



Sixth
Framework
Programme

KNAPPE

Knowledge and Need Assessment on Pharmaceutical Products in Environmental Waters

Contract n° 036864

Operative commencement date of the project: February 1st 2007

Final date of the project: September 30th 2008

Deliverable number: *D4.2*

Report on environmental impact and health effects of PPs

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Document Information

DOCUMENT TYPE	<i>document</i>
DOCUMENT NAME:	<i>Report on environmental impact and health effects of PPs</i>
REVISION:	
REV.DATE:	
CLASSIFICATION:	
STATUS:	<i>Pu</i>

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STATUS, CONFIDENTIALITY AND ACCESSIBILITY							
Status			Confidentiality			Accessibility	
S0	Approved/Released		R0	General public		Work-space	
S1	Reviewed		R1	Restricted to SWIFT6WFD members		Internet	
S2	Pending for review		R2	Restricted to European. Commission	x	Paper	x
S3	Draft for comments						
S4	Under preparation	x					

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Summary

Medicines play an important role in the treatment and prevention of disease in humans and animals. During their manufacture and use, they may be released to the environment by a number of routes. Even though the side effects on human and animal health have been widely documented, only recently have the potential environmental impacts of the manufacture and use of medicines been considered. In this report, we analyse the available data that has been published over the past few years on the ecotoxicity of pharmaceuticals and use the data alongside monitoring data to assess whether there is any evidence of unacceptable risks to the environment.

The data review showed that there is now a large body of data that has been generated over the past decade on the effects of pharmaceuticals on aquatic organisms. Using this data, generally, pharmaceuticals show low acute toxicity to fish, daphnids and algae and while the majority of pharmaceuticals also show low toxicity in standard chronic studies, a number of pharmaceuticals are highly toxic in standard chronic tests. A comparison of standard acute and chronic test endpoints with available monitoring data indicate that, with a few exceptions, pharmaceuticals do not pose an unacceptable risk to the environment;

The effects of a number of pharmaceuticals have also been assessed using non-traditional ecotoxicity tests and endpoints. The effect endpoints for the majority of these novel tests are many orders of magnitude lower than the traditional endpoints and existing uncertainty factors do not reflect these differences. Additionally, most of the novel endpoints can be linked to important ecological functions so can be regarded as ecologically relevant. However, even when novel data are included in the risk characterisation, most pharmaceuticals seem to pose a low risk to ecosystem health. There are however some exceptions that may need further assessment or control in the future.

1. Introduction

Medicines play an important role in the treatment and prevention of disease in humans and animals. During their manufacture and use, they may be released to the environment by a number of routes. Even though the side effects on human and animal health have been widely documented, only recently have the potential environmental impacts of the manufacture and use of medicines been considered.

Pharmaceuticals will have been released to the environment for decades, however it is only in the past few years that attempts been made to quantify the levels of these compounds in the environment. Using new analytical techniques such as LC-MS-MS, low levels of a range of pharmaceuticals, including hormones, steroids, antibiotics and parasiticides are being detected in soils, surface waters and ground waters internationally. Even though the reported concentrations are generally low (i.e. sub $\mu\text{g/l}$ in surface waters), the substances have been observed across a wide variety of hydrological, climatic and land-use settings and many of the substances have been detected throughout the year. As a result, questions have been raised over the impacts of veterinary medicines on organisms in the environment and on human health.

Pharmaceuticals compounds are either designed to be highly active and interact with receptors in humans and animals or they are toxic towards health threatening organisms such as bacteria, fungi and parasites. Many lower animals have receptor systems similar to humans and animals moreover many of the groups of organisms that affect human and animal health and which are targeted by pharmaceuticals play a critical role in the functioning of ecosystems. It is therefore possible that pharmaceuticals may cause subtle effects on aquatic and terrestrial organisms. For human medicines in particular, releases to the environment are likely to be almost continuous so organisms will be exposed for long durations. Because of this, over the past few years there has been a dramatic increase in the amount of research being performed into the potential effects and risks of pharmaceuticals in the natural environment. It is now timely to review this body of information in order to explore the implications of the published data in terms of environmental risks.

This report summarises work done during the KNAPPE project to explore the available data on the ecotoxicological impacts of human and veterinary medicines in the environment as well as work done, using this data and monitoring data, to assess the risks to aquatic systems.

2. Database development

To characterize the available ecotoxicity data on pharmaceuticals, ecotoxicology information was compiled from a search of the peer-reviewed literature and from online databases (Pharmacobase, US EPA) for both human and veterinary pharmaceuticals and this compilation was completed by December 2007. Before this information was used in any further analyses, a quality control was done by validating the data in the database with those in the primary literature for approximately 5 % of the studies. We did not examine the raw data for among-study differences in calculations of endpoints (e.g., LC50) and did not include any experiments using combinations of APIs.

Pharmaceutical classes were assigned to each compound based upon those used by the Drug Bank Database (University of Alberta) where possible. The included about 150 different types of drug classes (not including solvents, adjuvants, foaming or surface-active agents, formulants, pesticide synergists, uncoupling agents). Toxicity tests with the more common pharmaceutical classes include Insecticides (5308), Cholinesterase Inhibitor (2903), Lysozyme inhibitor (2434), Antiscabies Agent (2095), Estrogens (1166), Antibiotics (810), Anesthetics (topical, inhalants, intravenous, local) (752), Pentaerythritol Tetranitrate Reductase inhibitor (752), Anti-menopausal Agents (678), D-Alanyl-D-Alanine Carboxypeptidase inhibitor (628), Alpha-Amylase Pancreatic inhibitor (574), Agglutinin inhibitor (396), Antineoplastic Agents (includes hormonal and topical) (391), Epsp Synthase inhibitor (341), Analgesics (332), Anti-Infective Agents & Anti-Infectives (includes local and urinary compounds) (238), Anthelmintics (160), Anti-Inflammatory Agents (includes non-steroidal) (158), Tocolytic Agents (149), Green Fluorescent Protein inhibitor (142), Enoyl-[Acyl-Carrier-Protein] Reductase [Nadh inhibitor (130), Beta-Catenin inhibitor (125), Odorant Binding Protein Lush inhibitor (108) and 1,3,4,6-Tetrachloro-1,4-Cyclohexadiene H inhibitor (101).

