Appendix C
Aquatic Toxicity Testing Studies Conceptual Plan

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AQUATIC TOXICITY TESTING STUDIES CONCEPTUAL PLAN

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Introduction

Reclaimed ("highly treated") wastewater (or effluent) may be used to rehydrate wetlands (fresh– and/or salt-water) in the Biscayne Bay ecosystem. One potential source of this water is to provide a high quality reuse water through additional treatment of the existing Miami-Dade Water and Sewer Department's South District Wastewater Treatment Plant (SDWWTP) secondary effluent. After the associated treatment technologies are applied to the secondary effluent a level of water quality must be achieved before discharge into the wetland habitats (fresh-and/or salt- water). A critical concern that must be addressed here in the application of reclaimed water into the aquatic ecosystems is the safety of highly treated effluent and whether any substance(s) in the treated effluent water may produce adverse effects on non-target aquatic biota in the receiving ecosystem(s) (i.e., wetland habitats) and whether there are environmental risks to consider.

This document contains the Aquatic Toxicity Testing Studies Conceptual Plan for the effluent from the Coastal Wetlands Rehydration Demonstration Project's Water Reclamation Demonstration Plant (WRDP). The plan is based on a cursory, preliminary review of the literature including existing guidance provided by regulatory agencies in the U.S. and overseas. A more definitive toxicity and environmental fate testing plan will be prepared following a more comprehensive review of the literature. The final plan will contain the specific toxicity tests (laboratory and microcosm) and environmental fate tests to be conducted along with protocols and include the design, statistical procedures and methods to be used in conducting a probabilistic ecological risk assessment with the laboratory toxicity and fate test results.

It is understood that wastewater from a sewage treatment plant may contain numerous contaminants including nutrients. This toxicity testing plan will consider discussion of pharmaceuticals and personal care products (PPCPs) (also referred to as "microconstituents") which may be contained in wastewater influent and effluent. This group requires special consideration because they may have a profound effect on the test design since additional biological endpoints may have to be measured because of their activity and in some cases special tests may have to be conducted. For the purpose of this plan, PPCPs include human and veterinary drugs and the ingredients in cosmetics and other personal care products together with their respective metabolites and transformation products.

The toxicity testing plan will address evaluate the effluent from the WRDP and will assess whether the potential pollutants present include PPCPs. Another unknown that will be assessed is the actual quantity (or residue) of PPCPs (and other pollutants) present in biota and environmental matrices (water, sediment) after exposure to the whole effluent. The environmental fate testing part of the plan will address: the most likely transformation processes, degradation rates and residence times, the final environmental compartment (e.g., sediment, surface water) for the pollutant(s) and the eventual form (parent, metabolite) of the pollutant(s).

Below is a list of general considerations and background information from the literature that were used as a guide in developing the initial Conceptual Plan:

- Pharmaceuticals were initially identified in the mid-1970s associated with WWTP effluents (Hignite and Azarnoff 1977). However, it was not until the early 1990's that frequent reports were published on pharmaceuticals in the environment which is a result of advances in analytical technology (Ternes et al. 2004). Some of the frequently cited publications on analytical detection in environmental matrices and ecotoxicology for PPCP active ingredients and metabolites are included in Appendix A which is a Preliminary Literature Review (Task 8.2.1) relevant to PPCPs. In addition, Appendix B is a literature review compiled by the U.S. EPA for PPCPs.

- Sedlak and Pinkston (2001) estimated concentrations of drugs in untreated wastewater and the range was from 1ng/L to approximately 133,000 ng/L but the majority of compounds were estimated at 100 to 1,000 ng/L. The compounds expected to be present at the highest concentrations consisted of analgesics (e.g., acetaminophen, ibuprofen) and antibiotics (e.g., amoxicillin, cephalexin). Compounds estimated to be present at the lowest concentrations were potent drugs like hormones (e.g., medroxyprogesterone, equilin).

- The different groups of PPCPs that may be considered for South Florida are based on only two geographically relevant documents (Evaluation of Emerging

Contaminants of Concern at the South District Wastewater Treatment Plant Based on Seasonal Sampling Events, Miami-Dade County, Florida, 2004, A.C. Leitz, M.T. Meyer, U.S.G.S., SIR 2006-5240; and Human Use Pharmaceuticals in the Estuarine Environment: A Survey of the Chesapeake Bay, Biscayne Bay and Gulf of the Farallones, Pait, A.S. et al. 2006. National Status and Trends Program for Marine Environmental Quality, NOAA, Silver Spring, MD). In addition, increased focus on the potential ecological effects of pharmaceuticals was developed as a result of the growing number of studies reporting low levels of PPCPs in wastewater treatment effluents, surface waters and to a more limited extent groundwater, drinking water and sediment (Kummerer 2004). These detections and focused research efforts that have documented the presence of such compounds in various countries (Halling-Sorenson et al. 1998; Daughton and Ternes 1999; Kummerer 2004) provide more information on the potential PPCPs that may be detected in the eventual effluent from the WRDP. Recently (1999-2000) in the U.S., the U.S. Geological Survey monitored a broad range of wastewater contaminants (95) in water resources (139 streams in 30 states) including pharmaceuticals, antioxidants, phytosteroids, biocides, and flame retardants (Kolpin et al. 2002). Researchers detected 82 of the 95 compounds in at least one sample. The latter comprehensive monitoring study and several follow-up similar studies (Heberer 2002; McArdell et al. 2003; Huang and Sedlak 2001; Metcalf et al. 2003; Boxall et al. 2004; Jones et al. 2001) include detection of only a small percentage (<15%) of the PPCPs predicted to enter the environment. Their detection highlights that many organic substances are not being removed in WWTPs.

- A cursory review of a pharmaceutical database of several hundred citations indicates that the mean concentration in surface water was 0.043 ppb (0.043µg/L or 43 parts per trillion) for 27,000 total analyses. The maximum concentration was 15 ppb for sulfadimethoxine (veterinary antibiotic) (Lindsey et al. 2001)) with the next highest being acetaminophen (active ingredient in Tylenol) at 10 ppb (Kolpin et al. 2002) in surface water. For WWTP effluent the average

concentration was 0.361 ppb and the maximum concentration was 95.6 ppb. Salicylic acid (used in foods, antiseptics, personal care products and resins) was present at 95.6 ppb (Hignite and Azarnoff 1977) with ibuprofen at 95 ppb (Marchese et al. 2003).

- Pollution of surface waters by PPCPs most often occurs in concentrations of parts per billion (ppb, µg/L) to parts per trillion (or ng/L). Although these concentrations are low, they do have the potential for effects in aquatic systems, especially when potentially there may be multiple substances (mixtures) present in treated secondary effluent which are discharged into receiving water systems. When the combined effects of a mixture of pollutants in whole effluent are taken into account acute and chronic biological effects must be considered.

- PPCP substances, their precursors and transformation products are not only released into the environment by WWTPs but also as a result of manufacture and disposal of unused/unwanted drugs via burial. There is evidence that large quantities of prescription (over the counter-OTC) drugs are not consumed and eventually are disposed in domestic refuse.

- Pharmaceuticals are excreted unaltered in their free form (e.g., 90% of the drug propofol, used in anesthesia, is excreted unmetabolized; Kummerer 2001), others are metabolized to various extents, and some are converted to more soluble forms by formation of conjugates. Note that unmetabolized drugs enter wastewater as biologically-active substances and are often the most non-biodegradable substances in the environment (Stuer-Lauridsen et al. 2000). The transformation products, metabolites and conjugates add to the thousands of highly bioactive substances. The U.S. FDA refers to all metabolites and transformation products as structurally related substances (SRS) which can have greater, lesser or similar activities to the parent compound.

Unlike pharmaceuticals, personal care products (e.g., skin care, dental care, soaps, sunscreen agents, hairstyling products) do not pass through the body. They enter wastewater after their regular use during showering or bathing. Included in personal care formulations are fragrances and preservatives. The environmental fate of certain cosmetic ingredients, like preservatives and hair colorants, has not been investigated extensively, although persistence and bioaccumulation potential have been reported (Geyer et al. 2000).

