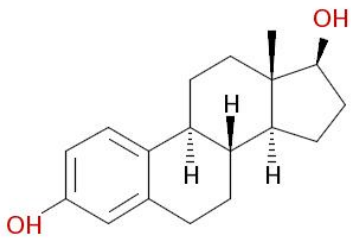
BETA-ESTRADIOL

This EQS dossier was prepared by the Sub-Group on Review of the Priority Substances List (under Working Group E of the Common Implementation Strategy for the Water Framework Directive).

The dossier was reviewed by the Scientific Committee on Health and Environmental Risks (SCHER), whose comments have been addressed as follows.

A footnote has been added regarding the NOEC for Danio rerio. The non-inclusion of amphibian data in the SSD, and the assessment factor used to derive the AA-QS, have been explained. The use of the equilibrium partitioning approach to extrapolate from the AA-$QS_{freshwater, eco}$ to the sediment EQS has been better justified The additional assessment factor applied to calculate the AA-$QS_{marine\ water,,eco}$ has been reduced from 10 to 5. In the assessment of secondary poisoning, clarification has been added that the BCF data should be used in preference to the log K_{ow} data, and additional mammalian toxicity studies referred to by the SCHER have been taken into account, leading to slight revision of the $QS_{biota,secpois}$.

1 CHEMICAL IDENTITY

Common name	17β-estradiol (E2)
Chemical name (IUPAC)	(17β)-Estra-1,3,5(10)-triene-3,17-diol
Synonym(s)	-
Chemical class (when available/relevant)	Hormone
CAS number	50-28-2
EU number	200-023-8
Molecular formula	$C_{18}H_{24}O_2$
Molecular structure	
Molecular weight ($g.mol^{-1}$)	272.4

2 EXISTING EVALUATIONS AND REGULATORY INFORMATION

Annex III EQS Dir. (2008/105/EC)	Not Included
Existing Substances Reg. (793/93/EC)	Not applicable
Pesticides(91/414/EEC)	Not relevant
Biocides (98/8/EC)	Not relevant
PBT substances	Not investigated
Substances of Very High Concern (1907/2006/EC)	No

POPs (Stockholm convention)	No
Other relevant chemical regulation (veterinary products, medicament, ...)	Directive 2004/27/EC (European Directive for approval of medicinal products)
Endocrine disrupter	Yes. The endocrine disrupting properties of estradiol are the key mechanism of action of the substance.

3 PROPOSED QUALITY STANDARDS (QS)

ENVIRONMENTAL QUALITY STANDARD (EQS)

$QS_{water,eco}$ is the "critical QS" for derivation of an Environmental Quality Standard

	Value	Comments
Proposed AA-EQS for [freshwater] [µg.l^{-1}] **Proposed AA-EQS for [marine water] [µg.l^{-1}]**	**0.0004 (0.4ng/l)** **0.00008 (0.08ng/l)**	**Critical QS is $QS_{water,eco}$.** **See section 7.3**
Proposed MAC-EQS for [freshwater] [µg.L^{-1}] **Proposed MAC-EQS for [marine water] [µg.L^{-1}]**	**Not derived**	**See section 7.2**

SPECIFIC QUALITY STANDARD (QS)

Protection objective*	Unit	Value	Comments
Pelagic community (freshwater)	[µg.l^{-1}]	0.0004 (0.4ng/l)	See section 7.3
Pelagic community (marine water)	[µg.l^{-1}]	0.00008 (0.08ng/l)	
Benthic community (freshwater)	[µg.kg^{-1} $_{dw}$]	0.33 0.128µg/kg (ww)	Derived by EqP, see section 7.4
	[µg.l^{-1}]		
Benthic community (marine)	[µg.kg^{-1} $_{dw}$]		
	[µg.l^{-1}]	-	
Predators (secondary poisoning)	[µg.kg^{-1} $_{biota\ ww}$]	0.67	See section 7.5
	[µg.l^{-1}]	Not able to back calculate due to uncertainties around BCF data	
Human health via consumption of fishery products	[µg.kg^{-1} $_{biota\ ww}$]	3.04	See section 7.6
	[µg.l^{-1}]	Not able to back calculate due to uncertainties around BCF data	
Human health via consumption of water	[µg.l^{-1}]		

* Please note that as recommended in the Technical Guidance for deriving EQS (EU 2011), "EQSs […] are not reported for 'transitional and marine waters', but either for freshwater or marine waters". If justified by substance properties or data available, QS for the different protection objectives are given independently for transitional waters or coastal and territorial waters.

4 MAJOR USES AND ENVIRONMENTAL EMISSIONS

4.1 USES AND QUANTITIES

Humans and livestock produce estrogens (such as estrone (E1), estradiol (E2) and estriol (E3)) naturally and these, along with the synthetic steroid ethinylestradiol (EE2), are the only important sources of estrogens in the environment. 17ß-Estradiol is the most active of the naturally occurring estrogenic hormones and is also a key intermediate in industrial synthesis of other estrogens and of various hormonal 19-norsteroids (Matthiessen *et al* 2007). Estradiol (in form of esters, e.g. estradiol valerate) is also a common agent in hormone replacement therapies. The marketed amount of estradiol in pharmaceutical products was 2 238 kg in Europe in 2009 (Source: IMS MIDAS, Database: ESTRO, Q4/2009). Very little change occurred during the previous 3 years, so this figure is assumed to be representative for Europe.

4.2 ESTIMATED ENVIRONMENTAL EMISSIONS

The amounts of natural estrogens including estradiol (whether in a free or conjugated form), excreted in the urine or faeces from any individual will depend on a number of factors such as sex, race, hormonal status (e.g. pre- *vs*. post-menopausal), smoking, stage of menstruation, use of oral contraceptives and pregnancy. There are characteristic changes in the concentration of estrogens in urine during the menstrual cycle and pregnancy. In terms of inputs to sewage treatment works, pregnant women excrete by far the largest amount of natural estrogens, followed by pre-menopausal women, oral contraceptive users, men and post-menopausal women, with children excreting the least (Orme *et al.*, 1983 *in* Young *et al.*, 2004). However, some evidence has shown that livestock (especially cows and pigs) can also provide inputs to freshwaters (Archand-Hoy *et al.*, 1998; Blok and Wösten, 2000; Shore *et al.*, 1993) which may be significant (Knight, 1980; Turan, 1995, Matthiessen *et al* 2007).

The amount of estradiol released following use is relatively low in comparison to the natural excretion of estradiol and its metabolites. In Denmark, the excretion of estradiol due to therapeutic use was estimated to represent 5% of the natural excretion from humans (Christensen, 1998). This is a realistic assumption, if the average natural excretion is assumed to be 3.2 $kg.d^{-1}$ or 1 168 $kg.y^{-1}$ as for Holland (18 millions inhabitants) Blok and Wosten, 2000), which can be extrapolated to 35 000 $kg.y^{-1}$ for whole Europe. This estimate gives a figure of approx. 6% of estradiol prescribed in relation to the natural human excretion.

In a model calculation for drinking water in the US, Caldwell *et al.(*2010) estimated that 6-10% of the modelled drinking water concentrations originated from prescribed estradiol in comparison to the endogenous estradiol introduced.