The parameters that went into the database included drug names and classes, species (and phylogeny), exposure duration and concentrations, endpoints measured (main ones being EC50, LC50, NOEC, LOEC, LOAEL, NOAEL), laboratory or field, eukaryotic versus prokaryotic, physical/chemical properties [CAS number, chemical formula, MW, Kow (estimated and experimental), Koc, Koa, SAR], and exposure conditions (marine, freshwater, brackish). The total number of studies on individual compounds included in this analysis is

23,168 (781 from field) and includes 6000, 3176 and 16079 studies on brackish, marine and freshwater species, respectively.

3. Traditional ecotoxicity studies

3.1 Distribution of ecotoxicity values

Traditional ecotoxicology studies were categorized into two main classes – acute or chronic. Acute studies were defined as those <72 h for algae, < 96 h for Daphnia and < 96 h for fish; exposures of longer duration were categorized as chronic for these taxa. We identified 543 acute and 1042 chronic for algae, 1562 acute and 417 chronic for Daphnia, and 8522 acute and 4924 chronic studies for fishes.

Figure 1 summarizes the numbers of acute toxicity studies for algae (EC50), cladocerans (LC50) and fishes (LC50) within several concentration ranges. The data demonstrate that, in general, pharmaceuticals are not highly acutely toxic to aquatic organisms with the majority of compounds having an LC50 or EC50 value of 1000 $\mu\text{g. L}^{-1}$ or higher. There are however selected substances that have LC50 or EC50 values in the low $\mu\text{g.L}^{-1}$ range.

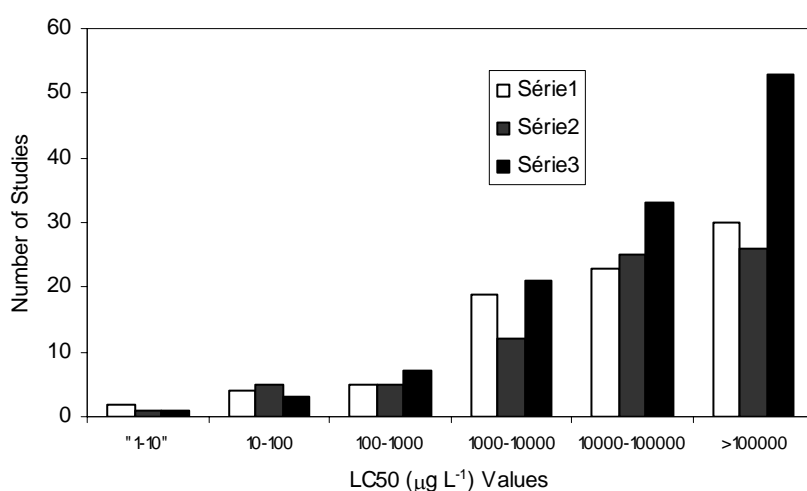


Figure 1: Distribution of traditional acute LC50 and EC50 values for pharmaceuticals to fish, daphnids and algae.

Figure 2 shows the number of longer term/chronic toxicity tests algae (EC50), Daphnia (LOEC) and fishes (LOEC). This figure shows that concentrations of API causing chronic effects in these three trophic groups are generally high although there are some instances where traditional chronic effects are observed in the sub $\mu\text{g.L}^{-1}$ range.

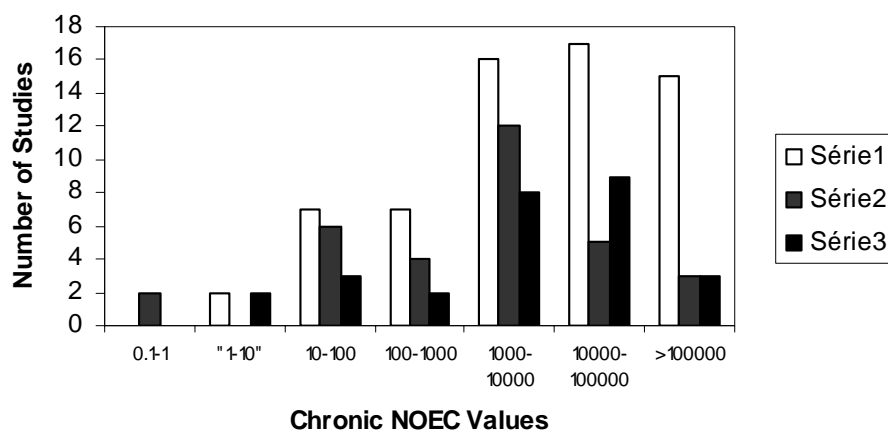


Figure 2 : Distribution of traditional chronic LC50 and EC50 values for pharmaceuticals to fish, daphnids and algae.

Mean acute daphnia EC50 values for the different pharmaceutical classes covered in the database are shown in Table 1. The most acutely toxic groups to daphnids are the cholinesterase inhibitors, adjuvants and the anti-infective agents.

