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Derivation of water quality guidelines for priority pharmaceuticals

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4	Derivation of water quality guidelines for priority pharmaceuticals
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15	DERIVATION OF WATER QUALITY GUIDELINES FOR PRIORITY
16	PHARMACEUTICALS
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28 Abstract- High reliability water quality guideline values (GVs) have been derived for four pharmaceuticals, carbamazepine, diclofenac, fluoxetine and propanolol in fresh waters using 29 a Burr Type III distribution applied to species sensitivity distributions (SSDs) of chronic 30 31 toxicity data. Data were quality assured and had to meet acceptability criteria for 'chronic' NOEC or EC10 endpoints including population relevance (namely, effect endpoints based on 32 development, growth, reproduction and survival). Biomarker response data (e.g. biochemical, 33 34 histological or molecular responses) were excluded from the derivation as they are typically not directly relevant to population-related impacts. The derived GVs for 95% species 35 36 protection were 4.3, 770, 1.6 and 14 µg/L for carbamazepine, diclofenac, fluoxetine and propranolol, respectively. These values significantly higher than the low reliability values 37 derived for the European Commission, Switzerland or Germany that are based on the 38 39 application of assessment factors to the most sensitive experimental endpoint (which may 40 include biochemical, histological or molecular biomarker responses). The GVs derived in this exercise were not exceeded in recent data for Australian rivers and streams receiving 41 42 pharmaceutical containing effluents from WWTPs.

43 Keywords

44 Pharmaceutical, carbamazepine, diclofenac, fluoxetine, propanolol

45

INTRODUCTION

49											
50		Our growing dependence on pharmaceuticals, and their increased availability to									
51	cons	umers, means that a number of the commonly used products are becoming detectable									
52	cons	tituents of wastewaters [1, 2]. Depending on the effectiveness of the wastewater									
53	treat	ment process, there are real prospects for these products to reach natural water systems,									
54	with the potential for effects on aquatic ecosystem health. Ecotoxicological investigations										
55	have been carried out for many of the popularly used pharmaceuticals, however, there have										
56	been limited attempts to derive water quality guidelines that enable regulatory agencies to										
57	determine whether measured environmental concentrations pose a concern.										
58		This paper collates the available data for four pharmaceuticals, carbamazepine,									
59	diclofenac, fluoxetine and propranolol, and derives high reliability guideline values for										
60	ecos	ystem protection of 99, 95 and 90% of species using species sensitivity distributions									
61	(SSE	Os) [3]. The latest revisions to the guideline derivation protocols [4] were applied. These									
62	invo	lve:									
63	(i)	Using effects endpoints for development, growth, reproduction or survival and									
64		focussing on chronic EC10 data, where available, rather than NOEC data and excluding									
65		biomarker responses (e.g. biochemical, histological or molecular responses);									
66	(ii)	Ensuring that all toxicity data meet the required definitions of chronic tests, in									
67		particular, for juvenile fish tests, exposure duration should be ≥ 21 days and ≥ 7 days for									
68		fish embryo tests;									
69	(iii)	High reliability guideline values require 8 or more data points for chronic exposure (no									
70		conversions of acute data to chronic) representing at least 4 taxonomic groups;									
71	(iv)	The goodness of fit of data to the Burr Type III distribution used in the SSD being									
72		acceptable; and									

73 (v) Careful evaluation of all data to ensure they meet acceptability criteria (Batley et al., 2013). 74 The basic data for each of the pharmaceuticals are summarised in Table 1. 75 76 **EXPERIMENTAL** 77 A thorough review of the literature was undertaken for all toxicity data relating to 78 carbamazepine, diclofenac, fluoxetine and propanolol and added to a new dataset determined 79 80 in our laboratories [5]. Since our priority is ecological protection based on populationrelevant endpoints, adverse effects on development, growth, reproduction and survival were 81 82 used to derive NOEC or EC10 values, as per the recommendation by Hutchinson et al. [6]. 83 This approach recognizes that biomarkers responses based on biochemical, histological and molecular endpoints may be highly useful for exposure monitoring [7, 8] and also in 84 developing adverse outcome pathways to help prioritize appropriate testing strategies for 85 ecotoxicology research and risk assessment [9]. Data were sorted into acute and chronic tests, 86 with the objective of obtaining at least 8 chronic NOEC or EC10 data points for species from 87 88 4 or more taxonomic groups. If this was achieved, acute data and chronic data having other endpoints (e.g. EC50 or LOECs) were discarded, otherwise lower reliability guidelines could 89 be generated using a combination of converted acute data (using an ACR or default value of 90 91 10) and chronic data. A quality check of the data as described by Hobbs et al. [10] was then undertaken and only data of high or acceptable quality were retained as recommended for 92 guideline derivation in Australia and New Zealand [4]. 93 94 Data were then screened to ensure that the endpoints reported were acceptable as

