Residual pharmaceutically active compounds (PhACs) in aquatic environment – status, toxicity and kinetics: a review

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ABSTRACT: Awareness of residual pharmaceutically active compounds (PhACs) in aquatic ecosystems is growing as research into these pollutants increases and analytical detection techniques improve. For most pharmaceuticals analyzed, the effects on aquatic organisms have usually been investigated by toxic assays in the laboratory. However, little is known about integral analysis of pharmacokinetics in aquatic organisms and specific relations between pharmacokinetic parameters and influence factors. Moreover, the influence of the organisms involved and numerous other external factors complicates development of standard tests for environmental evaluation. Current knowledge about residual pharmaceuticals in the aquatic environment, including status, toxic effects, and pharmacokinetics in aquatic organisms, are reviewed. Based on the above, we identify major gaps in the current knowledge and some directions for future research, such as improvement of techniques to remove residual pharmaceuticals from wastewater, and the establishment of standard pharmaceutical modes of action.

Keywords: residual PhACs; aquatic environment; status; toxicity; kinetics

Contents

1. INTRODUCTION

In recent years, potential risks associated with the release of pharmaceutically active compounds (PhACs) into the aquatic environment have become an increasingly important issue for environmental regulators and the pharmaceutical industry (Jorgensen and Halling-Sorensen, 2000; Crane et al., 2006; Wilga et al., 2008). It is estimated that worldwide consumption of active compounds amounts to some 100 000 tons or more per annum (Kummerer, 2004), with about 3000 different substances being used in medicine in the European Union (EU). The major entry route for PhACs into

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the aquatic environment is release from wastewater treatment works. Several investigations have shown that substances of pharmaceutical origin are often not eliminated during wastewater treatment, and also not biodegraded in the environment (Ternes, 1998; Daughton and Ternes, 1999; Zwiener and Frimmel, 2000). Other sources include PhACs used in intensive farming as veterinary drugs and feed additives in livestock breeding, especially in aquaculture, and these have become a considerable pollution source (Wollenberger et al., 2000; Heberer, 2002).

Due to the conservative nature of physiological processes, chemicals affect several aquatic species (e.g. algae, invertebrate and fish) in a manner similar to their effects on humans due to comparable target molecules (Huggett et al., 2003; Fent et al., 2006; Sumpter, 2008). Although several PhACs are unlikely to result in lethal toxicity in aquatic organisms because of low concentrations combined with low toxicity, prolonged exposure may lead to observable toxic effects. Up until now, a number of acute toxic reports have been published for different PhACs, but information on chronic toxic tests is relatively sparse. Moreover, this data alone may not be suitable for specifically addressing the questions of environmental effects. In order to judge the effects of pharmaceutical residues in aquatic systems, a new parameter, the ratio between acute and chronic toxicity (ACRs), which can show the sensitivity degree of tested organisms to some pollutants, has gradually gained great attention (Jjemba, 2006). These data have been thoroughly reviewed by Crane et al. (2006), and they are therefore not included in this paper.

To minimize the environmental effects of PhACs present in the aquatic environment, it is necessary to limit release of the residue chemical used in aquaculture and to know correct dosages for successful treatment and to minimise environmental hazards. Therefore, knowledge on the pharmacokinetic properties of the chemicals in the actual species is vital. A number of studies have addressed the kinetics of pharmaceuticals, such as enrofloxacin, flumequine, oxolinc acid and oxytetracyline, commonly used in aquaculture (Stoffregen et al., 1997; Hansen et al., 2003; Ueno et al., 2004; Fang et al., 2008). However, extrapolation of pharmacokinetic data obtained in one species to another species should be treated with caution, because pharmacokinetics parameters may be affected by factors such as tested species, water temperature, route of administration, and other experimental conditions (Samuelsen, 2006). Characterization of the pharmacokinetics of a chemical in fish is useful for estimation of the bioconcentration factor and half-life (Haug and Hals, 2000). Compartmental models that assume the fish to behave as one or more well-stirred compartments are the most common type of pharmacokinetic model used (Rigos et al., 2003; Zhang and Li, 2007). On the other hand, little is known about integral analysis of pharmacokinetics in aquatic organisms and specific relations between the pharmacokinetic parameters and influence factors.

The objective of this review is to briefly summarise the current status of residue PhACs in the aquatic environment, review available information about its toxic effects, and generally discuss pharmacokinetics in aquatic organisms. We also focus on major gaps in the current knowledge and future research needs.

2. Current status of residue PhACs in the aquatic environment

The occurrence of PhACs in the aquatic environment has been investigated in several studies in Austria, Brazil, Canada, Croatia, England, Germany, Greece, Italy, Spain, Switzerland, The Netherlands and the U.S (Jorgensen and Halling-Sorensen, 2000; Crane et al., 2006; Santos et al., 2007; Wilga et al., 2008).

PhACs are excreted in their native form or as metabolites and enter aquatic systems through different routes. Release from wastewater treatment works, mentioned above as the most important entry route, is attributed to the unmodified passing of large proportions of medication through patients' bodies, ending in urine and faeces occurring in wastewater (Bound and Voulvoulis, 2004). PhACs not completely degraded in sewage treatment plants (STPs) are discharged in treated effluents, resulting in the contamination of the aquatic environment. Where sewage sludge is applied to agricultural fields, contamination of soil may occur (Fent et al., 2006). Furthermore, modern intensive farming practices contribute to the total discharge, e.g., 200 tonnes of antibiotics have been administered annually in Denmark for therapy and as growth promoters in livestock (Wollenberger et al., 2000). PhACs in groundwater may, however, also come from other sources, such as landfill leachates (Eckel et al., 1993; Holm et al., 1995), or manufacturing residues (Reddersen et al., 2002). Although Figure 1 briefly shows possible sources and destinations of pharmaceutical residues in the aquatic environment, the available information is inconclusive and our understanding remains incomplete.

In wastewater treatment two elimination processes are important: adsorption and biodegradation. In general, adsorption of acidic pharmaceuticals to sludge is suggested to be secondary for the elimination of pharmaceuticals from wastewater and surface water (Ternes et al., 2004; Urase and Kikuta, 2005). However, some pharmaceuticals and zwitterions are capable of adsorbing large amounts of sludge, as has been shown for fluoroquinolone antibiotics (Golet et al., 2002). When a pharmaceutical is occurring mainly in the dissolved phase, biodegradation is suggested to be the most important elimination process in wastewater treatment. It can occur either in aerobic (and anaerobic) zones in activated sludge treatment, or anaerobically in sewage sludge digestion (Vieno et al., 2007). In addition, biological decomposition of micro-pollutants, including PhACs, increases with an increase in hydraulic retention time. In surface waters, biotic transformation reactions are probably more important than biotransformation such as photodegradation. Photolysis has been shown to be the main removal process for diclofenac in surface water (Buser et al., 1998).