Table 1: Mean water flea 48 h LC50 values for available chemical classes

Pharmaceutical class	Mean LC50 value ($\mu\text{g L}^{-1}$)
Cholinesterase Inhibitors	6.04
Adjuvants	38.4
Anti-Infective Agents	270
Cardio tonic Agents	4485
Insulin inhibitor	8900
Surface-Active Agents	18679
Alpha-Amylase	29500
Leghemoglobin inhibitor	39900
Cytosine Deaminase inhibitor	47000
Glycolipid Transfer Protein inhibitor	50000
D-Alanyl-D-Alanine Carboxypeptidase inhibitor	52000
Preservative	63700
Tocolytic Agents	72000
Lysozyme inhibitor	92676
Anti-bacterial Agents	126400
Synthetic Designed Peptide "Alpha-1" inhibitor	140000

Agglutinin inhibitor	263000
Beta-Lactamase Shv-1 inhibitor	270000
Pentaerythritol Tetranitrate Reductase inhibitor	274500
Beta-Trypsin inhibitor	340000
CNS	510000
Peroxiredoxin 5 inhibitor	1540000
Antiscabies Agent	1640000
Analgesics	1697666
L-2-Haloacid Dehalogenase inhibitor	2750000
Odorant Binding Protein Lush inhibitor	4450000
Solvents	9894000
Beta-Catenin inhibitor	10000000
Amidase Operon inhibitor	10000000
Green Fluorescent Protein inhibitor	33280000

3.2 Evidence for risks to the environment, based on traditional ecotoxicity data

In order to establish whether there is any evidence of risk of pharmaceuticals to aquatic systems, the traditional effects data were compared to occurrence data in surface water from the comprehensive review of Monteiro and Boxall (In press). Maximum Environmental Concentrations (MECs) were used in the analysis – these were the highest concentrations measured in any of the reviewed published monitoring study. If the concentration was below the limit of quantification, the MEC was set equal to the limit of quantification.

MECs are compared to effects data in Figures 3 and 4. None of the acute standard endpoints was higher than the MEC for this active ingredient. However, using an assessment factor of 1000, which is typically used for acute endpoints if data for all three trophic levels are available, would lead to risk quotients greater than 1 for Clarithromycin, 19-Norethisterone, Sulfamethoxazole, and acetaminophen.

Only for 10 active ingredients, had a long-term endpoint that was publicly available. MECs were higher than long-term standard tests for 17alpha-ethinylestradiol and 17alpha/beta estradiol. Assuming that the TGD assessment factor (i.e. 10) for long-term studies could be applied, there would also be an indication of a risk to surface water organisms for ibuprofen and sulfamethoxazole.