Input of natural estrogens from humans and livestock were estimated in The Netherlands (Blok and Wösten, 2000). They concluded that the daily excretion of estradiol and its metabolites by humans is 3.2 $kg.d^{-1,}$ while livestock excretes amounts of 46 $kg.d^{-1}$. Estradiol from humans ends up almost entirely in the sewage effluent system and from here can be discharged to surface waters in sewage effluent or spread to land if present in sewage sludge. Estradiol excreted from livestock can reach surface waters but is also spread to land through the application of manure to farmland. The average surface water concentration from natural estradiol and its metabolites excreted by humans were calculated around 2.5 $ng.l^{-1}$, assuming substantial degradation in sewage treatment plants, while the input from manure by run-off can lead to concentrations in ditches and major rivers of 40-150 $ng.l^{-1}$ and 2 $ng.l^{-1}$, respectively, the latter after degradation (Blok and Wösten, 2000). Although the situation in The Netherlands may be different from other European countries due to the high density of cattle in Holland, it can be assumed that generally the main contributor to natural estrogen levels in surface waters are humans and cattle, with slightly higher concentrations originating from natural human excreta. In comparison, the role of excreted estradiol originating from pharmaceutical treatment is only marginal and may contribute to much less than 10 % to the total load of estradiol in surface waters.

Estradiol is metabolized during human metabolism into the major transformation products estrone, estriol, estrone sulfate and estrone glucoronide (Hobkirk *et al.*, 1975; Lievertz, 1987; Slaunwhite *et al.*, 1973). The major site of metabolism for natural oestrogens is the liver, with the two major metabolic pathways being 2-hydroxylation and 16α-hydroxylation. These pathways result in a number of metabolites, conjugated with

glucuronide and/or sulphate, which are considered to be biologically inactive and largely excreted in the urine. The main urinary metabolites are conjugates of estriol, 2-hydroxyoestrone, estrone, 16α-hydroxyestrone and estradiol, in decreasing order of quantitative importance (Aldercreutz *et al.*, 1994 *in* Johnson and Harvey, 2002; IARC, 1979).

The residues of estradiol and its metabolites in raw sewage can be reduced substantially by municipal sewage treatment plants. The median inflow concentration of estradiol in treatment plants in Germany was reported to be 1-2 ng.l^{-1}, while after treatment the median was 0.2 - 0.7 ng.l^{-1} (Adler *et al.*, 2001). In Germany (Wiesbaden), it was calculated that more than 80% of the raw effluent load of estradiol is eliminated in the sewage treatment plant (Andersen *et al.*, 2003). Similar results were reported in other studies (Ternes *et al.*, 1999; Johnson *et al.*, 2000). Consequently, trace concentrations of estradiol can reach the environment from sewage effluents. The median concentrations of estradiol in effluents from Dutch waste water treatment plants as measured by Belfroid *et al.*, 1999 was 0.9 ng.l^{-1}, which is comparable to the findings in Germany (e.g. Adler *et al.*, 2001) according to Williams *et al. (*2003), following its emergence from treatment plants, estradiol is further degraded in the surface waters of English rivers. These measured levels are substantially lower than the concentrations estimated for Dutch rivers (Blok and Wösten, 2000).

5 ENVIRONMENTAL BEHAVIOUR

5.1 ENVIRONMENTAL DISTRIBUTION

		Master reference
Water solubility (mg.l^{-1})	3.6	Yalkowsky and Dannenfelser, 1992 in HSDB, 2010
	1.7 *(GLP study)*	Schering AG, 2000
Volatilisation	**According to vapour pressure and Henry constant values, the substance is not likely to volatilise from water phase.**	
Vapour pressure (Pa)	2.6 10^{-7} – 4.5 10^{-3} at 25°C (*calculated*)	US-EPA, 2008
	3 x 10^{-8} Pa, 25ºC (*GLP study)*	Schering AG, 1999
Henry's Law constant (Pa.m^3.mol^{-1})	1.4 10^{-6} – 3.6 10^{-5} (*calculated*)	US-EPA, 2008
Adsorption	**The range - is used for derivation of quality standards.**	
Organic carbon – water partition coefficient (K_{OC})	K_{OC} = 791.7 (*calculated from K_{OW}*) log Koc = 2.9 (*calculated from K_{OW}*)	US-EPA, 2008
	log Koc = 3.4 *(GLP study)*	Bayer Schering Pharma AG, 2007
Sediment – water partition coefficient($K_{susp\text{-}water}$)		*Calculated from K_{OC}*
Bioaccumulation	**The BCF value - on fish is used for derivation of quality standards.**	
Octanol-water partition coefficient (Log Kow)	4.01 (measured)	Hansch *et al.*, 1995
	4.03 *(GLP study)*	Schering AG, 2000
BCF (measured)	$BCF_{summer\ flounder}$ = 6.5	Specker and Chandler (2003)

5.2 ABIOTIC AND BIOTIC DEGRADATIONS

		Master reference
Hydrolysis	DT_{50} > 1 year, 25ºC *(GLP study)*	Schering AG, 2001
Photolysis	DT_{50}= 1 h	RIKZ (2001)
	Maximum at 279 nm (pH 1-9), no adsorption above 300 nm (pH 7) and 310 nm (pH 9)	Schering AG, 2001
Biodegradation	No data are available on the persistence of 17β-estradiol in soil. 17β-estradiol does not strongly adsorb to soil. Complete degradation with activated sludge in 14 – 28 days.	Tabak et al (1981)
	Not readily biodegradable Degradation >60% in OECD screening test (OECD301B), however, not in 10-day window *(GLP study)*	Schering AG, 1997

6 AQUATIC ENVIRONMENTAL CONCENTRATIONS

6.1 ESTIMATED CONCENTRATIONS

Compartment	**Predicted environmental concentration (PEC)**	**Master reference**
Freshwater	No data available	Daginnus *et al.*, 2009[(1)]
	$4.5\ 10^{-3}$ [(2)]	Blok and Wösten, 2000
Marine waters (coastal and/or transitional)	No data available	Daginnus *et al.*, 2009[(1)]
Sediment	No data available	Daginnus *et al.*, 2009[(1)]
Biota (freshwater)	No data available	Daginnus *et al.*, 2009[(1)]
Biota (marine)	No data available	Daginnus *et al.*, 2009[(1)]
Biota (marine predators)	No data available	Daginnus *et al.*, 2009[(1)]

[(1)] *Data originating from EU modelling-based prioritisation.*

[(2)] *Data from The Netherlands, corresponding to sum of human and domestic animals excreta*