3. Toxicity of residue PhACs on aquatic organisms

Although pharmaceuticals are designed to positively affect the health of humans or animals by affecting their physiological state in a very specific and efficient manner, they often have substantial adverse effects. When introduced into the aquatic environment, they may affect lower animals with identical or similar target organs, tissues, cells or biomolecules (Fent et al., 2006). Nevertheless, certain receptors in lower animals resembling those in humans are different or are completely lacking, which means that dissimilar modes of actions may

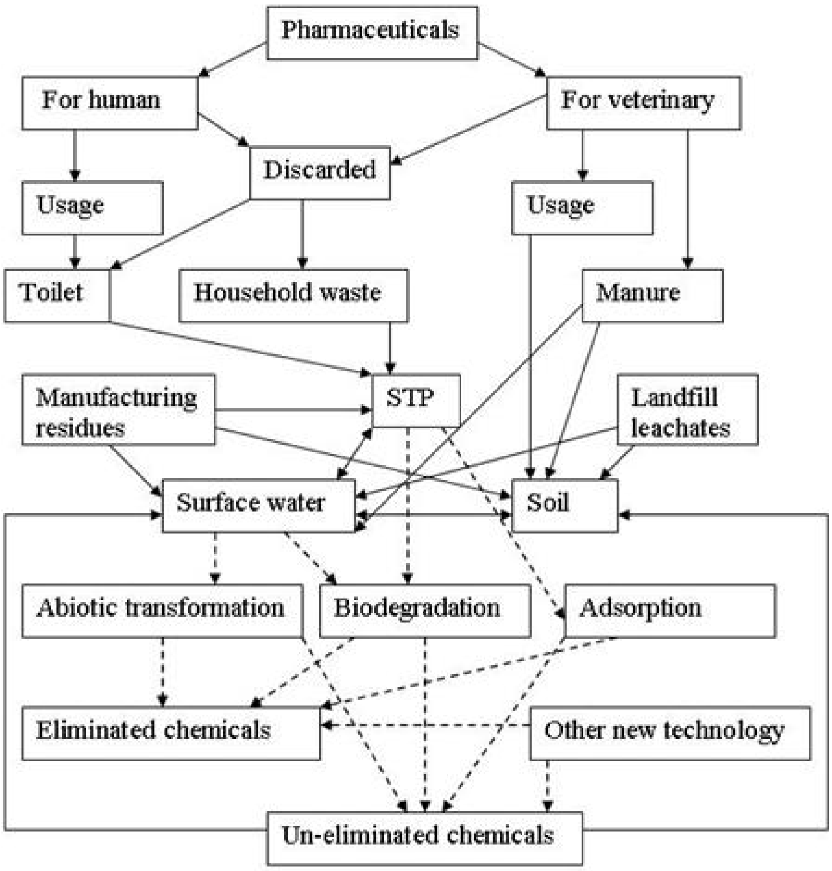

Figure 1. Possible sources and destinations of pharmaceutical residues in the aquatic environment (→ sources, ⇢ destination)

occur (Bolis et al., 2001; Bound and Voulvoulis, 2004).

It is well known that acute toxicity for aquatic organisms is unlikely to occur at the lower measured environmental concentrations. However, due to toxic effects caused by prolonged exposure to low concentrations, evaluation of the chronic potential of pollutants is crucial. Natural and synthetic steroids, particularly the oral contraceptive 17α-ethinyloestradiol, have presented the most prominent evidence of potential adverse effects (Thorpe et al., 2003). Knowledge of the chronic effects of most other PhACs is missing.

Current evaluation to assess the toxicity of pharmaceuticals to aquatic organisms requires 24 h to 96 h tests in which the test object is exposed to a constant chemical concentration for the duration of the test, according to guidelines of the Organization for Economic Cooperation and Development (OECD), United States Environmental Protection Agency (U.S.EPA), European Economic Community (EEC), and International Organization for Standardization (ISO).

Toxic effects of several pharmaceuticals on different species are summarized in Table 1.

3.1 Acute and chronic toxic effects

3.1.1 Algae

Most aquatic toxicity data for pharmaceuticals used by humans are evaluated with algae, probably related to financial considerations and convenience. Based on Table 1, algal species are sensitive to several different pharmaceuticals. Evidence is presented that the 72h-IC 50 of some antibiotics on *P. subcapitata* is always < 1 mg/l, the lowest being 0.002 mg/l. As expected, different chemicals lead to differences in toxicity for the same species, and the degree of sensitivity of different species exposed to the same chemical varies.

3.1.2 Invertebrates

Invertebrates, especially daphnids, are usually used as bio-indicator of residual pharmaceutical in the aquatic environment. This is related to the higher sensitivity of planktonic metamorphosis to pollution than other existing biological individuals. The information presented in Table 1 shows that some invertebrate taxa (*T. battagliai, R. filiformis* and *B. sowerbyi*) are more susceptible than others. Different results can be attributed to different experimental protocols, even when chemicals and test objects were similar. Huggett et al. (2002), evaluating the acute toxic effects of propranolol on *D. magna* according to the standard testing procedures of the U.S. EPA, found a 48h-EC50 value of 1.6 mg/l. However, Cleuvers (2003) obtained a value 7.5 mg/l when using the EEC Directive 92/69/EEC. The same phenomenon was found for the effect of clofibric acid, carbamazepine and metoprolol on *D. magna.*

Sediments may act as a sink for contaminants, including pharmaceuticals, and provide a continuous chronic source of these to sediment-dwelling organisms, including invertebrates. However, few studies have been performed to evaluate the influence of pharmaceuticals on sediment-dwelling organisms, such as benthic invertebrates (Drewes et al., 2002; Heberer, 2002).

3.1.3 Fish

Aquatic vertebrates, especially fish, are highly sensitive to endocrine modulation (Desbrow et al., 1998; Vos et al., 2000). Sensitivity can manifest itself through reduced fecundity, which means that partial life-cycle studies, such as the "fish early life stage" (ELS) test, may ignore important effects (Crane et al., 2006). Toxic effects of PhAC's on several fish species are indicated in Table 1.

Though there is little evidence of any direct adverse effects of residual pharmaceuticals in the aquatic environment on vertebrates such as fish at environmentally realistic concentrations, the ecotoxicological effects on fish should not be ignored. Several pharmaceuticals do have the potential to bioaccumulate through the food chain. Some researchers suggest that pharmaceuticals that are not retained by STWs, e.g., indomethacin, naproxen, salicylates, clofibric acid, carbamazepine, and iodocontrast agents, should be investigated for their long-term ability to impact fish health status (Brown et al., 2004).