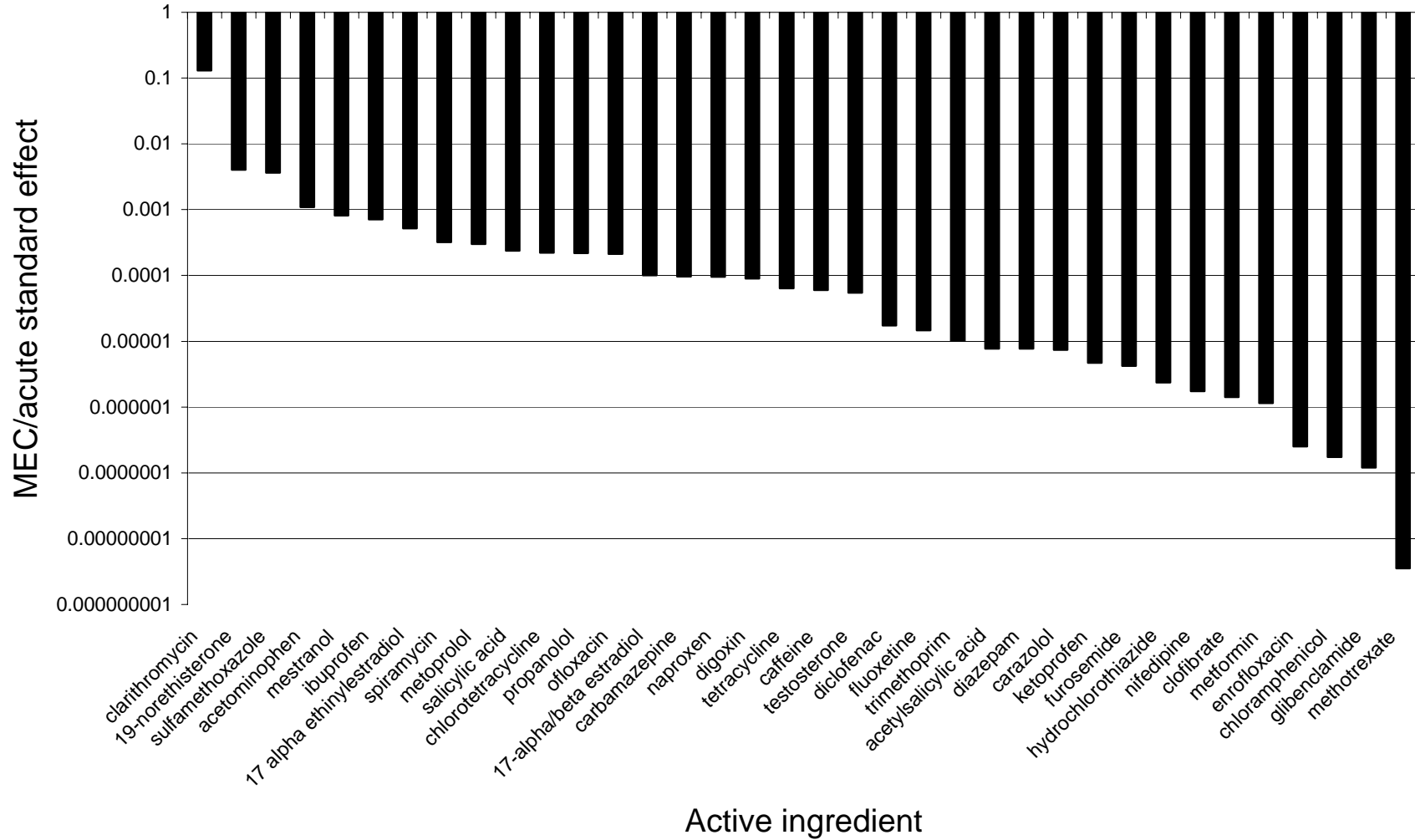


Figure 3: MEC:Traditional acute EC50/LC50 values for a range of pharmaceuticals

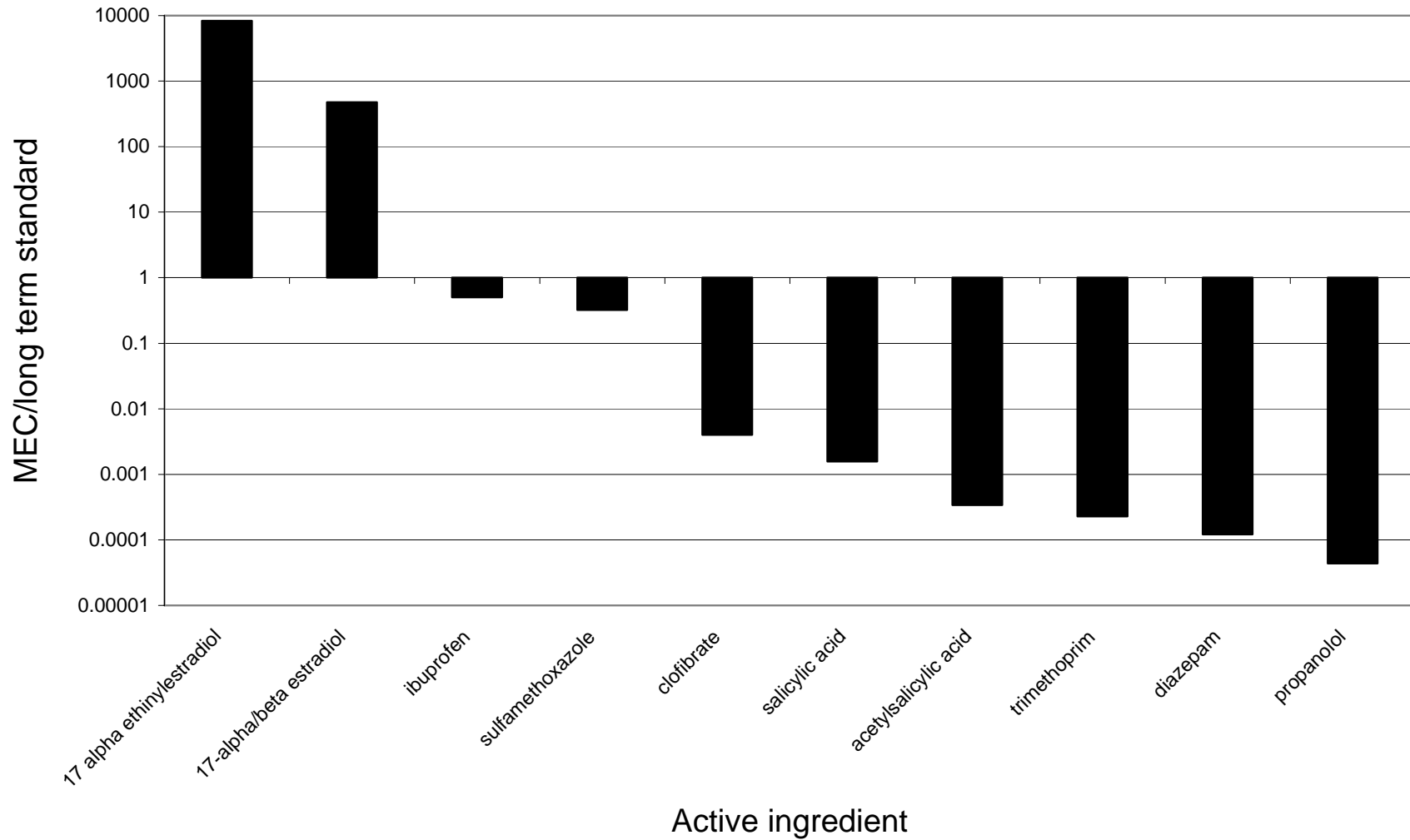


Figure 4: MEC:Traditional chronic EC50/LC50 values for a range of pharmaceuticals

4. Non traditional endpoints

4.1 What are the limitations of the standardized test endpoints and methods?

A number of studies have commented on the sufficiency of standardized ecotoxicity data for pharmaceuticals to characterize hazard (Brooks et al 2003, Ankley et al 2005). Such traditional methods include common model organism such as *Daphnia magna* and *Pimephales promelas* that are amenable to laboratory culture. Acute toxicity tests with these organisms include mortality as the primary response, compared to growth inhibition in the green algae models (e.g., *Selanastrum capricornutum*). Traditional chronic or subchronic responses generally include survival and reproduction (and sometimes growth) for *D. magna* and survival and growth for *P. promelas* following a 21 d or 7 d exposure period, respectively. Although such bioassays have high utility for environmental safety assessment of many industry chemicals, whole effluent toxicity and ambient toxicity studies, short term growth and reproduction responses are likely not related to target-mediated responses, which may be observed at concentrations that are orders of magnitude lower than standardized chronic toxicological benchmark concentrations (TBCs).