6.2 MEASURED CONCENTRATIONS

Compartment	Measured environmental concentration (MEC)			Master reference
Freshwater (µg.l^{-1})	<nd – 0.025			Johnson and Harvey, 2002
	DE	15 rivers	nd LD= 5 10^{-4}	Ternes *et al.*, 1999
		10 rivers	nd	Stumpff et al. (1996)
		40 sampl.	nd	Wegener et al. (2001)
	NL	11 loc.	nd – 5.5 10^{-3} (median nd) LD= 5 10^{-4}	Belfroid et al. (1999)
	UK	5 sites	nd – 0.025 LD= 3 10^{-4}	Fawell, et al., 2001
		R. Nene R. Lea	nd – 8.8 10^{-3} LD= 4 10^{-4}	Kanda et al., 2001
	USA		9 10^{-3} LD = 5 10^{-3}	Kolpin *et al.*, 2002
	China		nd – 7.5 10^{-3} LOD = 3 10^{-4} LOQ = 0.001	Zhao *et al.*, 2009
	LU	R. Alzette	0.001 – 0.035 LOD = 0.001 LOQ = 0.003	Pailler *et al.*, 2009
		R. Mess	0.001 – 0.006 LOD = 0.001 LOQ = 0.003	
	South Korea		nd LOD = 0.001	Kim *et al.*, 2007
	Japan		6 10^{-4} – 0.001 LOD = 3 10^{-4}	Isobe *et al.*, 2003
	Germany (Berlin)		nd LOQ = 2 10^{-4}	Zuehlke *et al.*, 2005
	China		0.1 LOD = 9 10^{-3}	Yang *et al.*, 2006
	Italy		0.002 – 0.006 LOD = 2 10^{-4}	Laganà *et al.*, 2004
Marine waters (coastal and/or transitional)	cf.table below			James *et al.*, 2009[(1)]

Compartment		Measured environmental concentration (MEC)			Master reference
WWTP effluent (µg.l^{-1})		nd – 0.021			Johnson and Harvey, 2002
		DE	16 STP	nd – 0.003	Ternes *et al.*, 1999
			20STP	nd – 0.021	Stumpff et al. (1996)
			3 STP	nd – 0.0052 LD= 1.5 10^{-4}	Kuch and Ballschmitter, 2001
		IT	6 STP	0.35 – 3.5 10^{-3}	Baronti, 2000
			5 STP	nd – 0.007 LD= 5 10^{-4}	Johnson *et al.*, 2000
		NL	5 STP	nd – 0.012 (mean = 9 10^{-4})	Belfroid et al., 1999
			3 STP	0.6 – 12 10^{-3}	Johnson *et al.*, 2000
		SE	1 STP	0.001	Larsson, 1999
		UK	7 STP	2.7 – 48 10^{-3}	Desbrow et al., 1998
			3 STP	nd – 0.0043	Kanda et al., 2001
			2 STP	nd – 9 10^{-4}	Niven et al., 2001
		Japan		4.9 10^{-4} – 0.012 LOQ = 1 10^{-4}	Nakada *et al.*, 2006
		LU		0.001 – 0.085 LOD = 0.001 LOQ = 0.003	Pailler *et al.*, 2009
		S. Korea		nd LOD = 0.001	Kim *et al.*, 2007
		Japan		3 10^{-4} – 2.5 10^{-3} LOD = 3 10^{-4}	Isobe *et al.*, 2003
		Taiwan Hospital effluent		0.025 (median) 0.23 (max) LD = 0.025	Lin and Tsai, 2009
		Germany		8 10^{-4} LOQ = 4 10^{-4}	Zuehlke *et al.*, 2005
		Italy		0.003 – 0.008 LOD = 8 10^{-4}	Laganà *et al.*, 2004
Sediment (µg.kg$^{-1}_{dw}$)	Sed 2 mm	No data (*0*)			James *et al.*, 2009[(1)]
	Sed 20 µm	No data (*0*)			
	Sed 63µm	No data (*0*)			
	-	UK	10 sites	< 0.1	Kanda et al., 2001
Biota	Invertebrates (µg.kg$^{-1}_{ww}$)	No data (*0*)			James *et al.*, 2009[(1)]
	Fish (µg.kg$^{-1}_{ww}$)	No data (*0*)			
	Marine predators	No data available			

(1) Data originating from EU monitoring data collection

▶ 17 alpha/beta oestradiol - Fraction Whole water for organic substances

♦ Summary statistics on the fraction

Analyses	6
Stations	4
Member States (MSs)	1
River Basin Districts (RBDs)	3
PNEC	-
PEC 1	1.09e-3 ug/l
PEC 2	1.09e-3 ug/l
Analyses <= DLs (used in PEC2 calculation)	0
% analysis <=DLs for which DLs>2PNEC	0 %
Minimum of the average by station	3.00e-4 ug/l
Maximum of the average by station	1.09e-3 ug/l
Minimum of analyses	3.00e-4 ug/l
Maximum of analyses	1.09e-3 ug/l

7 EFFECTS AND QUALITY STANDARDS

Some of the key acute and chronic toxicity studies for E2 are outlined in the tables below. In considering the toxicity data for E2 both the reliability and the ecological relevance of the endpoints have had to be taken into account. Vitellogenin production endpoints, for example, have not been considered as key data for the derivation of QSs for E2, as the ecological significance of these effects is uncertain. The focus was on endpoints with the potential to effect population sustainability, eg reproductive output, hatching, fertilisation success.

7.1 ACUTE AND CHRONIC AQUATIC ECOTOXICITY

ACUTE EFFECTS			Klimisch code according to	Master reference
Algae & aquatic plants (mg.l^{-1})	**Freshwater**	*Desmodesmus subspicatus* / 72h E_rC_{50} > 3.1 (*GLP study*)	1	Schering AG, (2002)
	Marine	*No data available*		
Invertebrates (mg.l^{-1})	**Freshwater**	*No data available*		
		No data available		
	Marine	*Acartia tonsa* / 96h EC_{50} > 1	2	Andersen *et al.*, (2001)
	Sediment	*No data available*		
Fish (mg.l^{-1})	**Freshwater**	*Oncorhynchus mykiss* / 96h LC_{50} > 0.5 *(GLP study)*	1	Schering AG, (1995)
		Japanese medaka/72hr LC50 0.46mg/l		Kashiwada et al (2002)
	Marine	*No data available*		
	Sediment	*No data available*		
Other taxonomic groups		*No data available*		

(1) The study was of good quality but the data can only be used as supporting information since only one concentration was tested.

CHRONIC EFFECTS Studies highlighted in red were used in the SSD derived in Section 7.3.			**Klimisch code according to**	**Master reference**
Algae & aquatic plants ($mg.l^{-1}$)	**Freshwater**	*Desmodesmus subspicatus* / 72h $NOEC_{growth\ rate}$ > 3.1 *(GLP study)*	1	Schering AG, (2002)
		Pseudokirchneriella subcapitata/ 72hr NOEC (growth) >0.523mg/l		Winther-Nielsen (2002)
	Marine	*No data available*		
Invertebrates ($mg.l^{-1}$)	**Freshwater**	*Ceriodaphnia dubia* / 7d $NOEC_{reduced\ juvenile\ production}$ = 10	2	Tatarazako *et al.*, (2002)
		Brachionus calyciflorus/ 4d NOEC (reduced fertilisation) >0.01	3	Preston et al (2000)
	Marine	*Balanus amphrite* / cypris larvae / 2d $NOEC_{larval\ settlement}$ = 1 10^{-4}	2	Billinghurst *et al.* (1998)
		Nitocra spinipes / <24h old / 18d $NOEC_{reproduction}$ ≥ 0.16	2	Breitholtz and Bengtsson, (2001)
		Tisbe battagliai / <24h old / 21d $NOEC_{reproduction}$ ≥ 0.1	2	Hutchinson *et al.* (1999)
		Acartia tonsa/21d NOEC (reproduction) >0.368		Bjomstad (2002)
	Sediment	*No data available*		
Fish ($mg.l^{-1}$)	**Freshwater**	*Danio rerio* / 200d $NOEC_{reduced\ egg\ survival}$ ≤ 5 10^{-6} (<5ng/l)	2 *(1)*	Nash *et al.*(2004)
		Danio rerio / 21d $NOEC_{secondary\ sexual\ characteristics}$ = 5 10^{-6} (5ng/l) $NOEC_{sex\ ratio}$ = 2.5 10-5 (25ng/l)	2	Brion *et al.*,(2004)
		Danio rerio/21d (F0) and 42d (F1) NOEC (egg production and fertility hatching) 0.000087mg/l (87ng/l)	2	Van der Ven (2007)
		Oryzias latipes / 86 – 110d $NOEC_{feminisation\ of\ males}$ = 1 10^{-5} (10ng/l)	2	Metcalfe *et al.*, 2001
		Oryzias latipes / 59d NOEC ($_{reduced\ fertility\ of\ F0\ generation}$) 0.0000029mg/l (2.9ng/l)	2	Seki *et al.*, 2005
		Oryzias latipes / 5-8d old larvae / 28d $LOEC_{feminisation\ of\ males}$ ≤1 10^{-5} (<10ng/l)	2	Nimrod and Benson, 1998