95 chronic tests according to agreed criteria [4, 10]. An SSD was then obtained from the data set

96	using the BurrliOz Version 2 software to derive guideline values (GVs) that were protective
97	of 99, 95 and 90% of species (PC99, PC95 and PC90) with 50% confidence.
98	
99	RESULTS AND DISCUSSION
100	Carbamazepine
101	A review of the literature found acute toxicity data reported for 6 species, and chronic
102	toxicity for 17 species. Of these, acceptable chronic toxicity data were available for 11
103	species (2 cladocerans, 2 green algae, 1 blue-green algae, 1 diatom, 1 midge, 1 rotifer, 1
104	cnidarian and 2 fish) representing 8 taxonomic groups (Table 2). The cladoceran,
105	Ceriodaphnia dubia, was the most sensitive, with an EC10 of 25 μ g/L [11]. The data
106	distribution using a Burr Type III fit in the SSD was such that it had a long tail (Figure 1),
107	which meant that a 99% protection GV could not be determined. The 95% protection GV was
108	4.3 μg/L (Table 6).
109	Carbamazepine enters the environment largely through discharges from wastewater
110	treatment plants, in which it is not effectively removed [12, 13]. It has been detected in
111	discharges from German plants at concentrations up to 6.3 μ g/L [14]. Loos et al. [15]
112	reported a mean concentration of 250 ng/L (maximum 12 μ g/L) in studies of 122 European
113	river waters. Indian rivers contained 6-128 ng/L [16] while in Spanish rivers 80-3090 ng/L
114	[17] and in the Pearl River in China, 43 ng/L [18]. It has a relative long half-life of 38 days in
115	natural waters in the presence of sunlight, with photolysis being the major degradation
116	pathway [12]. Tixier et al. [19] reported a half-life of 63 days in Lake Greifensee in
117	Germany, indicating that it was relatively persistent.
118	In all cases, detected concentrations in receiving waters were below the derived GV.

119 The guidelines recommended in Switzerland and Germany [20, 21] are considerably lower

120	(Table 7). The Swiss environmental quality standard (EQS) of 0.5 μ g/L was derived by
121	applying an assessment factor of 50 to the most sensitive reliable endpoint, that for
122	reproduction of <i>Ceriodaphnia dubia</i> (25 μ g/L) [22]. The available fish data were only for a
123	10-d exposure and considered not acceptable for a chronic test, although in Australia and
124	New Zealand, the 7-d test is acceptable for fish embryos and a 21-d test required for juvenile
125	fish [4]. In the Swiss study, the scope of the data analysis included both adverse effects data
126	and biomarker responses in contrast to our focus solely on population-relevant effects [22].
127	Their GV is clearly of low reliability compared to that derived in this paper. Ferrari et al.
128	[23] using a limited dataset and a log-normal distribution in a SSD, determined 95%
129	protection value (reported as a hazardous concentration to 5% of species, HC5) of 2.1 μ g/L.
130	(Table 7), comparable to our value of 4.3 μ g/L with a large dataset.
131 132	Diclofenac
133	Of 13 chronic data for diclofenac, 11 had EC10 or NOEC values suitable for GV
134	derivation. These comprised 2 cladocerans, 1 diatom, 2 green algae, 1 blue-green algae, 1
135	rotifer, 1 angiosperm, 1 arthropod and 2 fish, representing 8 taxonomic groups. The most
136	sensitive species was the midge, <i>Chironomus tepperi</i> with an EC10 of 760 μ g/L [5].
137	
138	Schmitt-Jansen et al. [24] exposed the green alga Scenedesmus vacuolatus to
139	diclofenac in ultrapure water to sunlight and noted an increase in toxicity measured as growth
140	inhibition, with time over 6 days, with the EC50 decreasing from 46.3 mg/L to 23 μ g/L after
141	6 days. There was a rapid decrease in diclofenac concentrations due to photodegradation and
142	the enhanced toxicity was clearly due to the presence of degradation products. These data
143	were not included as the tests were not conducted in natural waters and the pH was not

recorded, nor EC10 values calculated. It is unclear how the results relate to actual field 144 conditions. 145