- Pharmaceuticals and the active ingredients in personal care products usually have a mode of action (MOA) and are therefore "bioactive." Non-target aquatic organisms may have similar receptors to target organisms (like humans) for pharmaceuticals and thus may be adversely affected. Alternatively, non-target organisms may have receptor sites that do not exist in the target organisms but nonetheless unexpected adverse effects may occur.

- For pharmaceutical and some personal care products concerns for the aquatic environment are continuously linked to two factors: 1) the bioactivity of the active ingredient in humans, and 2) the potential to be continuously present, at low concentrations, from ongoing use (patient use primarily). They are thus characterized as "pseudo" persistent (Koschorreck and deKnecht 2004). The environmental half-life of parent pharmaceuticals is typically low (days) compared with other chemicals. However, the low persistence is counter-acted by continued replacement of the drugs, which potentially serves to produce chronic exposure for aquatic organisms (Daughton and Ternes, 1999). Note exceptions to low persistency- antiepileptic drug carbamazepine has a mean 50% dissipation time (DT50) of 82 (+/- 11) days under semi-field conditions and is one of the most persistent pharmaceuticals detected in the environment (Lam et al. 2003); and the cardiovascular drug propanolol downstream of a sewage treatment plant varied by a factor of 10 between two months (25-225ug/L) (Ashton et al. 2003).

- Daily loadings of PPCPs into sewage treatment plants are a function of the human population, dosages/duration of medications consumed, metabolic/excretory half-lives, and age of the population. Another important variable in Florida for PPCP loading into WWTPs are changes in populations during different seasons (e.g., "snowbirds") producing "slug" input of various substances into influents.

- The biodegradation fate of most chemicals in treatment plants is controlled by non-growth limiting (enzyme-saturating) substrate concentrations (copiotrophic metabolism). In contrast, PPCPs are present in treatment plants at concentrations at enzyme-subsaturating levels, which requires oligotrophic metabolism. These micro-constituents may be degraded by only a small number of specialist oligotrophic organisms whose presence is more prevalent in native environments characterized by low carbon fluxes (e.g., sediments and pore waters, where desorption mass transfer is limiting) than in treatment plants (Daughton and Ternes 1999). In general, many pharmaceuticals resist extensive microbial degradation (mineralization) (Velagaleti 1997).

- Some parent pharmaceuticals show low water solubility and preferentially sorb to suspended particles and are discharged from treatment plants in aqueous effluents. Metabolites and conjugates most often will partition into aqueous effluents. The three major fates of PPCPs are: 1) degradation to lower molecular weight compounds, 2) sequestration by solids (e.g., removal by sludge), and 3) conjugates that can later be hydrolyzed to yield parent drug (e.g., clofibric acid conjugates; Clofibrate is a lipid regulator) (Ternes 1998). Therefore, by following disappearance of a pharmaceutical it cannot be assumed that it was degraded-it may be in another state or back as parent compound. Identifying metabolites may be difficult because there may be many metabolites per parent compound and also standard reference materials may be difficult to obtain and may be costly.

- The conceptual toxicity testing plan (below) will include toxicity studies to evaluate biological effects on test organisms (i.e., native where possible and standard test species) as a result of exposure to treated effluent from the WRDP after it leaves the pilot plant. Whole effluent toxicity (WET) testing refers to aggregate toxic responses of aquatic organisms from the potential combined effects of all substances in a complex effluent. Therefore, biological responses from organisms in WET tests will be reflective of the nature of all components present (e.g., PPCPs, nutrients, metals, inorganic chemicals [NH_3, Cl_2 , etc.]) in the effluent. Tests are discussed in the section below. WET testing results provide data (e.g., survival, growth, reproduction, development) for acute and chronic exposures on the combined effect of the effluent. They do not traditionally define cause (e.g., chemical, physical, biological factor) –effect (i.e., response) relationships. The U.S. EPA has established toxicity identification evaluation (TIE) methods as a tool to isolate and characterize the physical-chemical nature of toxicants in complex effluents based on knowledge of how factors, such as pH, modify toxicity (Norberg-King et al. 2005). The goal of a toxicity-based approach to TIE is to separate the toxicant(s) from the nontoxic components in the effluent. Toxicants are "tracked" through all sample manipulations using the most relevant detector available, the test organism.

  It is possible through interpretation of the toxicity test results and subsequent chemical analyses of the fractions following the TIE manipulations to isolate, identify and confirm many of the sources of toxicity in complex effluents. A TIE should be conducted for WET tests that elicit adverse effects on aquatic organisms to define the causative agent(s), especially when an adverse biological effect can not be directly linked to the mode of action of any one of several toxic substances detected in the effluent.

Toxicological Testing Plan (8.2.2 Laboratory and 8.2.3 Outdoor Microcosm)

Introduction

The complex effluent from the SDWWTP, which is currently discharged via injection wells to the boulder zone may contain numerous organic and inorganic pollutants, including nutrients which may vary in concentration and quality over time with cyclical changes occurring daily, weekly, monthly and seasonally. At SDWWTP the U.S. Geological Survey analyzed the presence of emerging contaminants of concern (specifically endocrine disrupting chemicals) in 2004 and detected 20 organic wastewater compounds, 11 pharmaceutical compounds, 8 antibiotic compounds and 1 hormone in effluent (Leitz and Meyer, 2006). In a pilot study conducted by NOAA's National Status and Trends (NS&T) Program in 2002, cotinine (metabolite of nicotine), acetaminophen and the anthelmintic thiabendazole were detected in Biscayne Bay. Fewer detections of pharmaceuticals were found in Biscayne Bay than Chesapeake Bay (Pait et al. 2006). These studies indicate the need to study the ecological effects of the treated effluent and also to place particular consideration and emphasis on pharmaceuticals and personal care products the toxicity testing plan.

To guide the selection of toxicity studies we will determine through chemical analyses the substances present and their concentrations over time in effluent from the WRDP. We will define the modes of action (MOA) and typical effects produced by these substances based on currently available information.

The MOA (if available) may therefore serve not only as a guide in the selection of tests but it will also serve to indicate the type(s) of potential effects we are likely to observe from exposure to these substances. The latter will provide an indication of likely endpoints to measure in toxicity tests based on MOA. Tests (or endpoints) will attempt to encompass and therefore reflect MOAs specific to each substance(s) present in the effluent. We realize that the MOA for substances is primarily based on mammalian species and that often modes of action may occur in non-targets like aquatic organisms (e.g., algae/plants, invertebrates, fish). Many non-target organisms however do have similar receptors, but MOAs on non-targets are largely unknown. We are aware that given the multitude of organisms that may be exposed in the environment there are possibly many MOAs for a substance. Furthermore, the MOA of a substance is based

on exposure of organisms to single substances while exposure to effluents may produce different MOAs and effects as a result of joint action (or interaction) of multiple substances. Nonetheless because of the broad range of effects that could occur over a vast array of aquatic organisms exposed to complex effluents using knowledge of the MOA of chemical substances is a necessary step for toxicity tests with complex effluents (Daughton and Ternes 1999). Also note that some substances do not have a selective MOA but produce a generalized change in activity (or narcosis) of membranes. Narcosis is found in all organisms and is reversible.

Key aspects to consider in tests will be phylogenetic differences in comparative physiology across species and identification of critical life stages in the range of presently available aquatic toxicity tests with microorganisms, phytoplankton, plants, invertebrates, and vertebrates. Major consideration will be given to toxicity studies to support prediction of long-term, chronic effects on populations of organisms. Please note that acute toxicity of the treated effluent must also be considered since it may contain low levels of substances whose combined effects may produce immediate effects on survival.

Following is a brief background, a preliminary review of existing acute and chronic aquatic laboratory toxicity data on pharmaceuticals and a discussion of criteria for test selection (including species and endpoint selection) and the specific tests to be conducted.

Background

Globally, the widespread environmental presence of low level pharmaceuticals and other organic and inorganic compounds discharged from Wastewater Treatment Plant (WWTP) effluent and released into aquatic ecosystems has led to increased concern and focus on the potential ecological effects and risk to aquatic receptors. Awareness of pharmaceuticals in the aquatic environment arose at the time heightened concerns occurred over the presence and potential effects of endocrine active chemicals (Daston et al. 1997; Vos et al. 2000). It appears that concerns raised for endocrine-active chemicals were assumed to be the same issues that could be expected for pharmaceuticals.