		Oryzias latipes / 14d $NOEC_{reduced\ hatching\ success}$ = 2.7 10^{-4} (272ng/l)	2	Shioda and Wakabayashi, 2000
		Oryzias latipes / 21d $NOEC_{reduced\ fertility}$ = 2.27 10^{-4} (227ng/l)	2	Kang *et al.*, 2002
		Oryzias latipes/20day NOEC (reproduction) 3.4 10^{-5} mg/l (34ng/l)	2	Hirai (2006)
		Oryzias latipes/14d NOEC (egg production, fecundity, spawning, fertilization, hatching) 0.000379mg/l (379ng/l)	3	Jukosky (2008)
		Gambusia holbrooki / 84d *NOEC impregnation success 0.000020mg/l (20ng/l)*	2	Doyle and Lim (2005)
		Pimephales promelas / 91d[(2)] $EC_{10\ weight\ increase;\ feminization\ of\ males}$ > 8 10^{-6} *(GLP study) (>8ng/l)*	1	Schering AG, 1995
		Pimephales promelas / 19d $EC_{10\ reduced\ egg\ production}$ = 6.6 10^{-6} (6.6ng/l)	2	Kramer *et al.*, 1998
		Pimephales promelas/ 21d NOEC (reproduction) 0.000044mg/l (44ng/l)	3	Shappell et al (2010)
		Poecilia reticulata/ 90d NOEC (feminisation) 0.0001mg/l (100ng/l)	2	Toft (2003)
		Oryzias javanicus/187d NOEC (fertilisation, egg number) 0.0000095mg/l (9.5ng/l)	2	Imai (2005)
		Gabiocypris rarus/21d NOEC (sex ratio) 0.000005mg/l (5ng/l)	2	Liao (2009)
		Melanotaenia fluviatilis/ 14 NOEC (reproduction) 0.0001mg/l (100ng/l)	2	Polino (2007)
		Gambusia holbrooki/ 84day LOEC (sexual behaviour of males) 0.00002mg/l (20ng/l)	2	Doyle and Lim (2005)
		Onchorhynchus mykiss/35d NOEC 0.0000005mg/l (0.5ng/l)	2	Lahnsteiner et al
	Marine	*Cyprinodon variegatus* / 280d $NOEC_{reproductive\ rate}$ = 1 10^{-5} (10ng/l)	2	Cripe *et al.*, 2009
		Pomatoschistus minutus/ 240d $NOEC_{reproductive\ success}$ 0.000097mg/l (97ng/l)	2	Robinson (2007)
	Sediment	*No data available*		

Other taxonomic groups	**Amphibia**	*Xenopis laevis* / 84d $LOEC_{feminisation\ of\ males}$ = 2.74 10^{-3}	2	Kloas *et al.*, 1999
		Rana pipiens / 162 d $LOEC_{intersex}$ ≤ 1 10^{-3} ≤ 1000 ng/l	2	Mackenzie et al. (2003)

(1) The study by Nash et al (2004) was of good quality but the data can only be used as supporting information since only one concentration was tested.

(2) ***Stakeholder's comment (EFPIA – Bayer):*** *In this study, fertility was impaired at concentrations of 8.7 ng/L and higher. However, the observed fertilization rate at 8.7 ng/L of 80% is within the range typical for controls in these species. Therefore, this finding has no biological significance, because it can be considered to be within historical controls. The next higher concentration, i.e. 27.9 ng/L, showed almost no fertilization. Therefore, we assume that the biological significant NOEC in this study was 8.7 ng/L, the LOEC being 27.9 ng/L. Further chronic studies in fish showed that the NOECs for the most sensitive endpoints (sexual development, fecundity, growth) in fathead minnow and zebrafish were in the same order of magnitude. In the Länge et al. study (unpublished), the EC10 was derived with 8 ng/L. Other taxonomic groups were shown to be much less sensitive than fish.*

7.2 DERIVATION OF THE MAC-$QS_{WATER,ECO}$

Limited acute toxicity data is available for beta-estradiol. Three studies were located for freshwater species – 2 fish species and 1 algal species. In addition data was also available for one marine species, the invertebrate Acartia tonsa. Only four acute studies were therefore available for E2.

The available data set is sufficient to derive a MAC-QS for E2 although the dataset is limited and there is uncertainty about the exact effect concentration for three of the studies as the effect concentrations are reported as 'greater than' values. Based on information on the uses and sources of E2 however, long term, or continuous release into the aquatic environment is more likely than episodic releases. Chronic exposure of aquatic organisms is therefore expected rather than acute exposure. The need for a MAC-QS is therefore questioned. The available toxicity data (see table above) indicates that chronic exposure results in much lower effect concentrations than those arising from acute exposure, with large acute to chronic rations being observed for the more sensitive species. Even if acute exposures were to occur we would not expect environmental concentrations to reach levels at which acute toxicity would occur. In addition due to the specific mode of action of E2 the AA-QS has higher relevance as even short term exposure can have long term effects if exposure occurs during a critical life stage.

Based on the above it is not felt appropriate to derive a MAC-QS for E2.

7.3 DERIVATION OF THE AA-$QS_{WATER,ECO}$

The available chronic toxicity data for 17-beta-estradiol includes studies on algae, crustaceans, rotifer, amphibians and fish. The majority of the data however relates to studies on fish. As with ethinyl estradiol (EE2) the majority of studies on fish have examined a wide range of endpoints and been undertaken over a range of exposure durations.

Limited data are available on saltwater species and it is therefore difficult to assess whether there are significant differences between fresh and saltwater species. There is no reason to expect a difference and therefore it is proposed to pool the fresh and saltwater data.

7.3.1 Freshwater AA-$QS_{freshwater,eco}$

7.3.1.1 Deterministic approach

The deterministic approach involves the application of an assessment factor to the lowest reliable and relevant NOEC/EC10 with the size of the dataset influencing the size of the assessment factor applied.