146	Concentrations in the range 310-930 ng/L have been detected in the effluents from a
147	Swiss wastewater treatment plant, with concentrations only marginally reduced during
148	passage through the plant [25]. Diclofenac has been detected at <1-12 ng/L in Swiss lakes
149	and 11-310 ng/L in a nearby river [25] and from 110-220 ng/L in the Höje River in Sweden
150	downstream of a WWTP [26]. Photolysis is the major degradation pathway with half-lives
151	near 3 h at summer temperatures [24] (Buser et al. [25] reported 0.9 h), but up to 2 days in
152	winter in some locations [27]. Diclofenac is ionised at the pH of most waters (pKa=4.2), so is
153	not readily volatilised, nor does it readily attach to particulates [25].
154	The measured concentrations are below the GV derived in this study (Table 6), but
155	would exceed the proposed EQS for the European Commission (reported in Europe (Johnson
156	et al., 2013) (Table 7). A discussion paper on the EU guidelines [28] indicated that these
157	values are derived by applying an assessment factor of 10 to the lowest acceptable NOEC, for
158	a fish. For rainbow trout, both Schwaiger et al. [29] and Triebskorn [30] reported a LOEC of
159	1 μ g/L for a histopathological effect, while the latter referred to a threshold of 5 μ g/L for
160	histopathological lesions. A NOEC of 0.5 μ g/L was reported by Hoeger et al. [31] for
161	monocyte infiltration/accumulation in livers of brown trout exposed to diclofenac for 21
162	days. They concluded that the adverse effects in various organs could 'possibly compromise
163	fish health'. The EQS of 0.05 μ g/L proposed by the Swiss Ecotox Centre [32] was based on
164	the application of an assessment factor of 10 to the above NOEC for brown trout.
165	The current Australian and New Zealand approach to biomarker endpoints of this type
166	is that they should not be used in the derivation of water quality guidelines, unless their

ecological relevance can be demonstrated [4]. This approach is consistent with that of 167

Hutchinson et al. [33] who advocated that biomarker responses or signals (such as 168

9

169 vitellogenin, secondary sexual characteristics, gonadosomatic index, gonad histology, plasma steroids, enzyme induction and gene expression) may provide valuable mechanistic signals to 170 guide chronic testing for adverse effects and, at present, should not be used to directly derive 171 water quality guidelines. Moreover, it is recognized that interpretation of many biomarkers 172 responses in aquatic organisms is highly complex [33-35]. Acceptable population-relevant 173 effects endpoints include survival, length, weight, development, fecundity, fertilisation rate, 174 175 hatching success and sex ratios. The focus on population-relevant endpoints for setting GVs for pharmaceuticals is also proposed by Caldwell et al. [36, 37]. 176

The use of an assessment factor results in a conservative, very low reliability GV. By
contrast, the GV derived in this study would be classified as high reliability based on the
criteria being adopted for Australian and New Zealand water quality guideline derivation [4].
Using a limited data set, Ferrari et al. [23] applied a log normal distribution in an SSD to
derive an HC5 that protected 95% of species that was of the same order of magnitude as our
value of 770 µg/L.

SCHER [28] raised a concern regarding the solubility of diclofenac being exceeded in
some of the toxicity tests, however, data from Llinas et al. [38] suggest that this would only
be an issue in mildly acidic solutions below the diclofenac pKa. At the pH of natural waters,
solubility limitations would not be an issue.

187

188 Fluoxetine

There is a large toxicity database for fluoxetine, comprising both acute and chronic tests as well as others based on behavioural and biomarker endpoints. Of these only 13 reported chronic NOEC or EC/IC10 endpoints, comprising 6 green algae, 1 arthropod, 1 angiosperm, 3 crustaceans, 1 gastropod and 1 fish, representing 6 taxonomic groups (Table 4). Oakes et al. [39] found that the green alga *Desmodesmus subspicatus* was the most sensitive species to fluoxetine with a NOEC was $\leq 0.6 \ \mu g/L$. Given that NOECs are not a reliable endpoint, most jurisdictions, including Australia and New Zealand, recommend the use of EC/IC10 values as a more defensible alternative [4]. In the supplementary information to Oakes et al. [39], the plotted dose response curve showed an IC10 of 1 $\mu g/L$ and so this was included in the database used in this study. Along with this species, the New Zealand mud snail, *Potamopygus antipodarum* was also very sensitive (Table 4) [40, 41].