Increasingly, concerns over chemicals present in the aquatic environment have led to intensive research programs to establish fish reproductive and developmental toxicity tests for use in environmental risk assessment, including fish screening assays, "partial life-cycle" and "full life-cycle" tests (Hutchinson et al., 2003). Critical factors for evaluation include baseline reproductive biology, and definition of chemical sensitive life-stages. In addition, biomarker responses of tested fish (e.g., vitellogenin, gonadal-somatic index, and gonad histopathology) should be used to provide mechanistic data.

3.2 Acute-to-chronic ratios

When carrying out environmental risk assessment, the ratio between acute and chronic toxicity is of considerable importance. This is because consistent acute-to-chronic ratios (ACRs) allow use of acute data, with application of an appropriate assessment factor, as surrogates for chronic data (Crane et al., 2006). The ACRs are able to show the sensitivity degree of tested organisms to some pollutants; large values indicate that the progression from a slight toxic effect to an apparent toxic effect is more concealed and can be missed. Thus, ACRs result in the early detection of the potential danger of chemicals. From Table 1 it is evident that ACRs for sex hormones and β-adrenergic receptor blockers are very high in fish, with low values found for the influence of sertraline hydrochloride on algae, sertraline hydrochloride on *P. subcapitata*, and 4-*t*-pentylphenol on *O. latipes*.

There is little evidence from the available data on ACRs of a general need to perform chronic tests for all pharmaceuticals on aquatic organisms. However, more ACR data are required for the main classes of therapeutic pharmaceuticals and modes of action before this issue can be fully resolved. Chronic fish tests may be necessary for some substances, but it is likely that these can be focused more accurately through use of mammalian toxicity datasets.

4. Pharmacokinetics in aquatic organisms

Critical aquatic diseases have led to the use of several pharmaceuticals in aquaculture. Evaluation of the effect of a chemical on sick as well as healthy animals during the treatment period is of utmost importance. An ideal pharmaceutical would have a large margin of safety: i.e., dosages well above recommended would still be below the toxic threshold of the host (Park et al., 1994). In contrast, a component with only a narrow margin of safety would not be desirable, since a small miscalculation in dosage could result in a more serious toxicity problem than the disease being treated. Therefore, the kinetics of pharmaceuticals after application needs to be examined in detail in order to obtain suitable dosage regimens. The efficacy, safety and residues of the pharmaceuticals have usually been estimated by kinetic analyses (Haug and Hals, 2000). Thus, pharmacokinetics in aquaculture is important in order to determine optimal dosage regimens, to establish safe withdrawal periods, and to minimize the environmental effects.

Recently several researchers have investigated pharmacokinetics in aquatic animals, mostly finfish. A few papers have concentrated on pharmacokinetics in invertebrates. No similar research has been conducted with algae, probably because of their biological characteristics and the limitation of the measurement of pharmacokinetics parameters on algae. Current knowledge about pharmacokinetics in aquatic systems is summarized in Table 2.

4.1 Pharmacokinetics models and parameters

Pharmacokinetic models are relatively simple mathematical systems that represent complex physiological processes. They provide the ability to use past experiences of the behavior of pharmaceuticals for application in future research. The most commonly used pharmacokinetic models in aquatic organisms are one-, two- and three-compartmental models. Crustaceans, including crabs and shrimp, are the preferred invertebrates used as research objects. Plasma concentration–time data has been best fitted in open two-compartmental models following intramuscular injection in species such as *P. monodon*, *L. s. setiferus* (Reed et al., 2004) and *S. serrata* (Fang et al., 2008). Whereas the pharmacokinetics of oxytetracyline in *A. anguilla* and *O. mykiss* after oral administration were described by a one compartmental model, oxytetracyline blood concentration-time curves of *O. tshawytscha* and *O. mykiss* treated through the intra-arterial route were simulated by a three-compartmental open pharmacokinetic model. A two-compartmental model was found as the most suitable to describe oxytetracyline pharmacokinetics in *O. mykiss*, *S. quinqueradiata*, *C. gariepinus* and *A.anguilla* after intravascular administration. The different models suitable for different species might be ascribed to species differences and different routes of administration. In general, the same compartmental model has been used in order to compare the pharmacokinetic parameters among species.

Table 1. Toxic effects of some pharmaceuticals on aquatic organisms

Taxonomic tested groups	Tested organisms	Pharmaceuticals	Toxic effects				ACRs	References
			acute test	values	chronic test	values		
Algae	*Chlorella vulgaris*	ciprofloxacin	96h-EC50	20.6				Nie et al., 2008
		trichloroisocyanuric acid	96h-EC50	0.313				Nie et al., 2008
	Cholorella yenoidosa	furazolidone	48h-EC50	1.3				Canton and Vanesch, 1976
		pyrimethamine	48h-EC50	20				Canton and Vanesch, 1976
		robenidine	48h-EC50	0.56				Canton and Vanesch, 1976
		stenorol	48h-EC50	46				Canton and Vanesch, 1976
	Desmodesmus subspicatus	nitrofurazone	96h-EC50	1.45				Macri and Sbardella, 1984
	Pseudokirchneriella subcapitata	clarithromycin	72h-IC50	0.002				Isidori et al., 2005
		erythromycin	72h-IC50	0.020				Isidori et al., 2005
		lincomycin	72h-IC50	0.07				Isidori et al., 2005
		oxytetracyclin	72h-IC50	0.17				Isidori et al., 2005
		ofloxacin	72h-IC50	1.44				Isidori et al., 2005
		sertraline hydrochloride	72h-IC50	0.14	NOEC LOEC	0.05 0.075	2.8	Minagh et al., 2009
		sulfamethoxazole	72h-IC50	0.52				Isidori et al., 2005
	Tetraselmis chuii	florfenicol	96h-IC50	6.06				Ferreira et al., 2007
		oxytetracycline	96h-IC50	11.18				Ferreira et al., 2007
Invertebrate	*Artemia parthenogenetica*	clofibrate	24h-LC50	87.22				Nunes et al., 2005
		cofibric acid	24h-LC50	36.6				Nunes et al., 2005
		diazepam	24h-LC50	12.2				Nunes et al., 2005
		oxytetracycline	24h-LC50 48h-LC50	871 806				Ferreira et al., 2007
		SDS	24h-LC50	12.2				Nunes et al., 2005
	Artemia salina	flumequine	24h-LC50 48h-LC50 72h-LC50	477 308 96				Migliore et al., 1997
	Brachionus calyciflorus	clarithromycin	24h-LC50 48h-IC50	35.64 12.21				Isidori et al., 2005
		erythromycin	24h-LC50 48h-IC50	27.53 0.94				Isidori et al., 2005
		lincomycin	24h-LC50 48h-IC50	24.94 0.68				Isidori et al., 2005
		oxytetracyclin	24h-LC50 48h-IC50	34.21 1.87				Isidori et al., 2005
		ofloxacin	24h-LC50 48h-IC50	29.88 0.53				Isidori et al., 2005
		sulfamethoxazole	24h-LC50 48h-IC50	26.27 0.63				Isidori et al., 2005