NOECs are available for algae, invertebrates and fish, which based on the TGD-EQS (EC 2011) enables an assessment factor of 10 to be applied.

The lowest effect concentration is a NOEC of 0.5ng/l reported by Lahnsteiner et al (2006) for the trout (Onchorhynchus mykiss). As the available dataset includes long term studies on algae, invertebrates and fish an assessment factor of 10 could be applied. This would give a QS of 0.05ng/l. However the TGD-EQS (EC 2011) notes that in some cases it is possible to use a lower assessment factor than 10, with the example given being when the species tested can be considered to represent one of the more sensitive groups. Based on the known mode of action of beta-estradiol, fish and amphibians are expected to be sensitive. The available chronic data for fish has supported this. The fact that data is available for a number of fish species and that fish are expected to be among the most sensitive taxa based on the mode of action of E2 (and supported by the available chronic toxicity data) supports a reduction in the assessment factor. Application of an assessment factor of 5 to the NOEC of 0.5ng/l gives a QS of 0.1ng/l.

7.3.1.2 Species Sensitivity Distribution (SSD) approach

Chronic toxicity data for beta estradiol is available for a range of species including algae, crustaceans, rotifers, amphibians and fish.

The TGD-EQS (2011) notes that in order to apply the SSD approach the available dataset should preferably contain more than 15, but at least 10 NOECs/EC10s from different species covering at least 8 taxonomic groups. For estimating an AA-QS freshwater using the SSD approach the following taxa would normally need to be represented, ie

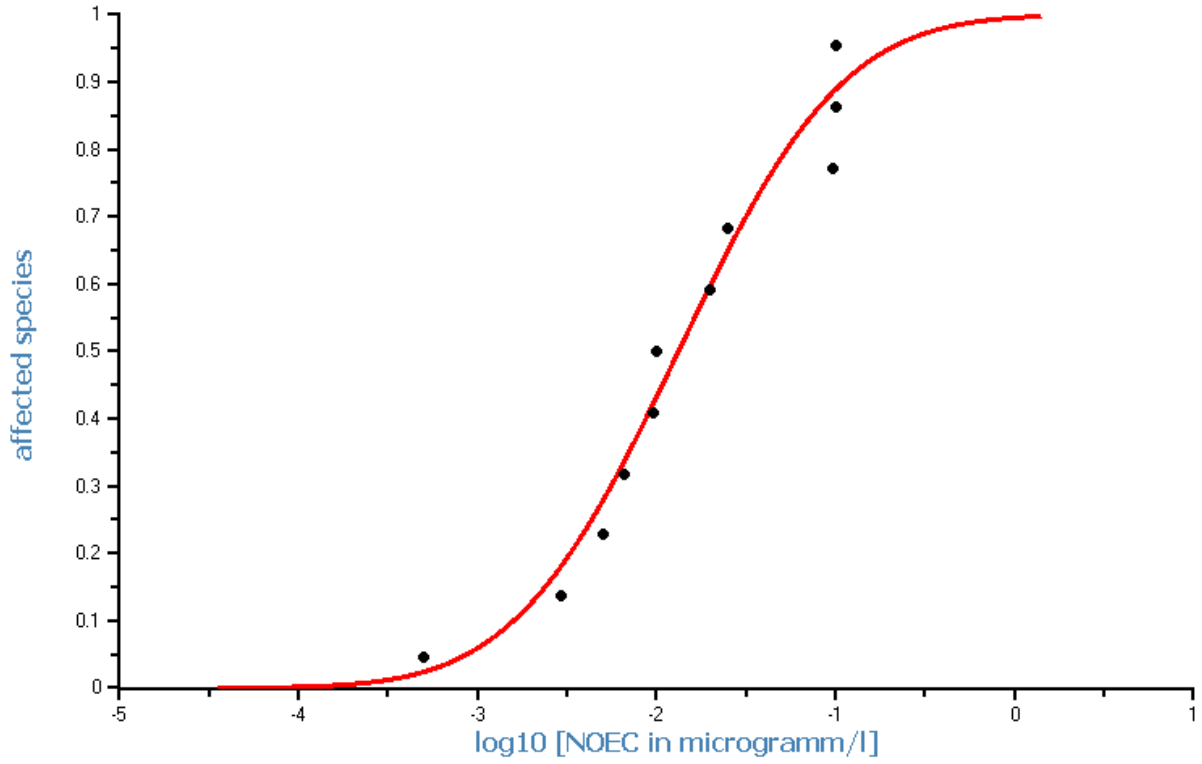
- a fish species
- a second family in the phylum Chordata
- a crustacean
- an insect
- a family in a phylum other than Arthropoda or Chordata
- a family in any order of insect or any phylum not represented
- algae
- a higher plant

The available chronic toxicity dataset for beta-estradiol does not meet the data requirements for using the SSD approach (EC 2011). However beta-estradiol is a naturally occurring hormone and has a specific mode of action with effects on the reproductive physiology of vertebrates. The TGD-EQS (2011) notes that if a chemical is known to have a specific mode of action an SSD can be derived for only those taxa that are expected to be particularly sensitive.

Knowledge of the mode of action of beta estradiol suggests that fish and amphibians are likely to be the most sensitive organisms. This is supported by the available chronic toxicity data which indicates that fish are particularly sensitive to beta-estradiol. Unfortunately limited data is available on the toxicity of E2 to amphibians which makes an assessment of their sensitivity difficult. Two amphibian studies report LOECs and it was not possible to derive NOECs for these studies as significant effects were observed at all the test concentrations. Due to the known mode of action of E2 it is therefore proposed that an SSD is derived for beta-estradiol based on data for the most sensitive taxonomic groups. The same approach was also applied to EE2.

Reliable chronic NOEC values were available for 11 species of fish. An SSD has therefore been derived based on 11 fish species. For several species a number of different studies have been reported. The TGD-EQS (EC 2011) indicates that where a number of data points are available for a species a geometric mean should be calculated to propose a single value for that species. This approach is not appropriate for all the available data for E2 as the studies are often non-standard and consider a range of endpoints and exposure durations and are therefore not directly comparable. In these cases it is proposed that the lowest NOEC value is used for a species rather than calculating a geometric mean using non-comparable NOECs.

The SSD based on the fish data is shown below. The distribution was found to fit a log normal distribution.



The HC5 from the above SSD is 0.0000008mg/l (0.8 ng/l). An assessment factor in the range of 1-5 should be applied to the HC5 based on the guidance given in the TGD-EQS (E.C., 2011). Based on the available dataset and the knowledge of the mode of action of E2 it is considered that an assessment factor of 2 is appropriate for the derivation of the AA-$QS_{freshwater,eco.}$ A lowering of the AF from 5 is warranted due to:-

- The mode of toxic action is well understood. The HC5 has been derived based on data for the most sensitive taxonomic group, ie fish.
- Studies are available for 11 species of fish and have considered a wide range of endpoints over various durations including population relevant endpoints such as hatching, fertilisation, changes in sex ratio.
- In addition where several studies were available for a species the lowest reliable effect concentration has been used adding a further level of conservatism.
- The SSD includes a NOEC from a study by Lahnsteiner et al (2006) which gave a NOEC which was much lower than the other NOECs reported by a factor of 10 fold

However there are still some uncertainties associated with the dataset, eg the limited information on the toxicity of E2 to amphibians. These uncertainties support the application of an AF. Based on the above an AF of 2 has been applied to the HC5 of 0.8ng/l. This gives a QS of 0.4 ng/l.

