This is an accepted manuscript of an article published by SETAC in Environmental Toxicology & Chemistry, 28 April 2016. Available at DOI: 10.1002/etc.3336

Derivation of water quality guidelines for priority pharmaceuticals

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Total number of words –6501

DERIVATION OF WATER QUALITY GUIDELINES FOR PRIORITY PHARMACEUTICALS

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Abstract- High reliability water quality guideline values (GVs) have been derived for four pharmaceuticals, carbamazepine, diclofenac, fluoxetine and propanolol in fresh waters using a Burr Type III distribution applied to species sensitivity distributions (SSDs) of chronic 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 development, growth, reproduction and survival). Biomarker response data (e.g. biochemical, 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 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 derived for the European Commission, Switzerland or Germany that are based on the application of assessment factors to the most sensitive experimental endpoint (which may 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 pharmaceutical containing effluents from WWTPs.

Keywords

Pharmaceutical, carbamazepine, diclofenac, fluoxetine, propanolol

INTRODUCTION

Our growing dependence on pharmaceuticals, and their increased availability to consumers, means that a number of the commonly used products are becoming detectable constituents of wastewaters [1, 2]. Depending on the effectiveness of the wastewater treatment process, there are real prospects for these products to reach natural water systems, with the potential for effects on aquatic ecosystem health. Ecotoxicological investigations have been carried out for many of the popularly used pharmaceuticals, however, there have been limited attempts to derive water quality guidelines that enable regulatory agencies to determine whether measured environmental concentrations pose a concern.

This paper collates the available data for four pharmaceuticals, carbamazepine, diclofenac, fluoxetine and propranolol, and derives high reliability guideline values for ecosystem protection of 99, 95 and 90% of species using species sensitivity distributions (SSDs) [3]. The latest revisions to the guideline derivation protocols [4] were applied. These involve:

(i) Using effects endpoints for development, growth, reproduction or survival and focussing on chronic EC10 data, where available, rather than NOEC data and excluding biomarker responses (e.g. biochemical, histological or molecular responses);

(ii) Ensuring that all toxicity data meet the required definitions of chronic tests, in particular, for juvenile fish tests, exposure duration should be ≥21 days and ≥7 days for fish embryo tests;

(iii) High reliability guideline values require 8 or more data points for chronic exposure (no conversions of acute data to chronic) representing at least 4 taxonomic groups;

(iv) The goodness of fit of data to the Burr Type III distribution used in the SSD being acceptable; and

(v) Careful evaluation of all data to ensure they meet acceptability criteria (Batley et al., 2013).

The basic data for each of the pharmaceuticals are summarised in Table 1.

EXPERIMENTAL

A thorough review of the literature was undertaken for all toxicity data relating to carbamazepine, diclofenac, fluoxetine and propanolol and added to a new dataset determined in our laboratories [5]. Since our priority is ecological protection based on population-relevant endpoints, adverse effects on development, growth, reproduction and survival were used to derive NOEC or EC10 values, as per the recommendation by Hutchinson et al. [6]. 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 developing adverse outcome pathways to help prioritize appropriate testing strategies for ecotoxicology research and risk assessment [9]. Data were sorted into acute and chronic tests, with the objective of obtaining at least 8 chronic NOEC or EC10 data points for species from 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 be generated using a combination of converted acute data (using an ACR or default value of 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 guideline derivation in Australia and New Zealand [4].

Data were then screened to ensure that the endpoints reported were acceptable as chronic tests according to agreed criteria [4, 10]. An SSD was then obtained from the data set

using the BurrliOz Version 2 software to derive guideline values (GVs) that were protective of 99, 95 and 90% of species (PC99, PC95 and PC90) with 50% confidence.