The malformation endpoint for the African clawed frog, *Xenopus laevis* [42] (Table 4) was deemed unacceptable for use in GV derivation as many non-contaminant factors can lead to malformations The 7-d juvenile fish data for fathead minnow [43] were considered acute and not chronic according to the Australian and New Zealand data selection criteria [4] which require a 21-d test, so this too was not included.

205

Fluoxetine is a racemate, a mixture of two sterioisomers with mirror-image structures 206 207 [4]. The (R)-enantiomer is known as dextro-propranolol. The (S)-enantiomer is known as levo-fluoxetine. The most common form is as a racemic mixture (1:1) of the sterioisomers, 208 supplied as the hydrochloride. To date only one study has examined the chronic toxicity of 209 210 the sterioisomers and found that (S)-fluoxetine was more toxic than (R)-fluoxetine to fathead minnow, *Pimephales promelas*, while there was no significant difference in the responses of 211 Daphnia magna [4]. Fluoxetine photodegradation has a relatively long half-life (160 days) 212 [44] and its relatively high K_{ow} means that it binds preferentially to particulate organic matter. 213 214 Measured concentrations of fluoxetine in natural waters are typically in the ng/L 215 range. Kolpin et al. [45] reported a median concentration of 12 ng/L for a range of US streams, and similar values have been reported for waters in Canada and the UK [39]. WWTP 216 217 effluent concentrations are typically <500 ng/L [46-48].

218	The high reliability GV for fluoxetine derived in this study was 1.6 μ g/L for 95%
219	species protection. No reported EQS values could be found, however, a number of studies
220	reported predicted no effects concentrations (PNECs) for fluoxetine in surface waters. These
221	were all obtained by applying assessment factors to the most sensitive data (Table 7). Thus
222	Oakes et al. [39] obtained a PNEC of 0.012 μ g/L by applying a factor of 50 to the <i>D</i> .
223	subspicatus data. Montforts [49] reported a PNEC of 0.031 μ g/L using a factor of 1000 with
224	algal toxicity data. Grung et al. [50] reported a PNEC of 0.004 μ g/L, while Verlicchi et al.
225	[2] reported a PNEC of 0.05 μ g/L. All of these values are conservative and of very low
226	reliability.
227	Sumpter et al. [51] have discussed the fact that both vertebrates and invertebrates use
228	serotonin as a neurotransmitter and, as such, fluoxetine as a serotonin reuptake inhibitor, may
229	have effects on fish (and invertebrate) behaviour (e.g. swimming speed, schooling
230	behaviour). Such non-standard endpoints have not been considered on our GV derivation.
231	
232	Propranolol
233	Although there are published results for over 20 chronic toxicity tests, only 12
234	reported chronic NOEC or EC10 values, with the remainder only giving EC50 or LOEC
235	values. Although both an EC10 and an EC5 were available for the green algae, Desmodesmus
236	subspicatus, because of the greater errors around the EC5, the EC10 value was used for
237	guideline derivation [52].
238	Data were obtained for 2 cladocerans, 1 diatom, 2 green algae, 1 blue-green algae, 1
239	rotifer, 1 angiosperm, 1 arthropod and 3 fish, representing 8 taxonomic groups. Of these, the

240 fathead minnow, *Pimephales promelas* [53] and the cladoceran, *Ceriodaphnia dubia*, were