E2 is structurally similar to the synthetic estrogen EE2 and they share the same mode of action. A QS has also been proposed for EE2, again based on an SSD for the most sensitive taxonomic groups. An understanding of the relative potencies of E2 and EE2 may help underpin the proposed QS for these two substances. A comparison of the relative potencies of these chemicals requires the chemicals to have been studied under the same conditions and exposure durations and therefore ideally within the same study. Studies on the relative potencies have included both in vivo and in vitro studies. Results from in vivo studies using endpoints such as the yeast screening assay indicate small ratios between the potency of E2 and EE2 with relative potencies in the range of 1: 0.7 – 3.2 being reported. In vivo studies would be preferred as they consider potentially more population relevant endpoints and also taken into account bioaccumulation and metabolism. Few studies were located however those obtained indicated relative potencies of greater than 10.

The HC5 value for EE2 is 0.07ng/l and for E2 is 0.8ng/l. This is an order of magnitude different. The proposed QS values are 0.035ng/l and 0.4 ng/l for EE2 and E2 respectively by applying an AF of 2 to the HC5 in each case. The potency data located would lend support to the view that the QS for E2 would be expected to be around an order of magnitude higher than that for EE2.

7.3.2 Saltwater AA-$QS_{saltwater,eco}$

Data were located for saltwater invertebrate and fish species but not for algae. The decision was made to pool the freshwater and saltwater data as was done for the closely related steroid EE2. It is proposed to take the freshwater QS as the basis for the saltwater standard and apply an additional assessment factor of 10 as proposed in the TGD-EQS (EC 2011). The guidance notes that an additional AF of 10 is applied when deriving the AA-QSsaltwater,eco where no data is available for additional marine taxonomic groups. A larger AF is recommended to cover the uncertainty associated with the greater diversity of marine ecosystems and the limited availability of effects data for marine species.

7.3.2.1 Deterministic approach

A $QS_{freshwater,eco}$ of 0.1ng/l has been proposed based on use of the deterministic approach (See Section 7.3.1.1). Application of an additional assessment factor of 10 to this value gives a $QS_{saltwater,\ eco}$ of 0.01ng/l. A lower additional assessment factor than 10 was not able to be applied as no additional marine taxonomic groups were available in the dataset.

7.3.2.2 Species Sensitivity Distribution (SSD) approach

A $QS_{freshwater,eco}$ of 0.4ng/l has been proposed based on use of the SSD approach (See Section 7.3.1.2). As noted above the TGD-EQS (EC 2011) notes that an additional assessment factor of 10 is applied when deriving the AA-$QS_{saltwater}$ where no data is available for additional marine taxonomic groups. A larger AF is recommended to cover the uncertainty associated with the greater diversity of marine ecosystems the limited availability of effects data for marine species. The TGD-EQS notes that additional taxa are those other than algae, crustaceans and fish unless these have a different life form or feeding strategy than the representatives in freshwater. Data for additional taxa are not available for E2 which indicates use of an additional AF of 10. Due to the known mode of action of E2, however the SSD has been derived only on the most sensitive taxonomic group, ie fish. As the SSD has been based on the most sensitive taxonomic groups this would support a lowering of the additional AF from 10. An additional AF is still required, however to take into account the diversity of the marine ecosystem and the fact there may be more sensitive marine species. It is therefore proposed that an additional AF of 5 is applied to the $QS_{freshwater,eco}$ to give an AA-$QS_{saltwater,eco}$ of 0.08ng/l.

7.4 DERIVATION OF THE $QS_{SEDIMENT}$

The criteria for triggering the development of a $QS_{sediment}$ are identified in the TGD-EQS (EC 2011). The criteria include log Koc and log Kow properties, toxicity to benthic organisms and evidence of accumulation of beta-estradiol in sediment.

No toxicity data is available for benthic organisms and sediment data was limited to a study in the UK (Kanda et al) which reported levels below the limit of detection (<0.1µg/kg). However a measured log Koc value of 3.4 is reported for beta-estradiol along with a log Kow of 4.01. These meet the criteria for the development of a $QS_{sediment}$.

The TGE-EQS (EC 2011) notes that the $QS_{sediment}$ can be derived using sediment toxicity tests and either the deterministic or probabilistic approach depending on the size of the dataset, or by using the equilibrium partitioning approach. The latter is applied in those situations where no or very limited sediment toxicity data is available. Due to the lack of sediment toxicity data the Equilibrium Partitioning approach will need to be used to derive the $QS_{sediment}$ for beta estradiol.

The TGD-EQS (2011) proposes the following equations for the derivation of a sediment threshold using the EqP approach. These have been used, along with the default values in the guidance, to derive the $QS_{sediment}$ for beta-estradiol.

$$QS_{\text{sed, EqP, ww}} = \frac{K_{\text{sed-water}}}{RHO_{\text{sed}}} \times QS_{\text{water, eco}} \times 1000$$

$$CONV\text{sed} = \frac{RHO_{\text{sed}}}{F\text{solid}_{\text{sed}} \times RHO\text{solid}}$$

$$QS_{\text{sed, EqP, dw}} = CONV\text{sed} \times QS_{\text{sed, EqP, ww}}$$

$$QS_{\text{sed, EqP, ww}} = \frac{314}{1300} \times 0.00000053 \times 1000$$ $QS_{sed,EqP,ww}$ = 0.000128mg/kg ww

$$CONV\text{sed} = \frac{1300}{0.2 \times 2500}$$ CONVsed = 2.6

$$QS_{\text{sed, EqP, dw}} = 2.6 \times 0.000128$$ $QS_{sed,EqP,dw}$ = 0.00033mg/kg dw

NB. The $K_{sed\text{-}water}$ used to derive the $QS_{sed,EqP,ww}$ was derived using the equation and default values outlined in the TGD-EQS (EC 2011)

$$K_{\text{sed-water}} = F\text{air}_{\text{sed}} \times K_{\text{air-water}} + F\text{water}_{\text{sed}} + F\text{solid}_{\text{sed}} \times \frac{K\text{p}_{\text{sed}}}{1000} \times RHO\text{solid}$$

Based on the above the $QS_{sediment}$ for beta estradiol is 0.000128mg/kg ww and 0.00033mg/kg dw. In deriving the $QS_{sediment}$ using the EqP approach there is a need to recognise that a number of assumptions are involved, and this is acknowledged in the TGD-EQS (EC 2011). The approach assumes, for example, that the sensitivities of benthic and pelagic organisms are similar, since the EqP approach uses the $AA\text{-}QS_{water,eco}$ as a basis. The $AA\text{-}QS_{freshwater,eco}$ for E2 has been derived on the basis of data from particularly sensitive taxa, ie fish, which may not be directly applicable to benthic organisms, and this needs to be borne in mind, but the approach is still justified in the absence of sediment toxicity data.