RESULTS AND DISCUSSION

Carbamazepine

A review of the literature found acute toxicity data reported for 6 species, and chronic toxicity for 17 species. Of these, acceptable chronic toxicity data were available for 11 species (2 cladocerans, 2 green algae, 1 blue-green algae, 1 diatom, 1 midge, 1 rotifer, 1 cnidarian and 2 fish) representing 8 taxonomic groups (Table 2). The cladoceran, *Ceriodaphnia dubia,* was the most sensitive, with an EC10 of 25 µg/L [11]. The data distribution using a Burr Type III fit in the SSD was such that it had a long tail (Figure 1), which meant that a 99% protection GV could not be determined. The 95% protection GV was 4.3 µg/L (Table 6).

Carbamazepine enters the environment largely through discharges from wastewater treatment plants, in which it is not effectively removed [12, 13]. It has been detected in discharges from German plants at concentrations up to 6.3 µg/L [14]. Loos et al. [15] reported a mean concentration of 250 ng/L (maximum 12 µg/L) in studies of 122 European river waters. Indian rivers contained 6-128 ng/L [16] while in Spanish rivers 80-3090 ng/L [17] and in the Pearl River in China, 43 ng/L [18]. It has a relative long half-life of 38 days in natural waters in the presence of sunlight, with photolysis being the major degradation pathway [12]. Tixier et al. [19] reported a half-life of 63 days in Lake Greifensee in Germany, indicating that it was relatively persistent.

In all cases, detected concentrations in receiving waters were below the derived GV. The guidelines recommended in Switzerland and Germany [20, 21] are considerably lower

(Table 7). The Swiss environmental quality standard (EQS) of 0.5 µg/L was derived by applying an assessment factor of 50 to the most sensitive reliable endpoint, that for reproduction of *Ceriodaphnia dubia* (25 µg/L) [22]. The available fish data were only for a 10-d exposure and considered not acceptable for a chronic test, although in Australia and New Zealand, the 7-d test is acceptable for fish embryos and a 21-d test required for juvenile fish [4]. In the Swiss study, the scope of the data analysis included both adverse effects data and biomarker responses in contrast to our focus solely on population-relevant effects [22]. Their GV is clearly of low reliability compared to that derived in this paper. Ferrari et al. [23] using a limited dataset and a log-normal distribution in a SSD, determined 95% protection value (reported as a hazardous concentration to 5% of species, HC5) of 2.1 µg/L. (Table 7), comparable to our value of 4.3 µg/L with a large dataset.

Diclofenac

Of 13 chronic data for diclofenac, 11 had EC10 or NOEC values suitable for GV derivation. These comprised 2 cladocerans, 1 diatom, 2 green algae, 1 blue-green algae, 1 rotifer, 1 angiosperm, 1 arthropod and 2 fish, representing 8 taxonomic groups. The most sensitive species was the midge, *Chironomus tepperi* with an EC10 of 760 µg/L [5].

Schmitt-Jansen et al. [24] exposed the green alga *Scenedesmus vacuolatus* to diclofenac in ultrapure water to sunlight and noted an increase in toxicity measured as growth inhibition, with time over 6 days, with the EC50 decreasing from 46.3 mg/L to 23 µg/L after 6 days. There was a rapid decrease in diclofenac concentrations due to photodegradation and the enhanced toxicity was clearly due to the presence of degradation products. These data 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 conditions.

Concentrations in the range 310-930 ng/L have been detected in the effluents from a Swiss wastewater treatment plant, with concentrations only marginally reduced during passage through the plant [25]. Diclofenac has been detected at <1-12 ng/L in Swiss lakes and 11-310 ng/L in a nearby river [25] and from 110-220 ng/L in the Höje River in Sweden downstream of a WWTP [26]. Photolysis is the major degradation pathway with half-lives near 3 h at summer temperatures [24] (Buser et al. [25] reported 0.9 h), but up to 2 days in winter in some locations [27]. Diclofenac is ionised at the pH of most waters (pKa=4.2), so is not readily volatilised, nor does it readily attach to particulates [25].