Pharmaceuticals are manufactured to produce a biological effect (i.e., a specific mode of action) and often have similar physical-chemical characteristics of xenobiotics (e.g., can pass through membranes) and they may be persistent (Zuccato et al. 2004) as a result of a specific drug or as a result of continued replacement by the wastewater treatment plant into the aquatic

environment which potentially serves to sustain chronic exposure for aquatic organisms (Daughton and Ternes 1999). The high polarity and low volatility of most pharmaceuticals supports the likeliness that will be ultimately transported to surface water if not removed in treatment (Breton and Boxall 2003) although they are also detected in sediments (Buser et al. 1998; Furlong et al. 2004). The potential environmental effects are largely unknown (Jorgensen and Halling-Sorenson 2000) although 10-15% of certain high-volume pharmaceuticals found in surface waters are toxic (EU 2001; Sanderson et al. 2003).

Although there is an increase in the number of publications concerning the potential toxicity of pharmaceuticals to aquatic organisms there is still little data on the topic, especially for chronic exposures (see below) and exposures to mixtures in effluents (Cleuvers 2003, 2004). In addition to information published in peer-reviewed literature there is unpublished aquatic toxicity data generated in support of regulatory new drug applications in Europe and North America (FDA 1998; EMEA 2001). Ecotoxicological data however are available for less than 1% of the pharmaceuticals in the peer-reviewed literature and ecotoxicological databases (ECE TOX in EU; ECOTOX in U.S.) (Sanderson et al. 2003; Jones et al. 2002; Stuer-Lauridsen et al. 2003; EU 2001) and only few pharmaceuticals have been subjected to ecological risk assessments. In the absence of experimental data, information is derived from quantitative structure-activity relationship (QSAR) predictions by applying U.S. EPA ECOSAR program (Jones et al. 2002; Sanderson et al. 2004).

The lack of ecological risk assessments for pharmaceuticals is partly a result of the fact that the predicted or measured environmental concentrations (PEC or MEC) are lower than the cut-off value for triggering them under regulation. For example, the U.S. Food and Drug Administration (FDA) regulates pharmaceuticals under the National Environmental Policy Act (NEPA) of 1969 through the environmental review process for new drug applications (NDAs) submitted (by drug companies) to FDA. The environmental assessment (EA) procedure for pharmaceutical companies is a two-stage process (FDA 1995). The company is required to estimate the expected introductory concentration (EIC) entering the environment based on 5-year production estimates. If the EIC of the drug (or metabolites) at point of entry (sewage effluents) in the aquatic environment is shown to be less that 1 ug/L (1 ppb) the drug (or metabolites) is considered acceptable and is given environmental "category exclusion" and no further EA is needed and no monitoring is conducted to confirm the environmental concentration after a new

drug is marketed. If the EIC is calculated to be over 1 ppb than a formal EA is conducted which includes environmental fate and a tiered set of ecotoxicity tests. The base set of tests include tests on microbial respiration and acute toxicity to at least one algal, invertebrate and fish species. Chronic testing is only conducted if the drug has potential to bioaccumulate. It should be noted that it has been shown that there is an average of five orders of magnitude between the worst-case current detected pharmaceutic concentrations in surface water and the lowest predicted effect concentrations for acute toxicity for algae, daphnids and fish, indicating low acute hazard (Sanderson et al. 2003)

The majority of aquatic toxicity studies to-date with pharmaceuticals, despite potential exposure to continuous low-level concentrations, have focused on short-term, acute toxicity with algae, daphnias and fish (Ascough et al. 2002; Halling-Sorenson et al. 1998; Webb 2004). Few chronic toxicity studies have been conducted with aquatic organisms being exposed to pharmaceuticals for all (life-cycle) or part (partial life-cycle) of their life span. However, chronic aquatic toxicity tests have been adopted in the most recent draft environmental risk assessment guidance document for human pharmaceuticals produced by the European Medicines Agency (EMEA 2005) in support of Directive 2001/83/EC. Clearly the lack of chronic toxicity data are a major uncertainty for predicting ecological risks of pharmaceuticals.

The recent focus on endocrine-disrupting chemicals (EDC) has yielded chronic ecotoxicity data on synthetic estrogens (Lange et al. 2001; Segner et al. 2003), aromatase inhibitors (Ankley et al. 2004), androgens (Ankley et al. 2003) and antiandrogens (Jensen et al. 2004). Compared with EDCs there is far less information concerning chronic toxicity in aquatic organisms than with other classes of pharmaceuticals.

Below is a preliminary review of the acute and chronic toxicity data for pharmaceuticals.

Acute Toxicity

A review of the acute toxicity data of pharmaceuticals was compiled by Halling-Sorenson et al. (1998) and Webb (2001, 2004). See Appendix C for a summary of the acute toxicity test results of over 100 pharmaceuticals for invertebrates, fish and algae. Fish, *Daphnia magna*, and algae were chosen as representatives of different trophic levels.

Most of the testing was with freshwater organisms. Algae were more sensitive to the pharmaceuticals followed by *Daphnia magna* and fish. The most toxic groups of the various

classes of pharmaceuticals were antidepressants, antibacterials and antipsychotics. Only 10 compounds had acute toxicity less than 1 mg/L. Acute studies however did not focus on the different MOAs of the pharmaceuticals and therefore differences in toxicity in different phyla. The acute toxicity database does however indicate and confirm that acute effects of "single" pharmaceutical compounds to aquatic organisms are unlikely to occur at measured environmental concentrations, since acute effect concentrations are 100-1000 times higher than residues found in the aquatic environment. For example, the lowest acute effect concentration of fluoxetine (serotonin reuptake inhibitor) was 20 μg/L, while the highest estimated environmental concentration was 0.01 μg/L. Therefore, acute toxicity many only be relevant in the case of a spill. Note that the main effect (response) measured in acute tests for fish and invertebrates is mortality and for algae it is growth. Sublethal, physiological effects in fish and invertebrates would go unnoticed in toxicity studies with acute exposures to pharmaceuticals.

Chronic toxicity

A review of the chronic toxicity data of pharmaceuticals was compiled by Webb (2004) and Crane and Watts (2006). See Appendix D for a summary of the chronic toxicity data for algae, invertebrates and fish species. Most chronic toxicity data are available for algae. Fish chronic toxicity data for pharmaceuticals are limited. Available chronic data do not investigate key targets in different organisms and different life stages and tests are usually preformed according to established guidelines. There are presently available standardized methodology for the conduct of chronic tests with fish and invertebrates by U.S. EPA and ASTM. The majority of chronic tests have focused on freshwater organisms however there are studies with marine species including amphipods (Lee and Arnold 1983), copepods (Hutchinson et al. 1999; Anderson et al. 2001) and echinoderms (Pagano et al. 2001). There is little data on chronic toxicity to benthic organisms (infaunal or epifaunal).

The clearest evidence of potential adverse effects from chronic exposure to pharmaceuticals is for the synthetic steroid 17 α-ethinyloestradiol (EE2) which shows effects at extremely low and environmentally relevant concentrations (Lange et al. 2001; Parrott and Blunt 2005). Although little is known about the chronic effects of most pharmaceuticals, an increasing amount is becoming available on the effects of antimicrobial substances (Kummerer 2004).

Criteria for test selection

Ecological considerations. In order to assist in the protection of the quality of surface water and the aquatic environment, aquatic toxicity tests must consider that aquatic ecosystems are mosaics of biomass, chemical processes and physical structure, integrated by biogeochemical cycling and energy flows. There are therefore a number of key aspects that should be protected- 1) ecosystem structure and biodiversity- especially the potential to affect populations of endangered and "keystone" species, 2) ecosystem functions including primary productivity (based on algae and plants) and the key phyla of primary consumers (invertebrates) that are critical to food webs, and 3) economically, commercially and socially important species, including shellfish, fish, and amphibian populations.

It is also important to be aware of interactions between ecosystem components and the potential for indirect (or secondary) effects after a direct effect has occurred.
Some of the latter endpoints will be assessed in the outdoor microcosm study. The use and application of aquatic toxicity tests assumes that ecosystem sensitivity is related to the most sensitive species and protecting ecosystem structure will protect ecosystem processes (Suter 1993).