241	the most sensitive [54]. Like fuoxetine, propranolol is a racemate [55], with the most
242	common form a racemic mixture (1:1) of the sterioisomers, supplied as the hydrochloride.
243	Propranolol has been detected in WWTP effluents in Germany at a median
244	concentration of 170 ng/L (290 ng/L maximum) [14] and in Sweden near 30 ng/L [26].
245	Downstream river water concentrations were closer to 12 ng/L (590 ng/L maximum) and 10
246	ng/L respectively. High concentrations are unlikely to persist as the laboratory-determined
247	half-life for photolytic decomposition was 1.1 h [56]. For sunlight exposure, Liu et al. [57]
248	extrapolating from laboratory studies calculated a half-life closer to 1 day in summer and 8
249	days in winter, with photodegradation being up to 19 times faster than biodegradation.
250	Our study yielded a high reliability guideline value for propranolol of 14 μ g/L. This is
251	almost 100-fold higher than the value recommended for Switzerland [32]. Their low
252	reliability EQS of 0.16 μ g/L (Ecotox Centre, 2013d) used an assessment factor of 50 applied
253	to a NOEC of 8 μ g/L for <i>Ceriodaphnia dubia</i> reproduction [54] (although the value reported
254	in Ferrari et al. was actually 9 µg/L).
255	
256	CONCLUSIONS
257	High reliability GVs have been derived for carbamazepine, diclofenac, fluoxetine and
258	propanolol in fresh waters applying a Burr Type III distribution in SSDs of chronic toxicity
259	data (NOECs or EC10s). Data were quality assured and had to meet acceptability criteria for
260	'chronic' endpoints. Sub-chronic biomarker data were excluded from the derivation and only
261	data for ecologically relevant, population-related effects were included. The derived GVs for
262	95% species protection were 4.3, 770, 1.6 and 14 μ g/L respectively, for the four
263	pharmaceuticals. These values significantly higher than the low reliability values derived for
264	the European Commission, Switzerland or Germany that are based on the application of

- assessment factors to the most sensitive endpoint. They are not exceeded in recent data for
- 266 rivers and streams receiving pharmaceutical containing effluents from WWTPs.

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- *Conflict of interest* The authors declare no conflict of interest.

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Table 1. Key properties of the studied pharmaceuticals

Pharmaceutical	Chemical Structure	Common name	Log Kan	Solubility,	рКа	Reference
Carbamazepine (anti-convulsant and mood stabiliser)	MW =236.3	Tegretol	2.45	112	13.9	[54]
Diclofenac (non- steroidal anti- inflammatory)	Сі сі сі о о МW=296.1	Voltarin	4.51	2,430	4.2	[54]
Fluoxetine (anti- depressant)	MW=309.3	Prozac, Sarafem	4.05	10,800	9.4	[39, 44, 58]
Propranolol (beta- blocker)	он NW=259.3	Inderal	3.12	609	9.5	[54, 59]

 Table 2. Chronic data used in carbamazepine guideline derivation

Taxonomic group	Common name	Scientific name	Life stage	Exposure duration (d)	Test medium	Test endpoint	Toxicity estimate	Toxicity value (mg/L)	рН	Temp (°C)	Reference
Blue-green algae	Blue-green algae	Synechococcus leopolensis	-	4	Moderately hard water	Growth inhibition	NOEC	17.5			[54]
Green algae	Green algae	Pseudokirchneri ella subcapitata	-	4	Freshwater	Growth inhibition	NOEC	0.52			[60]
Green algae	Green algae	Chlorella vulgaris	-	2	Freshwater	Growth inhibition	EC10	13 ^a		22	[61]
Arthropoda	Midge	Chironomus tepperi	Embryo	7	Freshwater	Larval survival	EC10	4.0			[5]
Diatom	Diatom	Cyclotella meneghiniana	-	4	Freshwater	Growth inhibition	NOEC	10.0			[54]
Rotifer	Rotifer	Brachionus calyciflorus	-	2	Freshwater	Reproduction	NOEC	0.38			[54]
Cnidarian	Cnidarian	Hydra attenuate		3	Freshwater	Morphology changes	NOEC	1	7	20	[62]
Crustacean	Water flea	Ceriodaphnia dubia	-	7	Freshwater	Reproduction	NOEC	0.025			[54]
Crustacean	Water flea	Daphnia magna		21	Freshwater	Reproduction	NOEC	0.4			[22, 63]
Fish	Zebrafish	Danio rerio	Embryo	10		Mortality	NOEC	25		23	[54]
Fish	Golden perch	Macquaria ambigua	Embryo	7	Freshwater	Larval survival	EC10	1.1			[5]