The measured concentrations are below the GV derived in this study (Table 6), but would exceed the proposed EQS for the European Commission (reported in Europe (Johnson et al., 2013) (Table 7). A discussion paper on the EU guidelines [28] indicated that these values are derived by applying an assessment factor of 10 to the lowest acceptable NOEC, for a fish. For rainbow trout, both Schwaiger et al. [29] and Triebskorn [30] reported a LOEC of 1 µg/L for a histopathological effect, while the latter referred to a threshold of 5 µg/L for histopathological lesions. A NOEC of 0.5 µg/L was reported by Hoeger et al. [31] for monocyte infiltration/accumulation in livers of brown trout exposed to diclofenac for 21 days. They concluded that the adverse effects in various organs could 'possibly compromise fish health'. The EQS of 0.05 µg/L proposed by the Swiss Ecotox Centre [32] was based on the application of an assessment factor of 10 to the above NOEC for brown trout.

The current Australian and New Zealand approach to biomarker endpoints of this type 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 Hutchinson et al. [33] who advocated that biomarker responses or signals (such as

vitellogenin, secondary sexual characteristics, gonadosomatic index, gonad histology, plasma steroids, enzyme induction and gene expression) may provide valuable mechanistic signals to guide chronic testing for adverse effects and, at present, should not be used to directly derive water quality guidelines. Moreover, it is recognized that interpretation of many biomarkers responses in aquatic organisms is highly complex [33-35]. Acceptable population-relevant effects endpoints include survival, length, weight, development, fecundity, fertilisation rate, 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].

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.

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

194 sensitive species to fluoxetine with a NOEC was ≤0.6 µg/L. Given that NOECs are not a
195 reliable endpoint, most jurisdictions, including Australia and New Zealand, recommend the
196 use of EC/IC10 values as a more defensible alternative [4]. In the supplementary information
197 to Oakes et al. [39], the plotted dose response curve showed an IC10 of 1 µg/L and so this
198 was included in the database used in this study. Along with this species, the New Zealand
199 mud snail, *Potamopygus antipodarum* was also very sensitive (Table 4) [40, 41].

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

205

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

The high reliability GV for fluoxetine derived in this study was 1.6 µg/L for 95% species protection. No reported EQS values could be found, however, a number of studies reported predicted no effects concentrations (PNECs) for fluoxetine in surface waters. These were all obtained by applying assessment factors to the most sensitive data (Table 7). Thus Oakes et al. [39] obtained a PNEC of 0.012 µg/L by applying a factor of 50 to the *D. subspicatus* data. Montforts [49] reported a PNEC of 0.031 µg/L using a factor of 1000 with algal toxicity data. Grung et al. [50] reported a PNEC of 0.004 µg/L, while Verlicchi et al. [2] reported a PNEC of 0.05 µg/L. All of these values are conservative and of very low reliability.

Sumpter et al. [51] have discussed the fact that both vertebrates and invertebrates use serotonin as a neurotransmitter and, as such, fluoxetine as a serotonin reuptake inhibitor, may have effects on fish (and invertebrate) behaviour (e.g. swimming speed, schooling behaviour). Such non-standard endpoints have not been considered on our GV derivation.

Propranolol

Although there are published results for over 20 chronic toxicity tests, only 12 reported chronic NOEC or EC10 values, with the remainder only giving EC50 or LOEC values. Although both an EC10 and an EC5 were available for the green algae, *Desmodesmus subspicatus,* because of the greater errors around the EC5, the EC10 value was used for guideline derivation [52].

Data were obtained for 2 cladocerans, 1 diatom, 2 green algae, 1 blue-green algae, 1 rotifer, 1 angiosperm, 1 arthropod and 3 fish, representing 8 taxonomic groups. Of these, the 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 µg/L. This is
251 almost 100-fold higher than the value recommended for Switzerland [32]. Their low
252 reliability EQS of 0.16 µg/L (Ecotox Centre, 2013d) used an assessment factor of 50 applied
253 to a NOEC of 8 µg/L for *Ceriodaphnia dubia* 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 µg/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 rivers and streams receiving pharmaceutical containing effluents from WWTPs.