For example, Kidd et al (2007) observed that *P. promelas* population disappeared following treatment with 5-6 ng.L⁻¹ of 17 α -ethinyl estradiol (EE2) in a whole lake experiment. However, an acute (48 hr) *P. promelas* LC50 tests with EE2 has been reported at ~1700 ug.L⁻¹, which would result in an acute-to-chronic (ACR) ratio of approximately 340000, a value markedly greater than typical uncertainty factors of 10-1000 applied to LC50 values during prospective ERAs under EMEA.

Other comparisons for novel endpoints and traditional acute and chronic endpoints for a range of pharmaceuticals are shown in Figure 5. While the differences between traditional data and novel endpoints are not as large as for EE2, they are also considerably larger than the uncertainty factors used in the EMEA guidelines.

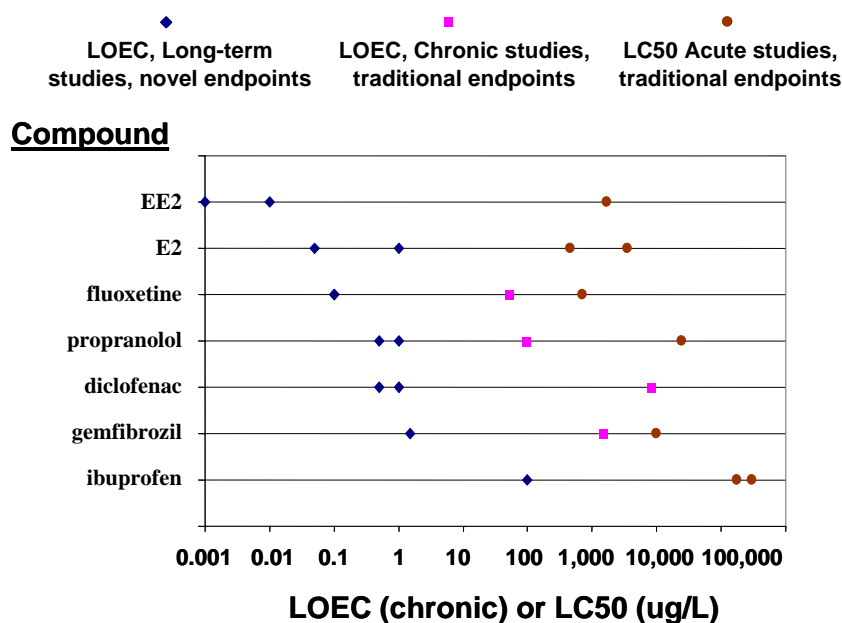


Figure 5: Comparison of traditional acute and chronic endpoints with a range of novel test endpoints for a range of pharmaceuticals

4.2 Ecological relevance of novel endpoints

A critical question that must be distinguished for non traditional responses in aquatic organisms to pharmaceuticals is whether the responses result in effects that can be related to ecologically relevant adverse responses. This is an important consideration, but to explore this question further one must define what ecological attributes are intended to be protected by an ecological risk assessment. Previous contributions on aquatic effects of human (Ankley et al 2005) and veterinary (Brooks et al 2008a) pharmaceuticals identified that ecosystem function and stability (or, sustainability), commercially and socially important species (e.g., fisheries) and biodiversity, including endangered or threatened species, as key aspects of aquatic ecosystems that should be protected. Protecting the structure and function of aquatic ecosystems takes into consideration the key food web interactions within a system. For example, if primary producers are the most sensitive to an API then protecting these taxa should maintain the structure (and functioning) of the ecosystem. Other key ecosystem processes that are not addressed by the standard toxicity testing include nutrient cycling through microorganisms, and competition and predation. Maintenance of biodiversity is critical since we know that diverse communities are more resilient to stressors. The structure and function of aquatic food webs is maintained by ensuring the sustainability of their

populations; these populations can be affected by direct toxicity of an API or indirectly through a change in predator or prey abundances (top-down or bottom-up effects). These indirect effects are more difficult to predict because of the inherent complexity and resilience of food webs. Challenges in assessing effects of aquatic pollutants at the population-, community- or ecosystem level have resulted in most studies assessing the effects of APIs and other chemicals on molecular through individual endpoints, though the latter is more ecologically relevant to higher levels of biological organization.

In Table 2, we have taken many of the novel endpoints that have been reported in the literature for pharmaceuticals and have attempted to link these to important ecological functions reproduction, growth, predator avoidance and feeding. For all the endpoints listed, it is possible to identify a link to an ecological function.

Table 2: Reported subtle effects of pharmaceutical compounds on aquatic and terrestrial organisms

Class	Compound, class	Organism	Endpoint	Ecological relevance	Reference
Androgen	Methyltestosterone	fathead minnow	nest holding, competition	reproduction	Martinovic <i>et al.</i> , 2007
		medaka	egg production, ovo-testis	reproduction	-
	Trenbolone	fathead minnow	sex characteristics	reproduction	Ankley <i>et al.</i> ,
Antifungal	Fadrozole	fathead minnow	sex characteristics	reproduction	Ankley Miller <i>et al.</i> ,
B-blocker	Propranolol	trout	heart rate	growth, food capture, predator avoidance	SETAC 2007 poster, Owen, Winter
Estrogen	17B-estradiol	goldfish	courting	reproduction	Bjerselius <i>et al.</i> , 2001 in Scott and Solman 2004
		fathead minnow	nest holding, competition	reproduction	Martinovic <i>et al.</i> , 2007
	Ethinylestradiol	zebrafish	ovo-testis	reproduction	Andersen <i>et al.</i> , 2003
		mummichog	sex steroid hormones	reproduction	MacLatchy <i>et al.</i> , 2003
		medaka	breeding behaviour	reproduction	Balch <i>et al.</i> , 2004
		fathead minnow	testicular necrosis	reproduction	Pawlowski <i>et al.</i> , 2004
			fertilization success, sex characteristics	reproduction	Parrott and Blunt 2005
			ovo-testis	reproduction	Kidd <i>et al.</i> , 2007
Lipid	Gemfibrozil	goldfish	sex steroid hormones	reproduction	Mimmeault <i>et al.</i> , 2006