Tentative QS_{water}	**Relevant study for derivation of QS**	**Assessment factor**	**Tentative QS**
$MAC_{freshwater, eco}$	MAC-QS not determined as not considered relevant based on the known exposure scenarios.		
$MAC_{marine\ water, eco}$			
$AA\text{-}QS_{freshwater, eco}$	SSD – HC5 0.8ng/l	2	0.4ng/l
$AA\text{-}QS_{marine\ water, eco}$		20	0.08ng/l
$AA\text{-}QS_{freshwater, sed.}$	-	EqP	0.128 $\mu g.kg^{-1}_{ww}$ 0.33 $\mu g.kg^{-1}_{dw}$
$AA\text{-}QS_{marine\ water, sed.}$	-	EqP	- $\mu g.kg^{-1}_{ww}$ - $\mu g.kg^{-1}_{dw}$

7.5 DERIVATION OF A QS FOR SECONDARY POISONING ($QS_{BIOTA,SECPOIS}$)

The criteria for triggering the development of a $QS_{biota,secpois}$ are identified in the TGD-EQS (EC 2011). The criteria include BCF and log Kow, other evidence of bioaccumulation potential, eg monitoring data, or whether the substance has high intrinsic toxicity to mammals and birds.

The TGD-EQS indicates that the starting point is measured BMF or BCF data. If no valid measured BMF or BCF data is available then the log Kow would be considered.

The limited BCF data for beta estradiol however reports a BCF of 6.5 for the flounder (Specker and Chandler, 2003). Specker and Chandler (2003) investigated the uptake of 17β-oestradiol in summer flounder *Paralichthys dentatus* exposed to a waterborne concentrations. The study found that whole body levels of 17β-oestradiol in larval fish were maximal within 30 minutes of the onset of exposure and were maintained for the remaining 48 hours of the exposure regime. In larval fish (mean body weight = 26.6 mg) the maximum whole body concentration was 11.4 µg/kg (= 41.7 nmol/kg), which represented a BCF of 1.5. In juvenile fish (mean body weight = 312 mg) whole body concentrations were the same from 30 minutes to 4 hours and were about an order of magnitude higher at 24 hours. The maximum whole body concentration was 93.7 µg/kg (= 344 nmol/kg) at an exposure concentration of 14.4 µg l^{-1} (53 nmol/l), which represented a BCF of 6.5. The BCF of 6.5 is a whole body BCF value and is below the BCF threshold of 100.

Although the reported whole body BCF for flounder is relatively low there are studies which indicate the potential for beta-estradiol to be present in plasma. Kramer *et al*. (1998) exposed male and female fathead minnow to 17β-oestradiol for 19 days at nominal concentrations that ranged from 27.2-2740 ng l^{-1}. The estimated BCF was 174 in males based on the relationship between waterborne and plasma 17β-oestradiol concentrations in surviving fish from all treatments. No BCF factor could be established for females since there was no concentration-response relationship.

Scott *et al.* (2005) investigated the extent of plasma bioconcentration of tritiated 17β-oestradiol in tench *Tinca tinca*. Water samples were collected over a 6-7 hour period and then the fish were sacrificed, bled and the gall bladder removed. Radioactivity was counted in all the samples. After 6-7 hours, the ratio of radioactivity in plasma compared to the surrounding water was 26.9 times based on exposure to an initial water concentration of 3 ng l^{-1}.

Maunder *et al*. (2007) investigated the relationship over time between the concentrations of 17β-oestradiol in a static exposure system and those in the blood of three-spined stickleback *Gasterosteus aculeatus*. Groups of three-spined stickleback were exposed (nominally) to either 1000 ng l^{-1} 17 β-oestradiol (E2) for 6 days. Both water and fish were sampled at intervals and 17β-oestradiol concentrations in both compartments were determined. The plasma time profile for 17β-oestradiol revealed rapid bioconcentration within the first 6 h of exposure. The plasma steroid levels attained at this time point (approximately 20 ng ml^{-1}) were up to 50-fold greater than the actual levels of steroid measured in the exposure water, while levels in the blood of control fish did not exceed 4 ng ml^{-1}. The substantial elevation of plasma 17β-oestradiol levels relative to the concentrations to which the fish were exposed in the ambient water suggests that it can be bound to sex hormone-binding globulin and delivered to target endocrine tissues at levels far in excess of what might be predicted on the basis of passive branchial uptake alone.

Limited BCF data is available for E2 and the BCF values from the available studies vary. This brings uncertainty as to the assessment of whether E2 meets the BCF threshold of 100.

Data available for the log Kow of beta-estradiol reports a value of 4.01. This is above the threshold value of log Kow >3 and therefore supports the derivation of a $QS_{biota,secpois}$. As noted above measured BCF or BMF data is preferred as the basis for determining whether there is a requirement to derive a $QS_{biota,secpois}$ but that other data can be used to inform the decision in the absence of reliable data. For E2 there is limited BCF data and the data which is available indicates differing conclusions. The log Kow supports the derivation of a $QS_{biota,secpois}$. It is therefore proposed to derive a value however the need for such a standard should be reviewed as additional BCF data become available.

The available data on the toxicity of beta-estradiol to mammals and birds was recently collated and reviewed on behalf of the Environment Agency. The data is summarised in the table below.

Mammalian and avian oral toxicity data for the assessment of non-compartment specific effects relevant for the food chain (secondary poisoning)

Type of study, reference & result	Details
Reproductive and developmental toxicity to mammals	
Sheehan *et al*. (1981) **Developmental LOAEL = 10 µg/kg bw**	Neonatal rats received 17β-oestradiol for 5 days from birth via daily injections at a dose of 10 µg/kg bw. At this dose, significant uterine wet weight gain was observed at day 3. At day 5, altered stroma with evidence of circular muscle differentiation was observed, while the luminal epithelium (cuboidal in control mice) became columnar.
Cook *et al*. (1998) **Reproductive NOAEL = 0.05 mg/kg diet (approximately 0.0025 mg/kg bw/day)**	Male Crl:CD BR rats received 17β-oestradiol orally for 90 days via their diet at doses of 0, 0.05, 2.5, 10 or 50 mg/kg diet (approximately 0, 0.0025, 0.125, 0.5 and 2.5 mg/kg bw/day). The NOAEL was based on decreased body weight (F0 and F1), decreased testis and epididymis weights (F1), interstitial cell atrophy, seminiferous tubule degeneration and reduced sperm production (F0). As well as the presence of germ cell debris in the lumen of tubules, testicular spermatid numbers, epididymal sperm numbers and sperm mobility were reduced and there was atrophy of epididymal tubules at the two top doses in the F0 organisms.
Biegel *et al*. (1998) **Reproductive LOAEL = 0.05 mg/kg diet (approximately 0.0025 mg/kg bw/day)**	Female Crl:CD BR rats received 17β-oestradiol for 90 days orally via their diet at doses of 0, 0.05, 2.5, 10 or 50 mg/kg diet (approximately 0, 0.0025, 0.125, 0.5 and 2.5 mg/kg bw/day). Serum hormones were measured at three time points during the 90-day exposure (1 week, 28 days and 90 days) and the F1 generation rats on postnatal day 98. The oestrous cycle was monitored daily in 10 rats/group over the course of the 90-day feeding study for the F0 generation and from postnatal days 21 to 98 for the F1 generation. The LOAEL was based on increased serum oestradiol concentrations at all time points and decreased serum progesterone concentrations on test day 90, which correlated with an absence of corpora lutea and ovarian atrophy. Serum luteinising hormone concentrations were consistently decreased at all time points at the top two doses and serum prolactin concentrations were increased at the highest dose. No F1 generation rats were produced at the two top doses.
Carcinogenicity studies in mammals	
IARC (1979) **Carcinogenic LOAEL = 0.5 mg/l**	Female C3H/HeJ mice received 17β-oestradiol for 19 months in their drinking water at unspecified doses. The LOAEL was based on a significant increase in mammary tumour formation.