Acknowledgement - The present study was funded by New South Wales Environmental Trust (Project 2009/RD/0008) and the Commonwealth Scientific and Industrial Research Organisation (CSIRO; Project R-705-02- 029).

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

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Table 1. Key properties of the studied pharmaceuticals

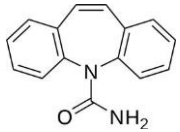
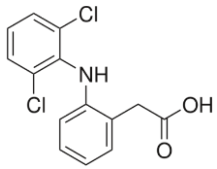
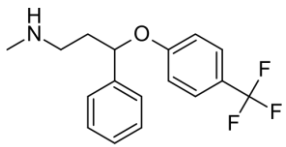
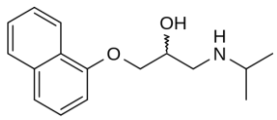
Pharmaceutical	Chemical Structure	Common name	Log K_{ow}	Solubility, mg/L	pKa	Reference
Carbamazepine (anti-convulsant and mood stabiliser)	 MW =236.3	Tegretol	2.45	112	13.9	[54]
Diclofenac (non-steroidal anti-inflammatory)	 MW=296.1	Voltarin	4.51	2,430	4.2	[54]
Fluoxetine (anti-depressant)	 MW=309.3	Prozac, Sarafem	4.05	10,800	9.4	[39, 44, 58]
Propranolol (beta-blocker)	 MW=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)	pH	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	*Pseudokirchneriella 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

Table 3. Chronic data used to derive diclofenac guideline

Taxonomic group	Common name	Scientific name	Life stage	Exposure duration (d)	Test medium	Test endpoint	Toxicity estimate	Toxicity value (mg/L)	pH	Temp (ºC)	Reference
Blue-green algae	Blue-green algae	*Synechococcus leopolensis*	-	4	Moderately hard water	Growth inhibition	NOEC	10			[54]
Green algae	Green algae	*Pseudokirchneriella 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	Reconstituted 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]

Table 4. Chronic data used to derive the fluoxetine guideline

Taxonomic group	Common name	Scientific name	Life stage	Exposure duration (d)	Test medium	Test endpoint	Toxicity estimate	Toxicity value (µg/L)	pH	Temp (°C)	Reference
Chlorophyta	Green alga	*Pseudokirchneriella subcapitata*	-	4	Moderately hard water	Growth inhibition	IC10	31.3	7.3	25	[66]
Chlorophyta	Green alga	*Pseudokirchneriella subcapitata*	-	4	Moderately hard water	Growth inhibition	LOEC	13.6	-	25	[47]
Chlorophyta	Green alga	*Pseudokirchneriella subcapitata*	-	4	Moderately hard water	Growth inhibition	IC50	27	8.1-8.5	18-22	[67]
Chlorophyta	Green alga	*Pseudokirchneriella 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]

[a]Estimated from the published dose response curve; [b]Not an acceptable endpoint as many factors can lead to malformations; [c]Juvenile 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)	pH	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	*Pseudokirchneriella subcapitata*	-	4	Moderately hard water	Growth inhibition	NOEC	5	7.8	23	[54]
Green algae	Green algae	*Pseudokirchneriella subcapitata*	-	3	Deionised water	Growth inhibition	NOEC	<0.78	-	24	[70]
							GM	**2.0**			
Green algae	Green algae	*Desmodesmus subspicatus*	-	3	Moderately hard water	Growth inhibition	EC5 EC10	0.18 0.33	7.8	23	[52]
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	Reconstituted 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	Dechlorinated 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

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] 0.05[f,j]	1.6
Propranolol	-	0.16	-		14

[a][74]; [b][32]; [c][21]; [d]HC5 (95% species protection) [e][23]; [f]PNEC values;

[g][50]; [h][39]; [h][49]; [i][2]