^a Estimated from dose-response curve

Taxonomic group	Common name	Scientific name	Life stage	Exposure duration (d)	Test medium	Test endpoint	Toxicity estimate	Toxicity value (mg/L)	рН	Temp (°C)	Reference
Blue-green algae	Blue-green algae	Synechococcus leopolensis	-	4	Moderately hard water	Growth inhibition	NOEC	10			[54]
Green algae	Green algae	Pseudokirchneri ella subcapitata	-	4	Moderately hard water	Growth inhibition	NOEC	10			[54]
Green algae	Green algae	Desmodesmus subspicatus	-	3	Freshwater	Growth inhibition	NOEC	50			[64]
Arthropod	Midge	Chironomus tepperi	Embryo	7	Freshwater	Larval survival	EC10	0.76			[5]
Angiosperm	Duckweed	Lemna minor	-			Growth inhibition	NOEC	3.5			[5]
Diatom	Diatom	Cyclotella meneghiniana	-	4	Freshwater	Growth inhibition	NOEC	10.0			[54]
Rotifer	Rotifer	Brachionus calyciflorus	-	2	Freshwater	Reproduction	NOEC	12.5			[54]
Crustacean	Water flea	Ceriodaphnia dubia	-	7	Freshwater	Reproduction	NOEC	1.0			[54]
Crustacean	Water flea	Daphnia magna	-	21	Reconstitute d hard water	Reproduction	NOEC	10	7.8	25	[65]
Fish	Zebrafish	Danio rerio	Embryo	10	Freshwater	Mortality	NOEC	4.0		23	[54]
Fish	Golden perch	Macquaria ambigua	Embryo	7	Freshwater	Larval survival	EC10	5.92			[5]

Taxonomic group	Common name	Scientific name	Life stage	Exposure duration (d)	Test medium	Test endpoint	Toxicity estimate	Toxicity value (µg/L)	рН	Temp (°C)	Reference
Chlorophyta	Green alga	Pseudokirchneri ella subcapitata	-	4	Moderately hard water	Growth inhibition	IC10	31.3	7.3	25	[66]
Chlorophyta	Green alga	Pseudokirchneri ella subcapitata	-	4	Moderately hard water	Growth inhibition	LOEC	13.6	-	25	[47]
Chlorophyta	Green alga	Pseudokirchneri ella subcapitata	-	4	Moderately hard water	Growth inhibition	IC50	27	8.1- 8.5	18-22	[67]
Chlorophyta	Green alga	Pseudokirchneri ella subcapitata	-	5	Moderately hard water	Growth inhibition	IC50	24 (turb) 39 (cell dens)	-	25	[48]
Chlorophyta	Green alga	Scenedesmus acutis	-	4	Moderately hard water	Growth inhibition	IC10	56	7.3	25	[66]
Chlorophyta	Green alga	Scenedesmus quadricauta	-	4	Moderately hard water	Growth inhibition	IC10	98 ^a	7.3	25	[66]
Chlorophyta	Green alga	Desmodesmus subspicatus	-	4	Moderately hard water	Growth inhibition	IC10	1.0			[39]
Chlorophyta	Green alga	Chlorella vulgaris	-	4	Moderately hard water	Growth inhibition	IC10	2900	7.3	25	[66]
Chlorophyta	Green alga	Dunaliella tertiolecta		4	Moderately hard water	Growth inhibition	IC10 est	24 ^a	-	25	[68]
Arthropod	Midge	Chironomus tepperi	Embryo	7	Moderately hard water	Larval survival	EC10	59			[5]
Angiosperm	Duckweed	Lemna minor	-	?	Moderately hard water	Growth inhibition	EC10	1190			[5]
Crustacean	Amphipod	Hyalella azteca	-	28	Moderately hard water	Growth inhibition	NOEC	13	7.9	20	[40]
Crustacean	Water flea	Ceriodaphnia dubia	-	7	Moderately hard water	Reproduction	NOEC	56	-	25	[48]
Crustacean	Water flea	Ceriodaphnia dubia	-	7	Moderately hard water	Reproduction	NOEC	89		25	[69]

							GM	71			
Crustacean	Water flea	Daphnia magna	-	21	Moderately hard water	Reproduction	NOEC	174	8.4	25	[43]
Crustacean	Water flea	Daphnia magna	-	21	Moderately hard water	Reproduction	NOEC	8.9	7.9	20	[40]
Crustacean	Water flea	Daphnia magna	-	21	Moderately hard water	Reproduction	NOEC	60			[39]
							GM	45.3			
Gastropod	New Zealand mud snail	Potamopyrgus antipodarum	Embryo	56	Moderately hard water	Survival	EC10	0.89	-	16	[41]
Gastropod	New Zealand mud snail	Potamopyrgus antipodarum	Embryo	42	Moderately hard water	Reproduction	NEC	5			[40]
							GM	2.0			
Amphibia	African clawed frog	Xenopus laevis	Embryo	4	Hard water	Malformation ^b	EC10	3000	7.6	23	[42]
Fish	Fathead minnow	Pimephales promelas	Juvenile	7	Moderately hard water	Growth ^c	EC10	9	8.4	25	[43]
Fish	Golden perch	Macquaria ambigua	Embryo	7	Freshwater	Larval survival	EC10	260			[5]