IARC (1979) **Carcinogenic LOAEL = 0.1 mg/kg diet (approximately 0.005 mg/kg bw/day)**	Groups of 48 C3H/HeJ mice received 17β-oestradiol for 24 months orally via their diet at doses of 0, 0.1, 1 or 5 mg/kg diet (approximately 0, 0.005, 0.05 and 0.25 mg/kg bw/day). The LOAEL was based on increased incidences of mammary adenocarcinomas, adenocarcinoma of the cervix, osteosarcoma of the cranium, adenocarcinoma of the uterus and adenocarcinoma of the cervix.
Highman *et al*. (1978; 1980) and Greenman *et al*. (1983) **Reproductive NOAEL = 0.1 mg/kg diet (approximately 0.005 mg/kg bw/day)** **Carcinogenic LOAEL = 0.1 mg/kg diet (approximately 0.005 mg/kg bw/day)**	Virgin female C3H/HeJ mice received 17β-oestradiol for 52 weeks orally via their diet at doses of 0, 0.1, 1 or 5 mg/kg diet (approximately 0, 0.005, 0.05 and 0.25 mg/kg bw/day) from 6 to 110 weeks of age. Unspecified changes to the stromal mucoid in the cervix and adenosis occurred at the top dose. The ovaries showed atrophy with absence of corpora lutea. Animals at lower doses showed less frequent and severe similar changes. The reproductive NOAEL was based on stromal mucoid changes in the vagina and cervix, epithelial keratinisation in the vagina and granular hyperplasia in the uterine horns. The carcinogenic LOAEL was based on increased incidences of cervical adenosis and mammary hyperplastic alveolar nodules and the shortened time to development of mammary adenocarcinomas. These changes increased with dose and time.
No data could be located for the mammalian sub-acute toxicity of 17β-oestradiol.	
No data could be located for acute, chronic, reproductive and developmental avian toxicity for 17β-oestradiol.	

The available data indicate that the lowest No Observed Adverse Effect Levels (NOAELs) for relevant reproductive endpoints in mammals were in the range 2.5 to 5 µg/kg body weight/day. No data could be located for acute, chronic, reproductive and developmental avian toxicity for 17β-oestradiol.

A NOAEL of 0.001mg/kg bw/day has been reported for mice in two studies by Tyl et al (2008 a b). The studies are one generational and two generational reproductive studies. A wide range of endpoints were considered including number of offspring, body weight, effects on reproductive organs. The lowest NOAEL related to the incidence of increased uterus, cervix and vagina weights. Using a conversion factor of 20 on this NOAEL gives a NOEC of 0.02mg/kg. An assessment factor of 30 should be applied to this endpoint value due to the chronic nature of the two generational study. This gives a $QS_{biota,secpois}$ of 0.00067mg/kg.

To convert this QS to a concentration in water the following equation is provided in the TGD-EQS (EC 2011).

$$QS_{freshwater} = QS_{biota,hh}/(BCFxBMF)$$

$$QS_{saltwater} = QS_{biota,hh}/(BCFxBMF1xBMF2)$$

The calculation of a water concentration from the $QS_{biota,sepois}$ therefore requires a BCF value. The BCF value reported for whole fish is 6.5. As noted previously this value is low and is below the criteria identifying the need to derive QS for secondary poisoning and biota. It is also in contrast to the log Kow of 4.01. Due to the uncertainty about the BCF value for beta-estradiol it is proposed that it is not possible to derive a back calculated for the water environment based on the available data.

Tentative QS_{biota}	**Relevant study for derivation of QS**	**Assessment factor**	**Tentative QS**

Biota	Mice 2 generational reproduction study/ NOAEL 0.001mg/kg bw/day (reproduction) (NOEC 0.02mg/kg	30	0.00067mg/kg

7.6 DERIVATION OF A QS FOR HUMAN HEALTH

7.6.1 Human health via consumption of fishery products ($QS_{biota,hh}$)

The $QS_{biota,hh}$ is calculated using the following equation as noted in the TGD-EQS (EC 2011). The TL can be an acceptable daily intake (ADI), tolerable daily intake (TDI) or NOAELoral (the latter divided by an assessment factor).

$$QS_{biota,hh} = \frac{0.1 \times TL \times 70}{0.115}$$

An ADI of 0.050µg/kg bw per day has been derived by WHO (2000). The ADI was determined by applying a safety factor to a NOEL of 0.3mg/day (equivalent to 5µg/kg bw per day) in studies of changes in several hormone dependent parameters in postmenopausal women. An assessment factor of 10 was used to account for normal variation among individuals, and an additional factor of 10 was added to protect sensitive populations.

Using the ADI derived by WHO (2000) within the above formula gives a $QS_{biota,hh}$ of 3.04µg/kg bw.

To convert this QS to a concentration in water the following equation is provided in the TGD-EQS.

$$QS_{freshwater} = QS_{biota,hh}/(BCF \times BMF)$$

$$QS_{saltwater} = QS_{biota,hh}/(BCF \times BMF1 \times BMF2)$$

The calculation of a water concentration from the $QS_{biota,hh}$ therefore requires a BCF value. The BCF value reported for whole fish is 6.5. As noted in section 7.5 this value is low and is below the criteria identifying the need to derive QS for secondary poisoning and biota. It is also in contrast to the log Kow of 4.01. Due to the uncertainty about the BCF value for beta-estradiol it is proposed that it is not possible to derive a back calculated for the water environment based on the available data.

Human health via consumption of fishery products		**Master reference**
CMR		

Tentative $QS_{biota, hh}$	**Relevant study for derivation of $QS_{biota, hh}$**	**Assessment Factor**	**Tentative $QS_{biota, hh}$**

Human health	5µg/kg bw per day (based on a NOEL of 0.3mg/day from studies on changes in several hormone dependent parameters in postmenopausal women (Used by WHO in the derivation of the ADI)	100 (ADI derived by WHO (2000))	3.04µg/kg bw

7.6.2 Human health via consumption of drinking water

No details of existing thresholds for beta-estradiol in drinking water were located. Where thresholds have not been derived by either the EU or WHO the TGD-EQS (EC 2011) notes that a provisional drinking water standard should be derived using the following formula:-

$$QS_{dw,hh} = \frac{0.1 \times TL_{hh} \times bw}{Uptake_{dw}}$$

The default values for *bw* and $Uptake_{dw}$ are 70kg and 2 litres respectively. The TL_{hh} refers to an available ADI or TDI. Using the ADI of 0.05µg/kg *bw* per day derived by WHO (2000) gives a $QS_{dw,hh}$ for beta-estradiol of 0.175µg/l

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