It is assumed that the effluent from the WRDP will be discharged into freshwater and/or saltwater wetlands. Therefore it will be necessary to have background information on the biological characteristics (e.g., diversity and abundance of phytoplankton, plants, macroinvertebrates, fish) and the physical/chemical properties of the water and sediment of the receiving wetland systems.

Test species. There are a number of criteria to consider when selecting species for aquatic toxicity laboratory tests. It is obviously important and essential that organisms are available year round and that they are easy to hold and acclimate in the laboratory. The relative sensitivity of different organisms to substances including pharmaceuticals must be considered.
For aquatic toxicity testing studies conducted in ecological risk assessment programs used for chemicals including pharmaceuticals regulatory agencies may require water column species from the following groups- phytoplankton/plants, zooplankton, vertebrates (fish and amphibians) and benthic invertebrates species (amphipods, chironomids) for sediment tests. There is no guarantee

that the specific species selected to represent each of the latter trophic groups will be sufficient to assess the potential hazard of drugs (or other chemicals) in the complex treated effluent. In order to support a more refined assessment of the treated effluent, it is suggested that a number of species (i.e., 3-5) from each trophic group are selected for both fresh- and salt-water toxicity testing. This would conform to the existing approach typically used by regulatory agencies in developing numerical water and sediment quality criteria. The laboratory test exposure scenarios would then include 3-5 species/trophic group in fresh- and salt-water including fresh- and salt-water sediment tests with 3-5 benthic species.

The specific species selected will also depend on the substances found in the complex secondary effluent from the SDWWTP. For example, if antibiotics are detected in effluents blue-green algae will be used because they are more sensitive than green algae (Holten Lutzhoft et al. 1999; Ferrari et al. 2003) and higher plants will be used as the chloroplast may be directly affected (Krajcovic et al. 1989). Final species selection will ultimately depend on the substances present in the discharged treated secondary effluent.

Where possible native species should be used in toxicity tests; alternatively, standard test species can be used. With standard test species there is large database of tests with different substances to provide a background on relative sensitivities. Using some standard test species as part of the toxicity testing for each group will allow one to cover potentially a broad range of sensitivities.

Endpoint selection. To estimate the potential impact on populations, the most commonly used effect endpoints measured are survival, development, growth and reproduction. Acute toxicity tests will be used to primarily assess effects of the "whole effluent" on survival. Chronic toxicity tests (partial and full life cycle) will assess effects of long- term exposure on survival, development, growth and reproduction. These endpoints have been widely accepted in a variety of U.S. and international standard aquatic toxicity test guidelines (e.g., USEPA, ASTM, ISO, OECD) and are used in probabilistic ecological risk assessments.

Some measurements like survival and reproduction data from laboratory test can be used to model predicted impacts of chemicals on wild fish populations (Brown et al., 2003). Growth is a relevant endpoint that can be used to assess the toxicity of chemicals to algae and higher plants (Cleavers and Ratte 2002; Lewis 1995), invertebrates (Sibley et al. 1997), and fish (Rand 1995;

USEPA 2002a, b). Reproduction in invertebrates and fish has also been a valuable endpoint evaluated in chronic studies (Rand 1995).

However, acute and chronic toxicity tests will also capture the range of MOAs (i.e., from substances in effluent) and potential organism responses elicited by the substances. Therefore, special endpoints/responses (e.g., inhibition of an enzyme, behavioral changes) will be measured and evaluated in acute and chronic tests based on the MOA of the specific substance(s) present in the effluent. The final definitive testing plan will list the specific test and/or endpoints based on potential substance(s) present and MOAs. Note that standard toxicity tests may tend to underestimate these specific effects if they do not address relevant receptor-mediated effects, contain the appropriate sensitive species, and consider exposure at different life stages.

Conceptual Toxicity Test Plan

The test plan includes two phases-laboratory toxicity testing and outdoor microcosm studies.

Laboratory Plan

The laboratory toxicity whole (treated) effluent toxicity (WET) tests will be conducted on-site, and at the plant, to eliminate physical-chemical changes that may occur as a result of transporting effluents off-site for testing. Flow-through exposures will be used for all acute and chronic tests but static acute exposures will also be considered for special scenarios. When the combined effects of a mixture of substances in whole effluent are taken into account both acute and chronic exposures must be considered. Acute and chronic WET tests will be conducted with fresh- and salt-water species and will include microbes, phytoplankton, vascular plants, zooplankton, benthic invertebrates and two classes of vertebrates (fish and amphibians). It should be qualified that if chemical analyses of effluents show the presence of primarily compounds like anesthetics (e.g., benzocaine, tricaine, esters of p-aminobenzoic acid) which produce a generalized “narcosis” effect in organisms, short-term acute testing may be sufficient because they typically have low potency with little systemic potential. Specific organism selection will be based on representation of major groups (phyla) from the freshwater and saltwater ecosystems that will be the receiving systems. The background ecology information of the receiving systems will assist in the final species selection. Laboratory tests will be conducted

to encompass the cyclical and seasonal changes that may occur in the quality and quantity of the effluent. Standardized, well- characterized test methods will be used, whenever possible. Specific toxicity tests can not be fully defined until an analysis of the effluent is conducted over time. The types of substances (e.g., drug) detected in the effluent and their mode of action (i.e., target site(s)) will define the type of test and/or special endpoints that should be measured because they are sensitive and specific enough to detect potential effects. For example, if steroidal estrogens are present (e.g., EE2), testing should include partial- and full-life cycle tests with a variety of vertebrate and invertebrate species focused on evaluating effects on early development (e.g., sexual differentiation) and reproduction because of the MOA of this group.

It is suggested that the following base set of laboratory tests be conducted with 3-5 fresh- and salt-water species from each group (note that with amphibians only one freshwater species will be used) below.

1) Algae and Microbes- three- to four-day exposures; measuring growth inhibition and stimulation, photosynthesis, and morphological and physiological changes
2) Vascular Plants- one to six week exposures; measuring growth (e.g.,, changes in chlorophyll a content, root length, plant number, shoot length, plant dehydrogenase activity)
3) Zooplankton- three to four week exposures, encompassing full life cycle (from neonate to adult and reproduction), depending on species; measuring survival and developmental changes, growth and reproduction
4) Benthic Invertebrates (infaunal and epifaunal)- up to four week exposures; measuring survival, growth, and reproduction
5) Fish- 30-60 day exposures (partial life cycle) up to 9 months (full life cycle), depending on species; measuring survival, growth, developmental abnormalities, reproduction (e.g., fecundity, embryo hatchability, number of spawns)
6) Amphibians- metamorphosis assay initiated with tadpoles and continued for two-four weeks through major developmental events measuring morphological changes and a number of molecular biomarkers. This type of test may also be considered a supplemental test or necessary when substance(s) present are known (or suspected) of affecting thyroid function because of the known sensitivity of metamorphosis to substances that adversely affect the thyroid system. Another amphibian test (FETAX) that will be considered is a

developmental toxicity assay using frog embryos for short-term exposures (<1 week) measuring embryo death, embryo malformations and growth. It has also been used extensively with effluents.

Water and tissue will be analyzed for chemical residues (parent and metabolites, if known) in all WET tests. When sediment is used (with benthic invertebrates) in toxicity tests it will be analyzed for residues as well along with the physical characteristics of the sediment. Water quality (e.g., hardness, alkalinity, specific conductivity, pH, dissolved oxygen, NH_3) and temperature will be measured in all tests. Responses at the molecular, cellular and tissue levels will be considered in all tests when we use the mode of action (if available) of substances to define special tests or special test endpoints (e.g., biochemical measurements, secondary sexual characteristics, tissue changes). In all tests critical (sensitive) life stages will always be considered. The definitive toxicity testing plan will be prepared with the comprehensive review of the literature and include suggestions of species to use (with rationale) and specific toxicity test designs with protocols for each test.