Table 1 continued

Taxono-mic tested groups	Tested organisms	Pharmaceuticals	Toxic effects				ACRs	References
			acute test	values	chronic test	values		
Invertebrate	*Ceriodaphnia dubia*	clarithromycin	48 h-EC50	18.66	IC50	8.61		Isidori et al., 2005
		erythromycin	48 h-EC50	10.23	IC50	0.22		Isidori et al., 2005
		lincomycin	48 h-EC50	13.98	IC50	7.20		Isidori et al., 2005
		metoprolol	48 h-LC50	8.8				Huggett et al., 2002
		ofloxacin	48 h-EC50	17.41	IC50	3.13		Isidori et al., 2005
		oxytetracyclin	48 h-EC50	18.65	IC50	0.18		Isidori et al., 2005
		sulfamethoxazole	48 h-EC50	15.51	IC50	0.21		Isidori et al., 2005
	Chironomus tentans	fluoxetine	48 h-LC50	15.2				Brooks et al., 2003
	Daphnia magna	acetaminophen	48 h-EC50 96 h -EC50	30.1 26.6				Kim et al., 2007
		captopril	48 h -EC50	> 100				Cleuvers, 2003
		carbamazepine	48 h -EC50	> 13.8				Ferrari et al., 2003
		carbamazepine	48 h -EC50	> 100				Cleuvers, 2003
		carbamazepine	48 h -EC50 96 h -EC50	> 100 76.3				Kim et al., 2007
		cimetidine	48 h -EC50 96 h -EC50	379.7 271.3				Kim et al., 2007
		clarithromycin	24 h -EC50	25.72				Isidori et al., 2005
		clofibric acid	48 h -EC50	> 200				Ferrari et al., 2003
		clofibric acid	48 h -EC50	72				Cleuvers, 2003
		diclofenac	48 h -EC50	22.4				Ferrari et al., 2003
		diclofenac	48 h -EC50	68				Cleuvers, 2003
		diltiazem	48 h -EC50 96 h -EC50	28.0 8.2				Kim et al., 2007
		erythromycin	24 h -EC50	22.45				Isidori et al., 2005
		fluoxetine	48 h -LC50	0.705				Brooks et al., 2003
		ibuprofen	48 h -EC50	108				Cleuvers, 2003
		ivermectin H_2B_{1a}	48 h -LC50	0.025 ppb	NOEC	0.01 ppb	2.5	Halley et al., 1989
		ivermectin monosaccharide	48 h -LC50	0.4 ppb	NOEC	0.1 ppb	4	Halley et al., 1989
		lincomycin	24 h -EC50	23.18				Isidori et al., 2005
		metformin	48 h -EC50	64				Cleuvers, 2003
		metoprolol	48 h -EC50	> 100				Cleuvers, 2003
		metoprolol	48 h -EC50	63.9				Huggett et al., 2002
		naproxen	48 h -EC50	174				Cleuvers, 2003
		nitrofurazone	24 h -EC50 48 h -EC50	40.04 28.67				Macri and Sbardella, 1984
		ofloxacin	24 h -EC50	31.75				Isidori et al., 2005

Table 1 continued

Taxonomic tested groups	Tested organisms	Pharmaceuticals	Toxic effects				ACRs	References
			acute test	values	chronic test	values		
Invertebrate	*Daphnia magna*	propranolol	48 h -EC50	7.5				Cleuvers, 2003
		propranolol	48 h -EC50	1.6				Huggett et al., 2002
		pyrimethamine	48 h -LC50	5.8				Canton and Vanesch, 1976
		robenidine	48 h -LC50	0.075				Canton and Vanesch, 1976
		sertraline hydrochloride	48 h -IC50 504h-LC50	1.3 0.12	NOEC LOEC NOEC LOEC	0.10 0.18 0.032 0.1	13 for 48 h 3.75 for 504 h	Minagh et al., 2009
		stenorol	48 h -LC50	0.018				Canton and Vanesch, 1976
		sulfachlorpyridazine	48 h -EC50 96 h -EC50	375.3 233.5				Kim et al., 2007
		sulfadimethoxine	48 h -EC50 96 h -EC50	248.0 204.5				Kim et al., 2007
		sulfamethazine	48 h -EC50 96 h -EC50	174.4 158.8				Kim et al., 2007
		sulfamethoxazole	24 h -EC50	25.20				Isidori et al., 2005
		sulfamethoxazole	48 h -EC50 96 h -EC50	189.2 177.3				Kim et al., 2007
		sulfathiazole	48 h -EC50 96 h -EC50	149.3 85.4				Kim et al., 2007
		trimethoprim	48 h -EC50 96 h -EC50	167.4 120.7				Kim et al., 2007
	Diaptomus forbesi	cypermethrin	24 h -LC50 48 h -LC50	0.04 µg/l 0.03 µg/l				Saha and Kaviraj, 2008
	Hyalella azteca	metoprolol	48 h -LC50	≥ 100				Huggett et al., 2002
	Palaemonetes pugio	clofibric acid			NOEC	< 1		Emblidge and DeLorenzo, 2006
	Ranatra filiformis	cypermethrin	24 h -LC50 48 h -LC50 72 h -LC50	0.12 µg/l 0.09 µg/l 0.065µg/l				Saha and Kaviraj, 2008
	Thamnocephalus platyurus	clarithromycin	24 h -LC50	33.64				Isidori et al., 2005
		erythromycin	24 h -LC50	17.68				Isidori et al., 2005
		lincomycin	24 h -LC50	30.00				Isidori et al., 2005
		ofloxacin	24 h -LC50	33.98				Isidori et al., 2005
		oxytetracyclin	24 h -LC50	25.00				Isidori et al., 2005
		sulfamethoxazole	24 h -LC50	35.36				Isidori et al., 2005
	Tisbe battagliai	17α-ethynylestradiol			NOEC	≥ 0.01		Hutchinson et al., 1999
		17β-oestradiol			NOEC	≥ 0.01		Hutchinson et al., 1999
		20-hydroxyecdysone	504 h-LC50	0.0534	NOEC	0.0269	1.98	Hutchinson et al., 1999
		oestrone			NOEC	≥ 0.01		Hutchinson et al., 1999
Fish	*Cyprinus carpio*	cypermethrin	24 h -LC50 48 h -LC50 72 h -LC50	5.2 µg/l 3.8 µg/l 2.6 µg/l				Saha and Kaviraj, 2008