regulator					
NSAID	Diclofenac	trout	liver, kidney, gill histopathological changes	growth	Triebkorn <i>et al.</i> , 2004
	Ibuprofen	medaka	time to reproduction	reproduction	Flippin <i>et al.</i> , 2006
SSRI	Fluoxetine	fathead minnow	feeding behaviour	growth, survival	Stanley <i>et al.</i> , 2007
			nest defence	reproduction	Klaper <i>et al.</i> , in press
		medaka	egg production	reproduction	Van Der Kraak <i>et al.</i> , unpublished
Antibiotic	Novobiocin	Cnidarian	Feeding	growth	Quinn <i>et al.</i> , 2008
Antiepileptic	Carbamazepine	Arthropoda	Activity	predator avoidance, feeding, growth, reproduction	Delange <i>et al.</i> , 2006
		Cnidarian	Feeding	growth	Quinn <i>et al.</i> , 2008
B-blocker	Propranolol	Athropoda	Heart rate	predator avoidance, feeding, growth, reproduction	Campbell <i>et al.</i> , 2004
		Athropoda	Heart rate	predator avoidance, feeding, growth, reproduction	Stanley <i>et al.</i> , 2006
Diuretic	Furosemide	Cnidarian	Feeding	growth	Pascoe <i>et al.</i> , 2003
Heart drug	Digoxin	Cnidarian	Feeding	growth	Quinn <i>et al.</i> , 2008
		Cnidarian	Feeding	growth	Pascoe <i>et al.</i> , 2003
Lipid	Gemfibrozil	Cnidarian	Feeding	growth	Quinn <i>et al.</i> , 2008

regulator					
NSAID	Acetylsalicylic acid	Cnidarian	Feeding	growth	Pascoe <i>et al.</i> , 2003
	Ibuprofen	Arthropoda	Activity	predator avoidance, feeding, growth, reproduction	Delange <i>et al.</i> , 2006
		Cnidarian	Feeding	growth	Quinn <i>et al.</i> , 2008
		Cnidarian	Feeding	growth	Pascoe <i>et al.</i> , 2003
		Mollusca	Fecundity (egg mass viability)	reproduction	Pounds <i>et al.</i> , 2008
	Naproxen	Cnidarian	Feeding	growth	Quinn <i>et al.</i> , 2008
SSRI	Fluoxetine	Mollusca	Spawning	reproduction	Fong <i>et al.</i> , 1998
		Arthropoda	Activity	predator avoidance, feeding, growth, reproduction	Delange <i>et al.</i> , 2006
	Fluvoxamine	Mollusca	Spawning	reproduction	Fong <i>et al.</i> , 1998
	Paroxetine	Mollusca	Spawning	reproduction	Fong <i>et al.</i> , 1998

4.3 Do the novel endpoints indicate a risk?

In order to explore whether the novel effects data indicate a risk to the aquatic environment, measured environmental concentrations were compared to the lowest toxic endpoints (either novel or traditional) obtained for a range of pharmaceuticals. The data used in the comparison are summarised in Appendix A.

The lowest effect datum was orders of magnitude lower than the MEC for 17alpha-ethinylestradiol, acetaminophen, 17alpha/beta estradiol, and salicylic acid indicating that these substances may pose a risk to the environment.