Supplemental tests. Bioconcentration tests (uptake phase: 30-day whole effluent exposure followed by depuration phase: 14- days in untreated water) with fish may be conducted to determine if accumulation of substances in the whole effluent occur in exposed biota and whether substance(s) are excreted (depurated) when placed in clean water. Chemical analyses of effluent will indicate the substances (organic, inorganic) present and the physical-chemical characteristics of the substance(s) detected will provide information on which substance should be considered for bioconcentration tests. Bioconcentration factors, uptake and depuration rates will be determined along with half-lives in these tests. Pharmaceuticals are typically water-soluble and based solely on log octanol:water partition coefficients (log K_{ow}) they are not expected to bioconcentrate to any appreciable extent in biota. In most cases bioconcentration tests should only be conducted when effluents contain substance(s) with log $K_{ow} > 3$. It should be noted that regardless of K_{ow} large molecules (mass>700) do not bioconcentrate. Also some substances with log $K_{ow} < 3$ should be considered when there is potential uptake via active transport.

Outdoor Microcosm Plan

Model ecosystems like microcosms will be conducted to evaluate the potential effects of long-term exposure to substances in whole effluent and their ultimate distribution and fate in small outdoor fiberglass tanks ($7.5m^3$). The term "microcosm" refers to a wide variety of experimental systems ranging from small laboratory flasks to large outdoor tanks. The distinguishing feature of microcosms is the inclusion of multiple ecological components (species, functional groups, or habitat types). Microcosms bridge the gap between simple laboratory test systems and full-scale field studies. Microcosms can be used to measure temporal changes in exposure and effects in diverse communities simultaneously and thus assess both direct and indirect effects as well as potential recovery. Microcosms have several disadvantages compared to natural ecosystem studies (Rand 1995) but nonetheless they are an essential tool in risk assessment to bridge the void between single-species laboratory tests and the natural environment. They will provide an ecosystem assemblage that will allow monitoring of both structural as well as functional responses to effluent exposure overtime. They have been extensively used to measure higher level responses to pesticides (Rand et al. 2000a, 2000b) but for effluents and pharmaceuticals, microcosms have been used on a limited scale (Brain et al. 2004; Richards et al., 2004).

Replicated outdoor freshwater microcosms will be seeded with water, sediment and organisms (e.g., native phytoplankton, periphyton, vascular plants, zooplankton, macroinvertebrates, fish). Microcosms will be exposed to effluent at different volume percents. Concentration of effluent is usually expressed as volume percent. For example, a 10% dilution equals 1 volume of effluent in 9 volumes of dilution water. The design of the outdoor microcosm study will include 3-4 volume percent treatments and an untreated control treatment with three replicates per treatment. The study will be conducted for three to four months. A microcosm study may be conducted two times during the course of a year to encompass changes in effluent quality and quantity that may arise as a result of seasonal variability. A salt-water microcosm study will be considered.

The sediment will be characterized. Physical/chemical water quality measurements in the different treatments (including the initial dilution water source) will be taken in all microcosms at the beginning, during and at the end of the study. Chemical analyses of water and sediment

will include organic contaminants (e.g., pesticides, PAHs, pharmaceuticals, active ingredients in personal care products), metals, nutrients, and industrial chemicals. Organisms will be identified and enumerated. Tissues will be sampled for chemical residues in biota (primarily fish and invertebrates).

Biological variables (structural & functional) will be measured and analyzed and include:

Phytoplankton

Chlorophyll-a

Total phytoplankton density

Individual genera

Taxonomic richness

Periphyton

Chlorophyll-a

Ash-free dry weight

Autotrophic index

Total periphyton density

Individual genera

Taxonomic richness

Zooplankton

Total zooplankton

Individual genera

Taxonomic richness

Macroinvertebrates

Total macroinvertebrates

Individual genera

Taxonomic richness

Fish

Individual fish weights and weights

Survival

Condition index

Functional Processes

Primary Productivity/Respiration

The sampling schedule, specific sampling methods, experimental design, data analysis and interpretation of results for a microcosm study will be discussed in a protocol and included in the final definitive toxicity plan.

Conceptual Environmental Fate Test Plan

Depending on treatment technologies used to remove pollutants from the secondary effluent from SDWWTP, low concentrations of certain pollutants, including pharmaceuticals may be found in the treated secondary effluent. Fate processes ultimately control the transport, transformation, and distribution of a substance in the environment. The final form or state (e.g., parent, metabolite) of the pollutant, the compartment (soil, sediment, water) where it mostly likely will be found and the exposure concentrations in the environmental compartment(s) needed for ecological risk assessments can be obtained from this fate information.

All organic substances, including all pollutants and pharmaceuticals in the treated secondary effluent (with) may be attenuated in the aquatic environment by the same processes that are important in wastewater treatment plants-biodegradation and sorption. In surface water, concentrations of pollutants may change as a result of photolysis and hydrolysis (and of course dilution). Particle-bound pollutants may settle on sediments and undergo aerobic and anaerobic degradation. The physical-chemical properties of the individual pollutants will determine the partitioning of the pollutant into different environmental compartments and the form. The important properties that affect the fate and transport of organic pollutants are: water solubility, dissociation constants, octanol-water partition coefficient (K_{ow}), and the distribution coefficient (K_d) (or organic carbon-normalized distribution coefficient (K_{oc})). The important processes that affect transformation of organic pollutants in the environment are: biodegradation rate, hydrolysis rate, photolysis rate, and oxidation-reduction rates. Volatilization and hydrolysis are not as important for pharmaceuticals (exception, certain antibiotics like β-lactam which has a fast hydrolytic half-life). For most individual pollutants (single substances) including pharmaceuticals, chemical and pharmaceutical companies have generated the physical-chemical characteristic data and information on transformation processes as part of their testing

requirements for registration. In some cases, models for Quantitative-Structure Activity Relationships (QSARs) have been used for predicting physical-chemical characteristics.

For those pollutants present in the treated secondary effluent the environmental fate tests will help us determine: where they will reside (e.g., bound to sediment, in water), the form/state(s) (e.g., parent, metabolite) they will be in, residence time and the exposure concentrations for each pollutant in the aquatic environment. Currently, there are three GIS-based models being used for estimating concentrations for pharmaceuticals in the environment. The P*h*ATE model (Anderson et al. 2004) has been used in the U.S. for surface waters. The model is based on 11 watersheds and it has a screening mode using conservative estimates and a more realistic mode using available fate data. The current version does not consider estuarine or marine environments. GREAT-ER (georeferenced regional exposure assessment tool for European rivers) is a catchment scale model for predicting concentrations of consumer products in surface waters (Feijtel et al. 1997). GIS-ROUT is an internet /GIS-based model that predicts surface water concentrations for chemicals at broad geographic scales using per capita loadings and U.S. municipal discharge information (Dyer et al. 2002; White-Hull 2002). Coupling GIS-ROUT with toxicity effect distributions (i.e., from laboratory toxicity test results on single-species or SSDs; species sensitivity distributions) will provide a measure of potential risk. Based on the pollutants present in the treated secondary effluent and data on their physical-chemical characteristics (i.e., obtained from databases) and the characteristics of the potential receiving systems (i.e., wetland systems) we will use fate models to estimate concentrations of the pollutants, relevant environmental compartment (e.g., surface water, sediment) and residence times in the receiving systems. There are a variety of U.S.EPA models that we will also consider.

We will also conduct environmental fate tests in the laboratory. The available physical-chemical, transformation and stability data will first be reviewed for all pollutants detected in the treated secondary effluent to determine the most important removal mechanisms for each pollutant. For example, the data from the SDWWTP may indicate that biodegradation is a primary removal process for certain pollutants. Therefore, aerobic and anaerobic biodegradation studies in sediment and water will be conducted. Standardized scientific methods are available for fate and transport tests by U.S.EPA and OECD and will be used for this type of testing. Photolysis also plays an important role in degradation of organic pollutants including pharmaceuticals. Therefore, photolysis studies will be considered as part of the fate testing plan.

Although hydrolysis is not a major removal process for pharmaceuticals it will be considered part of the environmental fate testing for other pollutants. Therefore, aerobic and anaerobic biodegradation, photolysis and hydrolysis fate tests will be considered for all detectable pollutants but the final decision on type(s) of tests to conduct will depend on the physical-chemical characteristics of the pollutant. Tests will be conducted using site-specific sediment and water from the potential receiving wetland systems, wherever possible. These tests will provide information on parent compound and metabolites-degradation rates (e.g., half-life) and residence times, final form and likely target compartment(s). Data from these fate tests with site-specfic data will be used to refine models for more accurate predictions of environmental concentrations in wetland habitats.