Table 1 continued

Taxono-mic tested groups	Tested organisms	Pharmaceuticals	Toxic effects				ACRs	References
			acute test	values	chronic test	values		
Fish	*Danio rerio*	erythromycin	96 h -LC50	≥ 1 000				Isidori et al., 2005
		lincomycin	96 h -LC50	≥ 1 000				Isidori et al., 2005
		ofloxacin	96 h -LC33.5	1 000				Isidori et al., 2005
		oxytetracyclin	96 h -LC50	≥ 1000				Isidori et al., 2005
		sulfamethoxazole	96 h -LC50	≥ 1000				Isidori et al., 2005
	Gambusia affinis	fluoxetine	168 h-LC50	546 ppb	NOEC	5.0ppb	109.2	Henry and Black, 2008
	Gambusia holbrooki	clofibrate acid	96-h LC50	7.7				Nunes et al., 2004
	Lepomis macrochines	ivemectin	96 h -LC50	4.8				Halley et al., 1989
	Lebistes reticulates	furazolidone	96 h -LC50	25				Canton and Vanesch, 1976
		pyrimethamine	48 h -LC50	7.5				Canton and Vanesch, 1976
		robenidine	48 h -LC50	0.2				Canton and Vanesch, 1976
		stenorol	48 h -LC50	1.6				Canton and Vanesch, 1976
	Oryzias latipes	4-*t*-pentylphenol	96 h -LC50	2.6	NOEC LOEC	0.001 0.01	2 600	Hutchinson et al., 2003
		fluoxetine	96 h -LC50 96 h -LC50 96 h -LC50	5.5 (pH = 7) 1.3 (pH = 8) 0.2 (pH = 9)				Nakamura et al., 2008
		metoprolol	48 h -LC50	> 100				Huggett et al., 2002
		propranolol	48 h -LC50	24.3				Huggett et al., 2002
		sulfachlorpyridazine	48 h -LC50 96 h -LC50	589.3 535.7				Kim et al., 2007
		sulfamethoxazole	48 h -LC50 96 h -LC50	> 750 562.5				Kim et al., 2007
	Oncorhynchus mykiss	furazolidone	48 h -LC50	≥ 30				Canton and Vanesch, 1976
		ivemectin	96 h -LC50	3.0				Halley et al., 1989
		pyrimethamine	48 h -LC50	5.9				Canton and Vanesch, 1976
		robenidine	48 h -LC50	0.075				Canton and Vanesch, 1976
		sertraline hydrochloride	96 h -LC50	0.38	NOEC LOEC	0.1 0.32	3.8	Minagh et al., 2009
		stenorol	48 h -LC50	2.9				Canton and Vanesch, 1976
	Pimephales promelas	atenolol			NOEC LOEC	1.0 3.2		Winter et al., 2008

Toxicity in mg/l unless otherwise stated. LC50 = concentration that caused 50% of death, IC50 = concentration that caused 50% of inhibition, EC50 = concentration that caused 50% of effect, NOEC = no observed effect concentration, LOEC = lowest observed effect concentration. ACRs=LC50 (or IC50 or EC50)/NOEC

Pharmacokinetics is based on the study of the variation of concentrations of PhACs in the body, because it is the only easily accessible parameter. The distribution ($t_{½}\alpha$) and elimination ($t_{½}\beta$) half-life is the time needed to divide the concentration in two. These parameters are useful for the determination of the frequency of administration of pharmaceuticals to obtain the desired plasma concentration, but could vary with dosage. According to Table 2, $t_{½}\alpha$ and $t_{½}\beta$ of oxolinc acid in *S. salar* increased along with increasing dosage. Bioavailability (F) indicates the percentage of the administered pharmaceuticals that arrives in the central compartment, and is influenced by the method of administration. It is demonstrated in Table 2 that F of a pharmaceutical is higher after intravenous compared to oral administration. The apparent volume of distribution at a steady state (V_{dss}) is an estimate of the pharmaceutical distribution independent of elimination processes. It is most useful for predicting the concentrations following multiple treatments to a steady-state or pseudo-equilibrium. Total clearance (Cl_t) is described as the fraction of the volume of distribution, which is a constant in linear kinetics for a pharmaceutical in a test organism, and cannot be influenced by dosage.

4.2 Factors that have an influence on pharmacokinetics

Differences in anatomy and physiology result in differences in pharmacokinetics between invertebrates and vertebrates. Some researchers have suggested that differences in certain pharmacokinetic parameters among species might be explained by differences in anatomical volumes and plasma protein and tissue binding of pharmaceuticals (Oie and Tozer, 1979; Barron et al., 1988). Shell and haemolymph (blood) volumes are the most pronounced differences between crustaceans and finfish. The shell, which is absent in finfish, has been demonstrated to be a site of pharmaceutical deposition in crustaceans (Barron et al., 1988, 1991). Furthermore, in crustaceans the volume of haemolymph comprises 22% of the total body weight, compared to 5% in finfish (Barron et al., 1988; Plakas et al., 1990), with the volume of distribution directly related to tissue binding and inversely related to plasma protein binding. Protein binding in finfish is always higher than that found in crustaceans, e.g., 23 and 14–21% in *P. japonicus* (Uno, 2004) and *P. setiferus* (Reed et al., 2004), respectively, compared to 51–55% in *O. mykiss* (Bjorklund and Bylund, 1991; Uno et al., 1997) and 68% in *P. altivelis* (Uno, 1996). A diminished binding of plasma protein results in an increase in extravascular distribution. From Table 2 it can be concluded that some pharmacokinetic parameters for the volume of distribution are less in crustaceans than finfish, e.g., with oxolinc acid injected intravascular at a similar dosage, $t_{½}\alpha$ and $t_{½}\beta$ values in *P. japonicus* and *P. monodon* were less than those found in the finfish *H. hippoglossus*. However, with oxytetracyline treatment $t_{½}\alpha$ and $t_{½}\beta$ values were larger in finfish than crustaceans. Fang et al.(2008) considered an open circulatory system in crustaceans, as contrasted to closed systems in finfish, as another reason for differences in certain pharmacokinetic parameters between crustaceans and finfish.

There is evidence to suggest that varied routes of administration of a pharmaceutical result in different pharmacokinetic parameters in the same aquatic animal. Routes commonly used include oral, intravascular injection, and bath treatment. In theory almost all treatments can be administered by injection. However, injection of individual fish is time-consuming. Bath treatment, although easy to apply with agents of high solubility in water, is restricted to recirculating systems or tanks of limited size. Oral administration allows the easy treatment of large numbers of adult fish at low labour costs, and has become the prime route of fish medication (Samuelsen, 2006). According to current knowledge, $t_{½}\alpha$ and $t_{½}\beta$ are always longer after oral as compared to intravascular administration. In contrast, F is usually higher after intravascular compared to oral administration. Bath treatment always presents a lower C_{max} (maximum concentration in the body) than other routes of administration (Table 2).

