21-d OECD Guideline 202 study	Reproduction Survival	30(100) μg/L	(1) Guideline study, GLP	Huels AG (1992)
Copepod Acartia tonsa	Eggs, larval development, exposed 5-d	Nauplii development	EC50 = 13 μg/L EC10 = 5.2 μg/L 48-h LC50 = 420 μg/L	(4) Insufficient information Concentration series unknown, control performance unknown. Positive control E2 had no effects on survival (48-h) at 1000 μg/L and development 5-d EC50 = 720 μg/L.	Andersen et al. (2001)
Copepod Tigeropsis japonicus	Nauplii to adult, 2 generation test, 0.01 to 10 μg/L OP	Nauplii stage Maturation stage Fecundity Sex ratio Survival	Development delays at 0.1 μg/L and higher No effects on mature copepods at 10 μg/L (fecundity, sex ratio, or	(2) Use with care Nominal concentrations only	Marcial et al. (2003)

Table C. Aquatic Toxicity Studies with Amphibians and Invertebrates Exposed to Octylphenol (OP) (μg/L)					
Compound and Validity Score	**Experiment**	**Endpoints**	**NOEC (LOEC)**	**Validity Score / Comments**	**Reference**
			survival)		
Sea urchin Arbacia lixula	72-h exposure of OP to sperm and eggs, 5 to 160 μg/L OP			(4) Insufficient information Apparent solvent effects observed for all endpoints. No statistical analysis provided to evaluate solvent effects	Arslan et al. (2007)
Sea urchin Paracentrotus lividus	72-h exposure of OP to sperm and eggs, 5 to 160 μg/L OP	Developmental effects Embryotoxicity	10(20) 72-h EC50 ~20 μg/L (estimated from data plot, no statistics)	(2) Use with care Nominal concentrations only	Arslan and Parlak (2007)
Sea urchin Strongylocentrotus purpuratuns	96-h exposure of OP to eggs, 0.0001 to 5 μg/L	Developmental effects	OP: EC50 = 0.174 μg/L E2: EC50 = 14.2 μg/L EE2: EC50 = 30.3 μg/L	(2) Use with care Unusual results, OP much lower effect concentrations than E2 or EE2 for several developmental effects, nominal concentrations only	Roepke et al. (2005)
Giant ramshorn snail Marisa cornuarietis Dogwhelk Nucella lapillus	Reproduction studies			(3) Not valid These experiments had no replication, no analytical confirmation of test concentrations, had varying density of organisms in the tanks, and employed incorrect statistics.	Oehlmann et al. (2000)
New Zealand mud snail Potamopyrgus antipodarum	Adult exposure for 9 wk	Growth, mortality, embryo production		(3) Not valid Numerous experimental challenges render the study not valid. A partial listing of the flaws are identified in the Annex XV dossier.	Jobling et al. (2003)
New Zealand mud snail Potamopyrgus antipodarum		Embryo production, unshelled embryos		(3) Not valid Numerous experimental challenges render the	Duft et al. (2003)

Table C. Aquatic Toxicity Studies with Amphibians and Invertebrates Exposed to Octylphenol (OP) (µg/L)					
Compound and Validity Score	**Experiment**	**Endpoints**	**NOEC (LOEC)**	**Validity Score / Comments**	**Reference**
				study not valid. A partial listing of the flaws are identified in the Annex XV dossier.	

d = days, wk = weeks, dph = days post-hatch

References for Tables A, B and C

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