^aEstimated from the published dose response curve; ^bNot an acceptable endpoint as many factors can lead to malformations; ^cJuvenile growth must be measured over>21 days

Table 5. Chronic data used to derive the propranolol guideline

Taxonomic group	Common name	Scientific name	Life stage	Exposure duration (d)	Test medium	Test endpoint	Toxicity estimate	Toxicity value (mg/L)	рН	Temp (°C)	Reference
Blue-green algae	Blue-green algae	Synechococcus leopolensis	-	4	Moderately hard water	Growth inhibition	NOEC	0.35	7.8	23	[54]
Green algae	Green algae	Pseudokirchneri ella subcapitata	-	4	Moderately hard water	Growth inhibition	NOEC	5	7.8	23	[54]
Green algae	Green algae	Pseudokirchneri ella subcapitata	-	3	Deionised water	Growth inhibition	NOEC	<0.78	-	24	[70]
							GM	2.0			
Green algae	Green algae	Desmodesmus	-	3	Moderately	Growth	EC5	0.18	7.8	23	[52]
		subspicatus			hard water	inhibition	EC10	0.33			
Arthropod	Midge	Chironomus tepperi	Embryo	7	Moderately hard water	Larval survival	EC10	2.06			[5]
Angiosperm	Duckweed	Lemna minor	-	?	Moderately hard water	Growth inhibition	EC10	29.5			[5]
Diatom	Diatom	Cyclotella meneghiniana	-	4	Moderately hard water	Growth inhibition	NOEC	0.094	7.8	23	[54]
Rotifer	Rotifer	Brachionus calyciflorus	-	2	Moderately hard water	Reproduction	NOEC	0.18	7.8	23	[54]
Rotifer	Rotifer	Brachionus calyciflorus	-	2	Deionised water	Reproduction	NOEC	1.0	-	24	[70]
Crustacean	Water flea	Ceriodaphnia dubia	-	7	Moderately hard water	Reproduction	NOEC	0.009	7.8	23	[54]
Crustacean	Water flea	Ceriodaphnia dubia	-	7	Reconstitute d hard water	Reproduction	NOEC	0.125		25	[71]
							GM	0.033			
Crustacean	Water flea	Daphnia magna	-	9	Hard water	Reproduction	NOEC	0.055	-	25	[72]
Fish	Rainbow trout	Oncorhynchus	Juvenile	40	Moderately hard fresh	Growth rate	NOEC	8.7 ^a	7.4	15	[73]

		mykiss			water						
Fish	Fathead minnow	Pimephales promelas	Embryo	21	Dechlorinat ed tap water	Hatchability	NOEC	0.01	7.5	25	[53]
Fish	Golden perch	Macquaria ambigua	Embryo	7	Freshwater	Larval survival	EC10	4.9			[5]

^a Corrected for analytical recovery data

Table 6.	Derived	water quality	guidelines	for the 4	pharmaceuticals
			0		

Pharmaceutical	PC99	PC95	PC90
		μg/L	
Carbamazepine	<1	4.3	32
Diclofenac	180	770	1400
Fluoxetine	0.23	1.6	3.8
Propranolol	3.5	14	29

Table 7. Comparison of derived GVs with other international values

Pharmaceutical	EC EQS ^a	Switzerland EQS ^b	German EQS ^c	Other values	This study ^d
		μg/l			
Carbamazepine	-	0.5	0.5	2.1 ^{d,e}	4.3
Diclofenac	0.1	0.05	0.05	580 ^{d,e}	770
Fluoxetine	-	-	-	0.004 ^{f,g} 0.012 ^{f,h} 0.031 ^{f,i}	1.6
Propranolol	-	0.16	-	0.05 ^{r,j}	14

^a[74]; ^b[32]; ^c[21]; ^dHC5 (95% species protection) ^e[23]; ^fPNEC values;

^g[50]; ^h[39]; ^h[49]; ^j[2]





Figure 1. SSDs for carbamazepine, diclofenac, fluoxetine and propranolol