Environmental factors have significant and variable effects on the rates of absorption and elimination of pharmaceuticals in aquatic organisms. Distribution and elimination are influenced by, among other factors, water temperature. Values for $t_{½}\alpha$ and $t_{½}\beta$ of enrofloxacin were higher at 19 than 26°C for *S. serrata*, a crustacean (Table 2). A similar tendency was found for fish, with $t_{½}\alpha$ and $t_{½}\beta$ in *C. idella* at 21°C shorter than values found for *O. tshawytscha* and *O. mykiss* at 11°C. Furthermore, pharmacokinetic parameters of oxolinc acid after intravascular administration in *H. hippoglossus* were different at water tempera-

Table 2. Kinetics parameters of some pharmaceuticals in aquatic organisms

Pharmaceuticals	Tested organisms		Pharmacokinetics parameters										References
	Taxon	*Species*	via	C_{max}	T_{max}	$t_{½}α$	$t_{½}β$	V_{dss}	Cl_T	MRT	F	Condition	
Enrofloxacin	Invertebrate	*Scylla serrata*	*p.o.* 19°C	7.26	6	5.0	79.1	1 637	16			oral (*p.o.*) 10 mg/kg bw at 19 and 26°C	Fang et al., 2008
			p.o. 26°C	11.03	2	1.5	56.5	1 111	18				
Ormetoprim		*Penaeus vannamei*	*i.s.*			0.49	17.8	34 382	1 765		32	intra-sinus (*i.s.*) 8.6 mg/kg bw; *p.o.* 41.7 mg/kg bw; 26°C	Park et al., 1995
			p.o.	0.70	4		8.3						
Oxolinc acid		*Penaeus japonicus*	*i.s.*	28.0	0	0.59	33.2	1 309	348			*i.s.* 10.0 mg/kg bw; *p.o.* 50 mg/kg bw; 25°C	Uno, 2004
			p.o.	17.8	7		34.3			40.3	32.9		
		Penaeus monodon	*i.v.*	13.8	0	0.84	17.7	2 061	90.1			intravascular (*i.v.*)10 mg/kg bw; *p.o.* 50 mg/kg bw; 28–29°C	Uno et al., 2006
			p.o.	4.20	4		19.8			20.9	7.9		
Oxytetracyline		*Litopenaeus setiferus*	*i.v.*			2.05	22.27	2 302	78.04			*i.v.* 11.1 mg/kg bw; 20°C	Reed et al., 2004
		Limulus polyphemus	*i.v.*	55.90			128.3	1 164	44	443.65		*i.v.* 25 mg/kg bw; *p.o.* 25 mg/kg bw; 19–22°C	Nolan et al., 2007
			p.o.	7.83			210.0	1 688	71	395.89	61.56		
		Litopenaeus vannamei	*i.v.*	32.22	0	0.23	16.42	1 140				*i.v.* 10 mg/kg bw; 28°C	Chiayvareesajja et al., 2006
		Penaeus japonicus	*i.s.*	158.8	0	0.45	24.7	748	22.7			*i.s.* 25.0 mg/kg bw; *p.o.* 50 mg/kg bw; 25°C	Uno, 2004
			p.o.	24.3	10		33.6			48.6	43.2		
		Penaeus monodon	*i.v.*			0.89	23.1	410	13.2	29.4		*i.v.* 10 mg/kg bw; *p.o.* 10 mg/kg bw; 30°C	Sangrungruang et al., 2004
			p.o.			4.08	6.93	1 430		20			
		Penaeus vannamei	*i.s.*	32.22	0		80.7		35		100	*i.s.* 10.0 mg/kg bw; *p.o.* 51.4 mg/kg bw; 28°C	Faroongsamg et al., 2007
			p.o.	43.52	7.0		91.9		35		80.62		
Sulphadimethoxine		*Penaeus vannamei*	*i.s.*			3.15	9.0	1 319	215		30	*i.s.* 42 mg/kg bw; *p.o.* 208.7 mg/kg bw; 26°C	Park et al., 1995
			p.o.	25.0	4		5.3						

Table 2 continued

Pharmaceuticals	Tested organisms		Pharmacokinetics parameters										References
	Taxon	*Species*	via	C_{max}	T_{max}	$t_{½}α$	$t_{½}β$	V_{dss}	Cl_T	MRT	F	Condition	
Astaxanthin	Fish	*Salmo salar*	oil *p.o.*	0.097	24		13.2				12	a single dose of astaxanthin in sesame oil or in gelatin via *p.o.* or intraperitoneal (*i.p.*); 9–12°C	Maltby et al., 2003
			oil *i.p.*	0.047	48		30.5				8.7		
			gel. *p.o.*	0.13	30		16.8				53.5		
			gel. *i.p.*	0.21	48		299.8				38.7		
Enrofloxacin		*Dicentrarchus labrax*	*p.o.*	1.39	8	6.03	25.02			43.48		*p.o.* 5 mg/kg bw; 15°C	Intorre et al., 2000
		Salmo salar	*i.v.*	2.17	3	1.4	34.2	6 100	140			*i.v.* 10 mg/kg bw; *p.o.* 10 mg/kg bw; 10°C	Martinsen and Horsberg, 1995
			p.o.	1.54	6						55.5		
		Salmo salar	*i.a.*	50 454	0	0.43	130.6	21 530	118.5	181.5	100	intraarterial (*i.a.*), *i.p.*, and intramuscular (*i.m.*) 10 mg/kg bw; and *p.o.* 5 and 10 mg/kg bw; 9.7°C	Stoffregen et al., 1997
			i.p.	1.48	1.29	0.17	34.32	6 608	132.8	49.76	89.34		
			i.m.	0.4525	0.288	0.025	84.98	22 050	179.8	122.6	65.97		
			p.o. 10	0.27	0.4213	0.037	105.1			151.7	49.44		
			p.o. 5	0.54	2.87	0.41	48.24			70.20	46.04		
		Sepia officinalis	*i.v.*			0.47	1.81	385.2	282.6	1.36		*i.v.* 5 mg/kg bw; *p.o.* 10 mg/kg bw; bath at 2.5 mg/l water for 5 h; 25°C	Gore et al., 2005
			bath	0.51	0.50		1.01			1.71			
			p.o.	10.95	1		1.01			1.94			
Eugenol		*Oncorhynchus mykiss*	bath	10.53			12.14					bath at 75 mg/l for 15 min,4°C	Guenette et al., 2007
Florfenicol		*Cyprinus carpio*	*p.o.*	12.3	3	7.6				15.4	29	*i.v.* 25 mg/kg bw; *p.o.* 50 mg/kg bw; 23–25°C	Yanong et al., 2005
			i.v.	18.0	24	13.9		1 000	50	40			
		Trichogaster trichopterus	*p.o.*	2.6	5.0	6.6				13.0	13	*i.v.* 25 mg/kg bw; *p.o.* 50 mg/kg bw 23–25°C	Yanong et al., 2005
			i.v.	28.0	3.0	2.5		2 000	320	4.8			
Flumequine		*Anuilla anguilla*	*i.v.*	9	75	33.2	256		35			*i.v.* 9.0 mg/kg bw; 23°C	Boon et al., 1991
		Angguilla anguilla	*i.v.*	11.2	0		314	3 400	12	283		*i.v.* 10 mg/kg bw; *p.o.* 10 mg/kg bw; 23°C	Hansen and Horsberg, 2000b