APPENDIX A- LITERATURE REVIEW

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APPENDIX B- U.S.EPA LITERATURE REVIEW

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APPENDIX C- ACUTE TOXICITY DATA FOR PHARMACEUTICALS

Table 1. Acute ecotoxicity data for human pharmaceuticals

Compound	Category[a]	Value ($mg l^{-1}$)	Endpoint/ Duration[b]	Species	Reference
Acarbose	Antidiabetic	>1000	EC_{50}	Unspecified fish	FDA-CDER (1996)
Acarbose	Antidiabetic	>1000	EC_{50}	*Daphnia* spp.	FDA-CDER (1996)
Acriflavine	Anti-infective	5	96h LC_{50}	*Morone saxoNlis* (larvae)	Hughes (1973)
Acriflavine	Anti-infective	30.0	48h LC_{50}	*Morone soxatilis* (fingerling)	Hughes (1973)
Acriflavine	Anti-infective	28.0	72h LC_{50}	*Marone soxoNlis* (fingerling)	Hughes (1973)
Acriflavine	Anti-infective	27.5	96h LC_{50}	*Morone saxoNlis* (fingerling)	Hughes (1973)
Acriflavine	Anti-infective	30.1	24h LC_{50}	*Oncorhynchus mykiss*	Wilford (1966)
Acriflavine	Anti-infective	19.9	43h LC_{50}	*Oncorhynchus mykiss*	Wilford (1966)
Acriflavine	Anti-infective	37.5	24h LC_{50}	*Salvelinus namaycush*	Wilford (1966)
Acriflavine	Anti-infective	28.0	48h LC_{50}	*Solvelinus namaycush*	Wilford (1966)
Acriflavine	Anti-infective	40.0	24h LC_{50} .	*Solmo trurto*	Wilford (1966)
Acriflavine	Anti-infective	27.0	48h LC_{50}	*Salmo trurta*	Wilford (1966)
Acriflavine	Anti-infective	43.5	24h LC_{50}	*Ictalurus punctatus*	Wilford (1966)
Acriflavine	Anti-infective	33.2	48h LC_{50}	*Ictalurus punctatus*	Wilford (1966)
Acriflavine	Anti-infective	48.0	24h LC_{50}	*Solvelinus fontinalls*	Wilford (1966)
Acriflavine	Anti-infective	14.8	48h LC_{50}	*Salvelinus fonNnalis*	Wilford (1966)
Acriflavine	Anti-infective	18.0	24h LC_{50}	*Lepomis mocrochirus*	Wilford (1966)
Acriflavine	Anti-infective	13.5	48h LC_{50}	*Lepomis macrochirus*	Wilford (1966)
Alendronate sodium	Metabolic disease	1450	LC_{50}	*Pimephales promelos*	FDA-CDER (1996)
Alendronate sodium	Metabolic disease	>1000	LC_{50}	*Oncorhynchus mykiss*	FDA-CDER (1996)
Alendronate sodium	Metabolic disease	22	LC_{50}	*Daphnia* spp.	FDA-CDER (1996)
Alendronate sodium	Metabolic disease	>0.5	MIC	Green algae	FDA-CDER (1996)
Aminosidine	Antibacterial; antiamebic	2220	48h EC_{50}	*Artemia*	Migliore et al. (1997)
Aminosidine	Antibacterial; antiamebic	847	72h EC_{50}	*Artemia*	Migliore et al. (1997)
Aminosidine sulfate (Neomycin E)	Antibacterial; antiamebic	1055	24h LC_{50}	*D. magna*	Di Delupis et al. (1992)
Aminosidine sulfate (Neomycin E)	Antibacterial; antiamebic	503	48h LC_{50}	*D. magna*	Di Delupis et al. (1992)
Amitriptyline	Antidepressant	1.2	24h EC_{50}	*D. magna*	Lilius et al. (1994)
Amitriptyline	Antidepressant	36.9	24h LC_{50}	*Artemia salina*	Calleja et al. (1994b)

Table 1. *Continued*

Compound	Category[a]	Value ($mg l^{-1}$)	Endpoint/ Duration[b]	Species	Reference
Amitriptyline	Antidepressant	0.78	24h LC_{50}	*Streptocephalus proboscideus*	Calleja et al. (1994b)
Amitriptyline	Antidepressant	5.55	24h EC_{50}	*D. magna*	Calleja et al. (1994b)
Amitriptyline	Antidepressant	0.80	2411 LC_{50}	*Brochionus*	Calleja et al. (1994b)
Amobarbital	Sedative;	85.4	96h EC_{50}	*Pimephales*	Russom et al. (1997)
Amopyroquin dihydrochloride	Antimalarial	47.0	2411 LC_{50}	*Oncorhynchus*	
Amopyroquin dihydrocl1loride	Antimalarial	35.3	48h LC_{50}	*Oncorhynchus*	
Amopyroquin dihydrochlonde	Antimalarial	15.5	24h LC_{50}	*Salvelinus*	
Amopyroquin dihydrochloride	Antimalarial	140	48h LC_{50}	*Sa/velinus*	
Amopyroquin dihydrochlonde	Antimalarial	42.0	24h LC_{50}	*Salmo trutta*	
Amopyroquin dihydrochloride	Antimalarial	360	48h LC_{50}	*Salmo truua*	
Amopyroquin dihydrochloride	Antimalarial	19.8	24h LC_{50}	*letalurus punetatus*	
Amopyroquin dihydrochloride	Antimalarial	12.5	48h LC_{50}	*letalurus punetatus*	
Amopyroquin dihydrochloride	Antimalarial	52.0	2411 LC_{50}	*Salvelinus*	
Amopyroquin dihydrochloride	Antimalarial	40.0	48h LC_{50}	*Salvelinus*	
Amopyroquin dihydrochloride	Antimalarial	330	24h LC_{50}	*Lepomis*	
Amopyroquin dihydrochloride	Antimalarial	18.5	48h LC_{50}	*Lepomis*	
Amphetamine	CNS stimulant; anorexic	28.8	96h EC_{50}	*Pimephales*	Russom et al. (1997)
Amphetamine	CNS stimulant; anorexic	60	24h EC_{50}	*D. magna*	Lilius et al. (1994)
Amphetamine	CNS stimulant; anorexic	1515	24h LC_{50}	*Artemia salina*	Calleja et al. (1994b)
Amphetamine	CNS stimulant; anorexic	S5	24h LC_{50}	*Streptocephalus proboscidws*	Calleja et al. (1994b)
Amphetamine	CNS stimulant; anorexic	270	24h EC_{50}	*D. magna*	Calleja et al. (1994b)
Amphetamine	CNS stimulant; anorexic	4.90	24h LC_{50}	*Brachionus*	Calleja et al. (1994b)
Aprotinin	Enzyme (protease)	>1000	EC_{50}	*Daphnia* spp.	FDMDER (1996)