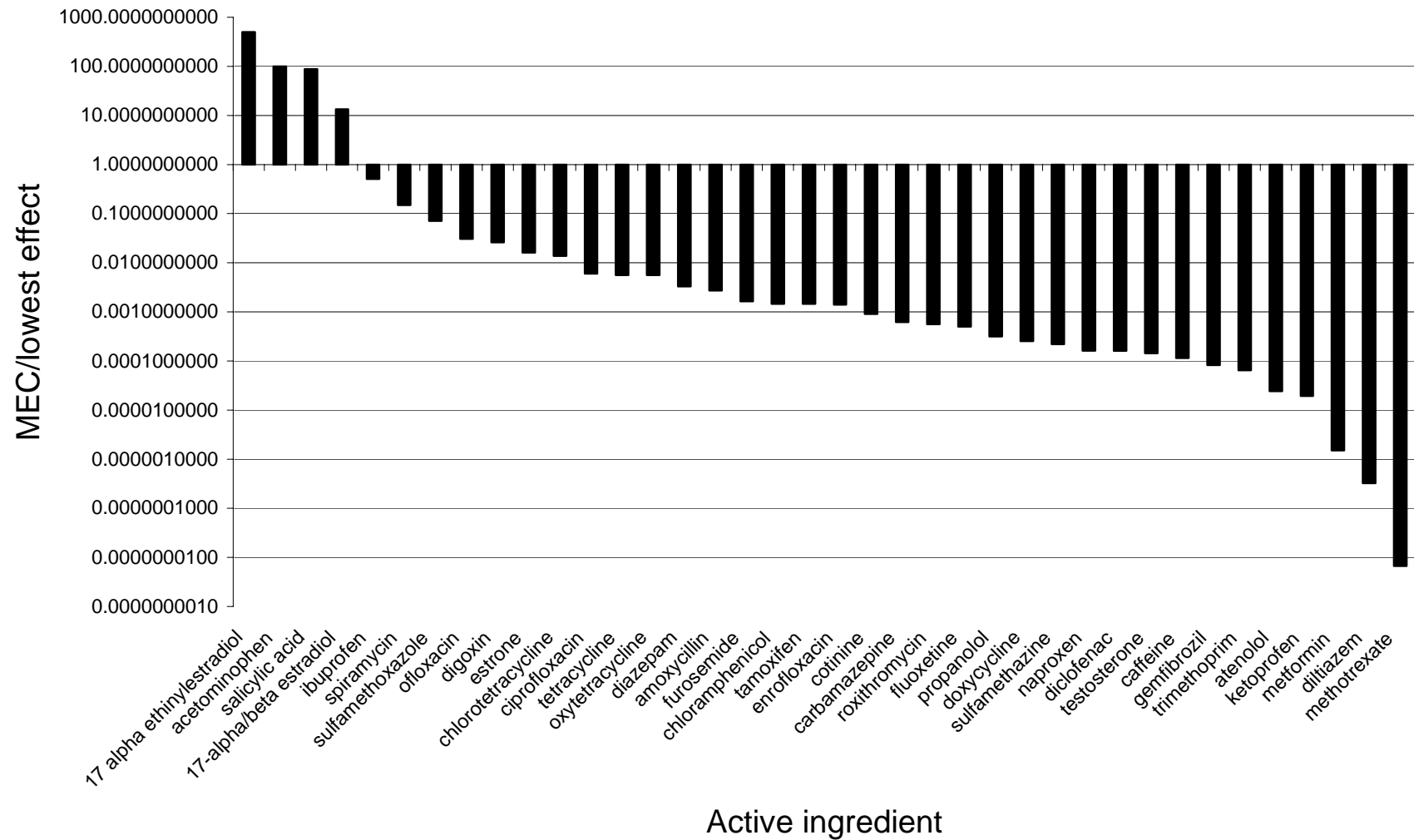


Figure 6: MEC:lowest ecotoxicity values for a range of pharmaceuticals

5. Conclusions and recommendations

1. A large body of data has been generated over the past decade on the effects of pharmaceuticals on aquatic organisms.
2. Generally, pharmaceuticals show low acute toxicity to fish, daphnids and algae.
3. While the majority of pharmaceuticals also show low toxicity in standard chronic studies, a number of pharmaceuticals are highly toxic.
4. A comparison of standard acute and chronic test endpoints with available monitoring data indicate that, with a few exceptions, pharmaceuticals do not pose an unacceptable risk to the environment;
5. The effects of a number of pharmaceuticals have been assessed using non-traditional ecotoxicity tests and endpoints.
6. The effect endpoints for the majority of the novel tests are many orders of magnitude lower than the traditional endpoints and existing uncertainty factors do not reflect these differences.
7. Most of the novel endpoints can be linked to important ecological functions so can be regarded as ecologically relevant.
8. Even when novel data are included in the risk characterisation, most pharmaceuticals seem to pose a low risk to ecosystem health. There are however some exceptions that may need further assessment or control in the future.

6. Recommendations

Based on the review and analysis of the data, the following recommendations have been developed:

1. For many pharmaceuticals, we still have limited data on their ecotoxicity. Some of this data will have been generated by pharmaceuticals companies. If this data were more freely available, it could be used alongside the available monitoring data to determine whether concentrations of pharmaceuticals are of ecological concern or not.
2. Further work is required to understand the significance of novel endpoints (including results from studies employing proteomics and metabolomics) in terms of their ecological relevance. These studies will help to establish whether or not the standard chronic tests appropriate.
3. Work is required to understand how risks of pharmaceuticals may change in the future as a result of climate change and pandemics;
4. More synthesis of published and unpublished data would be worthwhile. Ecotoxicity studies should report background conditions (measured exposure concentrations, pH, how NOEC, EC50 derived, include all information not just summary stats, confidence limits etc.) to facilitate this synthesis. Reported effects data should be compared to monitoring data in order to identify substances of most concern. Scientists and industry should be encouraged to share data (table of parameters). Studies yielding 'surprising' results should be repeated.
5. Further work is required to understand whether and how we can extrapolate from mammalian data to environmental effects. The use of contra-indications to indicate potential for ecological risks should be considered and the utility of 'omics' based approaches should be explored for risk assessment purposes. It would be helpful if case studies could be developed for read across from mammalian data to environmental risk for a range of substances.
6. The impacts of mixtures of a) pharmaceuticals of the same class; b) pharmaceuticals of different classes; and 3) pharmaceuticals and other substance types should be assessed. Modelling approaches are available from other sectors that could be used for this purpose.

7. Long-term studies at realistic exposure concentrations and under realistic environmental conditions might be useful for some pharmaceuticals although strong consideration would need to be given on how best to interpret these studies.
8. Most work has been performed on the aquatic environment. Further work into impacts on terrestrial systems is warranted.

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Table 3: Lowest effects data and maximum environmental concentrations used in the risk characterisation process.