Flu-mequine	Fish	*Ctenolabrus rupestris*	*i.v.*				31	2 150	140	16		*i.v.* 10 mg/kg bw; *p.o.* 10 mg/kg bw; 14.5°C	Hansen and Horsberg, 2000a
			p.o.	1.7	1		41				41		
		Dicentrarchus labrax	*i.v.*	11.617	0.5	1.05	10.71	1 510	156	9.73		*i.v.* 10.0 mg/kg bw; 18°C	Rigos et al., 2002b
		Gadus morhua	*i.v.*				75	2 400	24	99		*i.v.* 5 mg/kg bw; *p.o.* 10 mg/kg bw; 8°C	Hansen and Horsberg, 2000a
			p.o.	3.5	24		74				65		
		Hippoglossus hippoglossus	*i.v.*				32	2 990	120	25.1		*i.v.* and *p.o.* at 10 mg/kg bw; bath at 10 mg/l water for 2 h; 18°C	Hansen and Horsberg, 1999
			p.o.	1.4	7		43				56		
			bath	0.08	0						5		
		Ictalurus punctatus	*i.v.*	3.01	14		25	530	15		44	*i.v.* 1.0 mg/kg bw; 24°C	Plakas et al., 2000
		Salmo salar	*i.v.*	4.86	0.5	1.3	23		95			*i.v.* 4.9 mg/kg bw; *p.o.* 25 mg/kg bw; 5°C	Rogstad et al., 1993
			p.o.	2.26	12						46		
		Salmo salar	*i.v.*	9.51	3	3.1	22.8	3 500	180			*i.v.* 25 mg/kg bw; *p.o.* 25 mg/kg bw; 10.2°C	Martinsen and Horsberg, 1995
			p.o.	1.42	6						44.7		
		Scophthalmus maximus	*i.v.*				34	3 750	170	22.2		*i.v.*and *p.o.* at 10 mg/kg bw; bath at 10 mg/l water for 2 h; 10.3°C	Hansen and Horsberg, 1999
			p.o.	1.9	7		42				59		
			bath	0.13	3								
Methyl-testosterone		*Oncorhynchus mykiss*	*i.a* .2			4.13	54.9	6 060	640	9.57		*i.a.* 2 and 20 mg/kg bw; *p.o.* 30 mg/kg bw; 15°C	Vick and Hayton, 2001
			i.a. 20			8.23	58.6	26 800	903	22.7			
			p.o. 30	3.03	8.8				1190	13.8	73.1		
Metomidate		*Hippoglossus hippoglossus*	*i.v.*	5.78	0.33		5.8	210	99			*i.v.* 3 mg/kg bw; 10.3°C	Hansen et al., 2003
		Scophthalmus maximus	*i.v.*	2.6	0.33		2.2	440	260			*i.v.* 3 mg/kg bw; *p.o.* 7 mg/kg bw; 18°C	Hansen et al., 2003
			p.o.	7.8	1		3.5				100		
Morphine sulfate		*Oncorhynchus mykiss*	*i.p.*	87	1	1.43	13.9		153	7.0		*i.p.* 40 mg/kg bw; 10°C	Newby et al., 2006

Table 2 continued

Pharma-ceuticals	Tested organisms		Pharmacokinetics parameters										References
	Taxon	Species	via	C_{max}	T_{max}	$t_{1/2}\alpha$	$t_{1/2}\beta$	V_{dss}	Cl_T	MRT	F	Condition	
Morphine sulfate	Fish	*Pseudopleuronectes americanus*	*i.p.*40	87	1	2.2	34.1		75.6	27.9		*i.p.* 40 mg/kg bw and 7.5 mg/kg/day for 4 days; 10°C	Newby et al., 2006
			i.p. 7.5×4				19.1	1 420		29.3			
Oxolinc acid		*Dicentrarchus labrax*	*i.v.*	20.39	1	0.69	17.77	2 690	64	42.27		*i.v.* 10 mg/kg bw; 15.2°C	Poher et al., 1997
		Gadus morhua	*i.v.*	1.2		1.3	84	5 500	47	116		*i.v.* 12.5 mg/kg bw; *p.o.* 25 mg/kg bw; 8°C	Samuelsen et al., 2003a
			p.o.	2.5	24		82				55		
		Hippoglossus hippoglossus	*i.v.*	5.82	3	7	52	3 000	44	67		*i.v.* 10 mg/kg bw; *p.o.* 25 mg/kg bw; *i.p.* 25 mg/kg bw; 9°C	Samuelsen and Ervik, 1999
			i.p.	2.7	80		50				92		
			p.o.	1.2	21.5		48				15		
		Ictalurus punctatus	*i.v.* 14°C	3.7	24	0.68	69.3	880	8.9		91.8	*i.v.* 5 mg/kg bw; 14 and 24°C	Kleinow et al., 1994
			i.v. 24°C	301	8		40.9	939	16.3		56.0		
		Oncorhynchus mykiss	*i.v.* f.w.	15.0	0.25	0.5	52.6	2 900	50	59		*i.v.* 10 mg/kg bw in fresh water and sea water; 8.5°C	Hustvedt and Salte, 1991
			i.v. s.w.	18.5	0.25	0.2	29.1	2 600	83.3	37			
		Oncorhynchus mykiss	*i.v.*			0.15	81.3	1 817	16.9		90.7	*i.v.* 5 mg/kg bw; 14°C	Kleinow et al., 1994
		Salmo salar	*i.v.*	3.58	0.5	0.7	10		204			*i.v.* 4.9 mg/kg bw; *p.o.* 25 mg/kg bw; 5°C	Rogstad et al., 1993
			p.o.	0.99	24						40		
		Salmo salar	*i.v.*	3.54	6	4.7	18.2	5 400	280			*i.v.* 25 mg/kg bw; *p.o.* 25 mg/kg bw; 10.2°C	Martinsen and Horsberg, 1995
			p.o.	0.61	12						30.1		
		Salmo salar	*i.v.*	2.51	1.5	1	15	5 700	400	14		*i.v.* 20 mg/kg bw; *p.o.* 40 mg/kg bw; 10°C	Samuelsen et al., 2000
			p.o.	0.5	19		18				25		
		Sparus aurata	*i.v.*	36.27	0.5	0.51	12.60	2 110	150	14.25		*i.v.* 20 mg/kg bw; *p.o.* 30 mg/kg bw; 20°C	Rigos et al., 2002a
			p.o.	0.99	24						14		
Oxytetracyline		*Anguilla anguilla*	*p.o.*	380	1	2.08	115	450	2.98	126		*p.o.* 50 mg/kg day for 7 days; 28°C	Ueno et al., 2004
		Ctenopharyngodon idellus	*p.o.*	4.99	5.69	5.45	83.66			124.71		*p.o.* 100 mg/kg bw; 21°C	Zhang and Li, 2007
		Oncorhynchus mykiss	*i.v.*			1.528	60.3	1 170	16.2	79.3		*i.v.* 20 mg/kg bw; 16°C	Bjorklund and Bylund, 1991