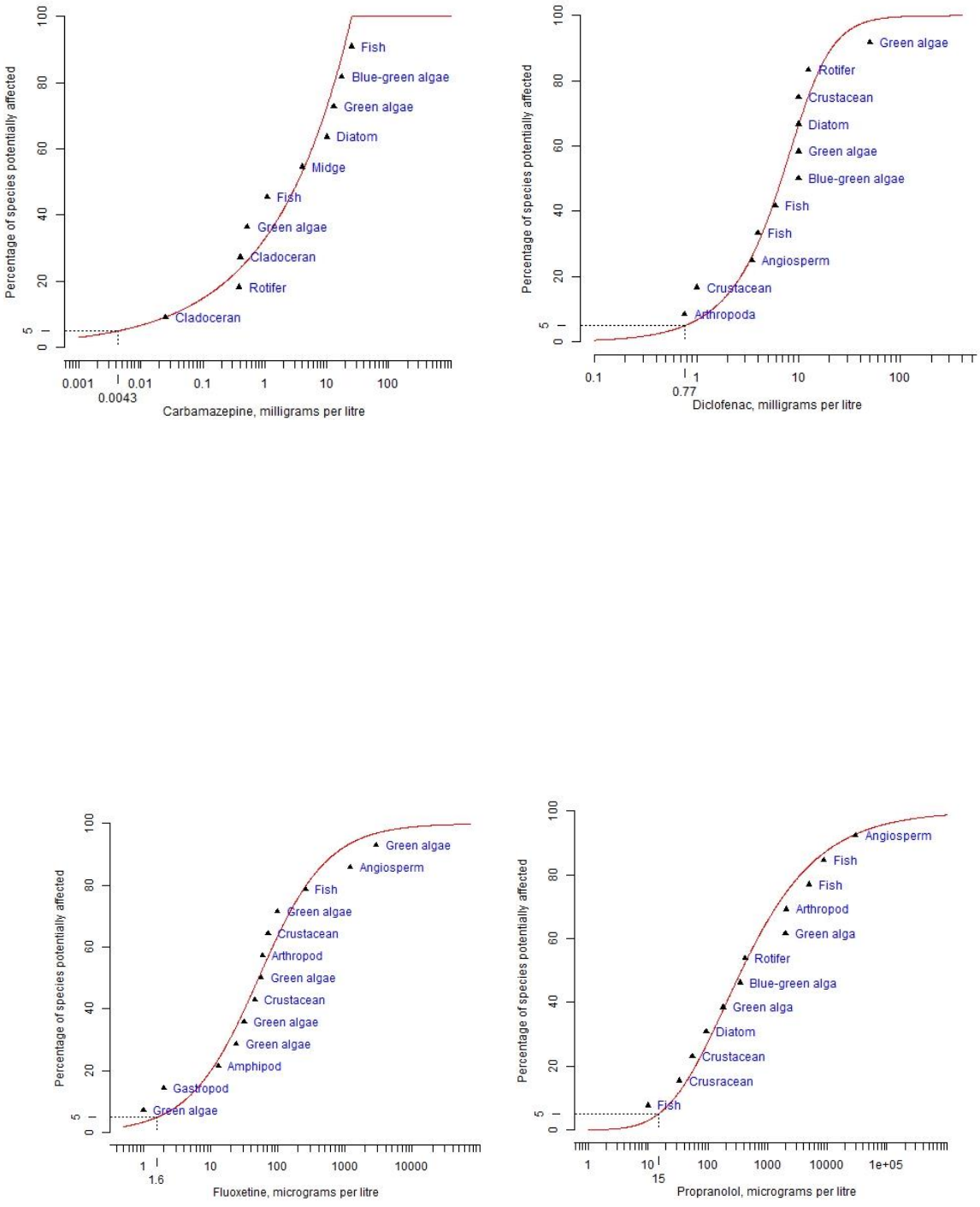


Figure 1. SSDs for carbamazepine, diclofenac, fluoxetine and propranolol