Class	Compound	MEC [$\mu\text{g/l}$]	Lowest overall endpoint	Effect concentration $\mu\text{g l}^{-1}$	MEC/Lowest effect
analgesics and antiinflammatories	acetaminophen	10.000	<i>Hyallela azteca</i> 28 d 3 generations LOEC sex ratio	1.00E-01	1.00E+02
	acetylsalicylic acid	0.340	<i>Daphnia magna/longespina</i> 21 d NOEC	1.00E+03	
	diclofenac	1.200	<i>Lemna minor</i> 7 d EC50	7.50E+03	1.60E-04
	diazepam	0.033	<i>Hydra</i> polyp regeneration LOEC	1.00E+01	3.30E-03
	ibuprofen	5.044	<i>Hydra</i> polyp regeneration LOEC	1.00E+01	5.04E-01
	ketoprofen	0.300	<i>Vibrio fischeri</i> 10 min EC50	1.56E+04	1.92E-05
	naproxen	2.000	<i>Anabena flos-aquae</i> 72 h EbC50	1.23E+04	1.63E-04
	salicylic acid	8.800	<i>Hyallela azteca</i> 28 d 3 generations LOEC	1.00E-01	8.80E+01
fluoroquinolone antibiotics	ciprofloxacin	0.030	<i>Microcystus aeruginosa</i> X d EC50	5.00E+00	6.00E-03
	enrofloxacin	0.020	<i>Penaeus vannamei</i> 48 h EC50	1.43E+01	1.40E-03
	ofloxacin	0.306	<i>Pseudomonas putida</i> EC50	1.00E+01	3.06E-02
macrolide antibiotics	clarithromycin	0.260	<i>Pseudokircheriella subcapitata</i> 72 h EC50	2.00E+00	1.30E-01
	roxithromycin	0.560	<i>Lemna gibba</i> 7 d EC50	1.00E+03	5.60E-04
	spiramycin	0.740	<i>Microcystis aeruginosa</i> 7 d EC50	5.00E+00	1.48E-01
penicillin antibiotics	amoxicillin	0.006	<i>Synechococcus leopolensis</i> 4 d EC50	2.20E+00	2.73E-03
sulfonamide antibiotics	sulfamethazine	0.220	<i>Lemna gibba</i> 7 d EC50	1.00E+03	2.20E-04
	sulfamethoxazole	1.900	<i>Synechococcus leopolensis</i> 96 h EC50	2.68E+01	7.09E-02
tetracycline antibiotics	chlorotetracycline	0.690	<i>Microcystis aeruginosa</i> 7 d EC50	5.00E+01	1.38E-02
	doxycycline	0.080	<i>Lemna gibba</i> 7d EC50	3.16E+02	2.53E-04
	oxytetracycline	0.340	<i>Penaeus vannamei</i> 48 h EC50	6.11E+01	5.56E-03

	tetracycline	0.140	<i>Vibrio fischeri</i> 24 h EC50	2.51E+01	5.58E-03
other antibiotics	chloramphenicol	0.060	<i>Penaeus stylirostrus</i> 48 h EC50	4.13E+01	1.45E-03
	trimethoprim	0.710	<i>Anabaena variabilis</i> 144 h EC50	1.10E+04	6.45E-05
anti depressants	fluoxetine	0.012	<i>Pseudokircheriella subcapitata</i> 48 h EC50	2.40E+01	5.00E-04
antiepileptics	carbamazepine	7.100	<i>Ceriodaphnia dubia</i> 48 h EC50	1.15E+04	6.20E-04
antineoplastic agents	methotrexate	0.000	<i>Tetrahymena pyriformis</i> 48 h EC50	4.50E+04	6.67E-09
	tamoxifen	0.071	<i>Acartia tonsa</i> 5 d EC50	4.90E+01	1.45E-03
β-blockers	atenolol	0.241	<i>Hydra vulgaris</i> 7 d polypstructure LOEC	1.00E+04	2.41E-05
	carazolol	0.110	<i>Daphnia magna</i> 48 h EC50	1.48E+04	7.43E-06
	metoprolol	2.200	<i>Desmodesmus subspicatus</i> 72 h EC50	7.30E+03	3.01E-04
	propranolol	0.590	<i>Streptocephalus proboscideus</i> 24 h EC50	1.87E+03	3.16E-04
hormones and steroids	17 alpha ethinylestradiol	0.831	<i>Pimephales promelas</i> 308 d EC50	1.66E-03	5.01E+02
	17-alpha/beta estradiol	0.200	<i>Oncorhynchus mykiss</i> , 21 d EC 50	1.50E-02	1.33E+01
	19-norethisterone	0.872	<i>Pseudokirchneriella subcapitata</i> 72 h EC50	2.16E+02	4.04E-03
	mestranol	0.407	<i>Pseudokirchneriella subcapitata</i> 72 h EC50	5.00E+02	8.14E-04
	estrone	1.600	<i>Tisbe battagliai</i> 10 d LC50	1.00E+02	1.60E-02
	testosterone	0.214	<i>Acartia tonsa</i> 5 d EC50	1.50E+03	1.43E-04
lipid regulators	clofibrate	0.040	<i>Daphnia magna</i> 21 d EC50	1.06E+02	3.77E-04
	gemfibrozil	1.550	<i>Vibrio fischeri</i> 10 min EC50	1.88E+04	8.24E-05
other	caffeine	6.000	<i>Artemisia salina</i> 1 d LC50	5.27E+04	1.14E-04
	cotinine	0.900	<i>Lemna gibba</i> 7 d EC50	1.00E+03	9.00E-04
	digoxin	0.260	<i>Hydra vulgaris</i> polyp regeneration	1.00E+01	2.60E-02
	diltiazem	0.049	<i>Vibrio fischeri</i> 24 h EC50	1.52E+05	3.22E-07

	furosemide	0.255	<i>Ceriodaphnia dubia</i> 48 h EC50	1.56E+02	1.63E-03
	glibenclamide	0.012	Fish, Daphnia and Algae	1.00E+05	1.20E-07
	hydrochlorothiazide	0.236	Fish, Daphnia and Algae	1.00E+05	2.36E-06
	metformin	0.150	<i>Anabaena</i> sp. EC50	1.00E+05	1.50E-06
	nifedipine	0.010	<i>Danio rerio</i> 96 h LC50	5.77E+03	1.73E-06