Oxytetracyline	Fish	*Oncorhynchus mykiss*	*i.a.*			0.74	18.95		6.43			*i.a.* and *p.o.* in 50 mg/kg bw; 11°C	Abedini et al., 1998
			p.o	5.77	18.17	40.03	479.43				30.30		
		Oncorhynchus tshawytscha	*i.a.*			0.62	6.79		7.02			*i.a.* and p.o. in 50 mg/kg bw; 11°C	Abedini et al., 1998
			p.o.	5.32	17.88	72.51	428.19				24.84		
		Salvelinus apinus	*i.v.* 10			1.5	266.3	1 980	6.54	301.2		*i.v.* 10 and 20 mg/kg; 6.3°C	Haug and Hals, 2000
			i.v. 20			1.8	326.9	2 140	6.27	357.1			
			p.o. 50	1.51	30.3		367.0				4.2	*p.o.* 50 and 100 mg/kg; 6.3°C	
			p.o. 100	3.93	17.8		444.2				7.3		
		Sparus aurata	*i.v.*	2.5	24	2	53	2 900	50	56		*i.v.* 40 mg/kg bw; 20°C	Rigos et al., 2003
Ormetoprim		*Salmo salar*	*i.v.*				22		100		100	*i.v.* 5 mg/kg bw; *p.o.*5 mg/kg bw; 10°C	Horsberg et al., 1997
			p.o.	1.44	12		17		117		85		
Sarafloxacin		*Anguilla anguilla*	*p.o.*	2.64	12		30					*p.o.* 15 mg/kg bw; 24°C	Ho et al., 1999
		Salmo salar	*i.v.*	5.73	3	1.4	24.0	2 300	100			*i.v.* 10 mg/kg bw; *p.o.* 10 mg/kg bw; 10.2°C	Martinsen and Horsberg, 1995
			p.o.	0.08	12						2.2		
Sulfadiazine		*Salmo salar*	i.v.				26		20		100	*i.v.* 25 mg/kg bw; *p.o.* 25 mg/kg bw; 10°C	Horsberg et al., 1997
			p.o.	7.92	24		27		44		46		
Sulfadimethoxine		*Salmo salar*	*i.v.*				7		49		100	*i.v.* 25 mg/kg bw; *p.o.* 25 mg/kg bw; 10°C	Horsberg et al., 1997
			p.o.	4.12	12		13		318		16		
Trimethoprim		*Salmo salar*	*i.v.*				21		73		100	*i.v.* 5 mg/kg bw; *p.o.* 5 mg/kg bw; 10°C	Horsberg et al., 1997
			p.o.	1.52	12		28		69		100		
Vetoquinol		*Gadus morhua*	*p.o.*		12		79				72	*p.o.* 25 mg/kg bw ; 8°C	Samuelsen et al., 2003b
		Hippoglossus hippoglossus	*p.o.*	6.7	14.5		42				64	*p.o.* 25 mg/kg bw; 9°C	Samuelsen and Ervik, 1999
		Salmo salar	*p.o.*	3.8	7		16				71	*p.o.* 40 mg/kg bw; 10°C	Samuelsen et al., 2000

C_{max} (μg/ml) = maximum concentration; T_{max} (h) = time to reach maximum concentration; $t_{½}α$ (h) = distribution half-life; $t_{½}β$ (h) = elimination half-life; V_{dss} (ml/kg) = apparent volume of distribution at steady state; Cl_T (ml/kg/h) = total body clearance; MRT(h) = mean residence time; F (%)= bioavalability tures of 14 and 24°C, respectively. Metabolic and excretory rates increase at higher temperatures, probably due to a higher rate of bile production (Curtis et al., 1986), membrane lipid composition (Hazel, 1984) and urine production (Haug and Hals, 2000). Furthermore, salinity could influence pharmacokinetic parameters in aquatic organisms. In *O. mykiss*, $t_{1/2}\alpha$, $t_{1/2}\beta$, V_{dss}, and MRT (mean residence time) values for oxolinc acid were less in sea than fresh water, although the Cl_T was longer (Table 2). Rigos et al. (2003) postulated that salinity may lead to low F of oxytetracyline in marine fish due to the formation of complexes between tetracyclines and cations found in water and feed, resulting in a possible reduction of absorption across membranes.

Some sampling techniques, e.g., the dorsal aorta cannulation technique, might have an influence on pharmacokinetic parameters. Several publications have reported that kinetics of pharmaceuticals differed between cannulated and non-cannulated fish (Martinsen et al., 1993; Sohlberg et al., 1996; Haug and Hals, 2000), and this could limit the value of the technique. Furthermore, cannulation and repeated blood sampling could increase stress in fish, leading to a higher metabolic rate (Bonga, 1997), and a lower swimming activity (Haug and Hals, 2000). These factors might have an influence on pharmacokinetics in fish, but their significance is still uncertain.

5. Conclusions

As some pharmaceuticals originating from human therapy are not eliminated completely in municipal STPs, and are discharged as contaminants into the aquatic environment, although at low concentrations, the residual pollutants could lead to toxic effects on aquatic organisms. In order to solve the load of pharmaceuticals residues in the aquatic environment, STP processes should be optimised by identification of gaps in knowledge, and on the assessment of the risks connected with emission.

Residual pharmaceuticals may also induce unexpected effects in aquatic organisms. Data obtained from acute tests has clearly demonstrated that results are influenced by the organism involved. Different organisms can differ completely in their sensitivity to pharmaceuticals, and several factors can influence toxicity. Therefore, extrapolation across species and environmental conditions should be treated with caution. Standard toxicity tests for pharmaceuticals on aquatic organisms are needed to clarify their ecotoxicologocal effects in the environment. Moreover, some pharmaceuticals are expected to be found in combinations in the aquatic environment, thus the potential of combined effects of pharmaceutical mixtures should be addressed in the future.

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