Table 1. *Continued*

Compound	Category[a]	Value ($mg l^{-1}$)	Endpoint/ Duration[b]	Species	Reference
Aspirin	Analgesic; antipyretic; anti-inflammatory	1468	24h EC_{50}	*D. magna*	Lilius et al. (1994)
Aspirin	Analgesic; antipyretic; anti-inflammatory	382	24h LC_{50}	*Artemia salina*	Calleja et al. (1994b)
Aspirin	Analgesic; antipyretic; anti-inflammatory	178	24h LC_{50}	*Streptocephalus proboscideus*	Calleja et al. (1994b)
Aspirin	Analgesic; antipyretic; anti-inflammatory	168	24h EC_{50}	*D. magna*	Calleja et al. (1994b)
Aspirin	Analgesic; antipytetic; anti-inflammatory	141	24h LC_{50}	*Brachionus calyciflorus*	Calleja et al. (1994b)
Atropine sulfate	Anticholinergic; mydriatic	258	24h EC_{50}	*D. magna*	Lilius et al. (1994)
Atropine sulfate	Anticholinergic; mydriatic	15773	24h LC_{50}	*Attemia salina*	Calleja et al. (1994b)
Atropine sulfate	Anticholinergic; mydriatic	661	24h LC_{50}	*Streptocephalus proboscideus*	Calleja et al. (1994b)
Atropine sulfate	Anticholinergic; mydriatic	356	24h EC_{50}	*D. magna*	Calleja et al. (1994b)
Atropine sulfate	Anticholinergic; mydriatic	334	24h LC_{50}	*Brachionus calycif/orus*	Calleja et al. (1994b)
Azithromycin	Antibacterial	>120	LC_{50}	Unspecified amphipod	FDA-COER (1996)
Azithromycin	Antibacterial	120	EC_{50}	*Daphnia* spp.	FDA-COER (1996)
Bacitracin	Antibacterial	34.	24h LC_{50}	*Artemia salina* (nauplii)	Migliore et al. (1997)
Bacitracin	Antibacterial	21.	48h EC_{50}	*Artemia salina* (nauplii)	Migliore et al. (1997)
Bacitracin	Antibacterial	34.	24h LC_{50}	*Artemia salina* (nauplii)	Brambilla et al. (1994)
Bacitracin.	Antibacterial	21.	48h LC_{50}	*Artemia salina* (nauplii)	Brambilla et al. (1994)
Bacitracin	Antibacterial	126	24h LC_{50}	*D. magna*	Brambilla et al. (1994)
Bacitracin	Antibacterial	30.	48h LC_{50}	*D. magna*	Brambilla et al. (1994)
Bacitracin	Antibacterial	126	24h LC_{50}	*D magna*	Di Delupis et al. (1992)
Bacitracin	Antibacterial	30.	48h LC_{50}	*D. magna*	Di Delupis et al. (1992)
Bicalutamide	Non-steroidal antiandrogen	>5	EC_{50}	*Daphnia* spp.	FDA-COER (1996)
Bicalutamide	Non-steroidal antiandrogen	>1	EC_{50}	Unspecified green algae	FDA-COER (1996)

Table 1. *Continued*

Compound	Category[a]	Value ($mg l^{-1}$)	Endpoint/ Duration[b]	Species	Reference
Bicalutamide	Non-steroidal antiandrogen	>1	EC_{50}	Unspecified blue-green algae	FDA-COER (1996)
Budesonide	Anti-infiammatory	20	EC_{50}	*Daphnia* spp.	FDA-CDER (1996)
Budesonide	Anti-infiammatory	>19	LC_{50}	Unspecified fish	FDA-COER (1996)
Caffeine	CNS stimulant	151	96h EC_{50}	*Pimephales promelas*	Russom et al. (1997)
Caffeine	CNS stimulant	684	24h EC_{50}	*D. magna*	Lilius et al. (1994)
Caffeine	CNS stimulant	3457	24h LC_{50}	*Artemia salina*	Calleja et al. (1994b)
Caffeine	CNS stimulant	410	24h LC_{50}	*S. proboscideus*	Calleja et al. (1994b)
Caffeine	CNS stimulant	160	24h EC_{50}	*D. magna*	Calleja et al. (1994b)
Caffeine	CNS stimulant	4661	24h LC_{50}	*Brachionus*	Calleja et al. (1994b)
Carvedilol	Antihypertensive; antianginal	>3	EC_{50}	*Daphnia* spp.	FDA-CDER (1996)
Carvedilol	Antihypertensive; antianginal	1	LC_{50}	Unspecified fish	FDA-COER (1996)
Cefprozil	Antibacterial	>642	EC_{50}	*Daphnia* spp.	FDA-COER (1996)
Ceftibuten	Antibacterial	>600	EC_{50}	*Daphnia* spp.	FDA-CDER (1996)
Ceftibuten	Antibacterial	>520	LC_{50}	Arnphipod	FDA-CDER (1996)
Cetirizine HCI	Antihistarninic	330	EC_{50}	*Daphnia* spp.	FDA-CDER (1996)
Chloramine T	Antibacterial	23.6	24h LC_{50}	*Penaeus setirerus*	Johnson (1976)
Chloramine T	Antibacterial	22	96h LC_{50}	*Rasbara heteromorpha*	Tooby et al. (1975)
Chloramphenicol	Antibacterial; anti rickettsial	543	24h EC_{50}	*D. magna*	Lilius et al. (1994)
Chloramphenicol	Antibacterial; a nti rickettsia I	2042	24h LC_{50}	*Artemia salina*	Calleja et al. (1994b)
Chloramphenicol	Antibacterial; antirickettsial	305	24h LC_{50}	*Streptocephalus proboscideus*	Calleja et al. (1994b)
Chloramphenicol	Antibacterial; antirickettsial	1086	24h EC_{50}	*D. magna*	Calleja et al. (1994b)
Chloramphenicol	Antibacterial; anti rickettsial	2074	24h LC_{50}	*Brachionus*	Calleja et al. (1994b)
Chloroquine phosphate	Antimalarial; antiamebic; antirheumatic	50	24h EC_{50}	*D. magna*	Lilius et al. (1994)
Chloroquine phosphate	Antimalarial; antiamebic; antirheumatic	2043	24h LC_{50}	*Artemia salina*	Calleja et al. (1994b)
Chloroquine phosphate	Antimalarial; antiamebic; antirheumatic	11.7	24h LC_{50}	*Streptocephalus proboscideus*	Calleja et al. (1994b)
Chloroquine phosphate	Antimalarial; antiamebic; antirheumatic	43.5	24h EC_{50}	*D. magna*	Calleja et al. (1994b)

Table 1. *Continued*

Compound	Category[a]	Value ($mg l^{-1}$)	Endpoint/ Duration[b]	Species	Reference
Chloroquine phosphate	Antimalarial; antiamebic; antirheumatic	4.39	24h LC_{50}	*Brachianus ca/ycif/arus*	Calleja et al. (1994b)
Cimetidine	Anti~ulcerative	740	EC_{50}	*Daphnia* spp.	FDA~CDER (1996)
Cimetidine	Anti~ulcerative	>1000	LC_{50}	*Lepamis macrachirus*	FDA~CDER (1996)
Cisapride	Peristaltic stimulant	>1000	EC_{50}	*Daphnia* spp.	FDA~CDER (1996)
Cisapride	Peristaltic stimulant	>1000	LC_{50}	*Lepamis macrachirus*	FDA~CDER (1996)
Cladribine	Antineoplastic	233	EC_{50}	*Daphnia* spp.	FDA~CDER (1996)
Clofibrate	Antihyperlipo-proteinemic	28.2	24h EC_{50}	*D. magna*	K6pf (1995)
Clofibrate	Antihyperlipo-proteinemic	12.0	EC_{50}	Unspecified algae	K6pf (1995)
Clofibrinic acid	Antihyperlipo-proteinemic	106	EC_{50}	*D. magna*	Henschel et al. (1997)
Clofibrinic acid	Antihyperlipo-proteinemic	86.0	48h EC_{50}	*Brachydania reria* (embryos)	Henschel et al. (1997)
Clofibrinic acid	Antihyperlipo-proteinemic	89	72h EC_{50}	*Scenedesmus subspicotus*	Henschel et al. (1997)
Cyclosporine	Immunosuppressant	>100	LC_{50}	*Oncorhynchus mykiss*	FDA~CDER (1996)
Cyclosporine	Immunosuppressant	20	EC_{50}	*Daphnia* spp.	FDA~CDER (1996)
Dextroproproxyphene HCI	Narcotic analgesic	14.6	24h EC_{50}	*D. magna*	Lilius et al.(1994)
Dextroproproxyphene HCI	Narcotic analgesic	308	24h LC_{50}	*Artemia salina*	Calleja et al. (1994b)
Dextroproproxyphene HCI	Narcotic analgesic	7.6	24h LC_{50}	*Streptacepha/us prabascideus*	Calleja et al. (1994b)
Dextroproproxyphene HCI	Narcotic analgesic	19	24h EC_{50}	*D. magna*	Calleja et aL (1994b)
Dextroproproxyphene HCI	Narcotic analgesic	42	24h LC_{50}	*Brachianus co/ycil/arus*	Calleja et al. (1994b)
Diazepam	Anxiolytic; muscle relaxant	65.4	24h LC_{1O}	*Artemia salina*	Calleja et al. (1994b)
Diazepam'	Anxiolytic; muscle relaxant	103	24h LC_{50}	*Streptocepha/us proboscideus*	Calleja et al. (1994b)
Diazepam	Anxiolytic; muscle relaxant	14.1	24h EC_{50}	*D. magna*	Calleja et al. (1994b)
Diazepam	Anxiolytic; muscle relaxant	> 10	24h LC_{50}	*Brochionus co/ycif/arus*	Calleja et al. (1994b)
Diazepam	Anxiolytic; muscle relaxant	4.3	24h EC_{50}	*D. magna*	Lilius et al. (1994)
Didanosine	Anti(retro)viral	>1020	EC_{50}	*D. magna*	FDA~CDER (1996)
Diethylstilbestrol	Oestrogen	4.0	LC_{50}	*D. magna*	Coats et aL (1976)
Diethylstilbestrol	Oestrogen	>10	LC_{50}	*Physa* spp.	Coats et aL (1976)
Diethylstilbestrol	Oestrogen	>1	48h LC_{50}	*Gombusia alfinis*	Coats et aL (1976)

Table 1. *Continued*

Compound	Category[a]	Value ($mg l^{-1}$)	Endpoint/ Duration[b]	Species	Reference
Diethylstilbestrol	Oestrogen	1.09	48h LC_{50}	*D. magna*	Zou and Fingerman (1997)
Diethylstilbestrol	Oestrogen	1.2	48h LC_{50}	*D. magna*	Baldwin et al. (1995)
Diethylstilbestrol	Oestrogen	316	14d LC_{50}	*Pimepha/es promelas*	Panter et al. (1999)
Digoxin	Cardiotonic	24	24h EC_{50}	*D. magna*	Lilius et al. (1994)
Dirithromycin	Antibacterial	>2880	LC_{50}	*Oncorhynchus mykiss*	FDA-COER (1996)
Dirithromycin	Antibacterial	>48	EC_{50}	*D. magna*	FDA-COER (1996)
Dorzolamide HCI	Carbonic anhydrase inhibitor, treatment of glaucoma	>1000	LC_{50}	*Pimephales prome/as*	FDA-COER (1996)
Dorzolamide HCI	Carbonic anhydrase inhibitor, treatment of glaucoma	699	EC_{50}	*D. magna*	FDA-COER (1996)
Erythromycin	Antibacterial	388	24h LC_{50}	*D. magna*	Di Delupis et al. (1992)
Erythromycin	Antibacterial	211	48h LC_{50}	*D. magna*	Di Delupis et al. (1992)
Erythromycin phosphate	Antibacterial	818	24h LC_{50}	*Sa/velinus namaycush*	Marking et al. (1988)
Erythromycin phosphate	Antibacterial	410	96h LC_{50}	*Salvel/nus namaycush*	Marking et al. (1988)
Erythromycin thiocyanate	Antibacterial	>80	48h LC_{50}	*Oncorhynchus mykiss, Sa/ma trutta, font/nalis, Ictafurus punctatus, Lepamis macrochirus* and *Sa/velinus namaycush*	Wilford (1966)
Ethinyloestradiol	Oestrogen	5.7	24h EC_{50}	*D. magna*	K6pf (1995)
Ethinyloestradiol	Oestrogen	0.84	EC_{50}	Unspecified algae	K6pf (1995)
Ethinyloestradiol	Oestrogen	6.4	48h EC_{50}	*D. magna*	Schweinfurth et al. (1996b)
Ethinyloestradiol	Oestrogen	1.6	96h EC_{50}	*Oncorhynchus mykiss*	Schweinfurth et al. (1996b)
Etidronic acid	Metabolic bone Disease	200	96h LC_{50}	*Oncorhynchus mykiss*	Gledhill and Feijtel (1992)
Etidronic acid	Metabolic bone disease	868	96h LC_{50}	*Lepomis macrochirus*	Gledhill and Feijtel (1992)
Etidronic acid	Metabolic bone disease	695	48h LC_{50}	*Icta/urus punctatus*	Gledhill and Feijtel (1992)
Etidronic acid	Metabolic bone disease	3.0	96h EC_{50}	Unspecified algae	Gledhill and Feijtel (1992)
Etidronic acid	Metabolic bone disease	527	48h EC_{50}	*D. magna*	Gledhill and Feijtel (1992)
Famciclovir	Antiviral	>986	LC_{50}	*Lepomis macrochirus*	FDA-CDER (1996)
Famciclovir	Antiviral	820	EC_{50}	*D. magna*	FDA-COER (1996)

Table 1. *Continued*

Compound	Category[a]	Value ($mg1^{-1}$)	Endpoint/ Duration[b]	Species	Reference
Famotidine	Anti-ulcerative	>680	LC_{50}	*Pimephafes promelas*	FDA-COER (1996)
Famotidine	Anti-ulcerative	398	EC_{50}	*D. maqno*	FDA-COER (1996)
Finasteride	Treatment of benign prostatic hypertrophy	21	EC_{50}	*Daphnio* spp	FDA-COER (1996)
Finasteride	Treatment of benign prostatic hypertrophy	20	LC_{50}	*Oncorhynchus mykiss*	FDA-COER (1996)
Flumazenil	Benzodiazepine antagonist	>500	EC_{50}	*D. moqna*	FDA-COER (1996)
Flumequine	Antibacterial	476.8	24h EC_{50}	*Artemia salina* (nauplii)	Migliore et al. (1997)
Flumequine	Antibacterial	307.7	48h EC_{50}	*Artemia salina* (nauplii)	Migliore et al. (1997)
Flumequine	Antibacterial	96.4	72h EC_{50}	*Artemia salina* (nauplii)	Migliore et al. (1997)
Flumequine	Antibacterial	477	24h LC_{50}	*Artemia salina* (nauplii)	Brambilla et al. (1994)
Flumequine	Antibacterial	308	48h LC_{50}	*Artemia salina* (nauplii)	Brambilla et al. (1994)
Flumequine	Antibacterial	964	72h LC_{50}	*Artemia salina* (nauplii)	Brambilla et al. (1994)
Flutamide	Androgen	>1000	14d LC_{50}	*Pimephafes promelos*	Panter et al. (1999)
Fluticasone propionate	Corticosteroid antiasthmatic	0.55	EC_{50}	*Daphnia* spp.	FDA-COER (1996)
Fluoxetine HCI	Antidepressant	0.94	EC_{50}	*Daphnia* spp.	FDA-COER (1996)
Fluoxetine HCI	Antidepressant	2.0	LC_{50}	*Oncorhynchus mykiss*	FDA-COER (1996)
Fluoxetine HCI	Antidepressant	0.03	EC_{50}	Unspecified green algae	FDA-COER (1996)
Fluoxetine	Antidepressant	1.55	4h LOEC	*Sphaerium* spp.	Fong *et* al. (1998)
Fluvoxamine maleate	Antidepressant	63	MIC	Unspecified algae	FDA-COER (1996)
Fluvoxamine	Antidepressant	0.003	4h LOEC	*Sphaerium striatinum*	Fong et al. (1998)
Gabapentin"	Antiepileptic adjunctive	>1100	EC_{50}	*Daphnia* spp.	FDA-CDER (1996)
Ibuprofen	Analgesic; anti-infiammatory	7.1	96h EC_{50}	*Skeletonema costatum*	Knoll/BASF (1995)
Ibuprofen	Analgesic; anti-inflammatory	9.06	48h EC_{50}	*D. magna*	Knoll/BASF (1995)
Ibuprofen	Analgesic; anti-inflammatory	173	96h LC_{50}	*Lepomis mocrochirus*	Knoll/BASF (1995)
lopromide	Diagnostic aid (radiopaque medium)	>962	LC_{50}	*Oncorhynchus mykiss*	FDA-COER (1996)
lopromide	Diagnostic aid (radiopaque medium)	>973	LC_{50}	*Lepomis macrochirus*	FDA-COER (1996)

Table 1. *Continued*

Compound	Category[a]	Value ($mg1^{-1}$)	Endpoint/ Duration[b]	Species	Reference
lopromide	Diagnostic aid (radiopaque medium)	137	MIC	Unspecified green algae	FDA-CDER (1996)
lopromide	Diagnostic aid (radiopaque medium)	>1016	EC_{50}	*Daphnia*	FDA-CDER (1996)
lopromide	Diagnostic aid (radiopaque medium)	>	24h EC_{50}	*D. magna*	Schweinfurth et al. (1996a)
lopromide	Diagnostic aid (radiopaque medium)	>	48h EC_{50}	Unspecified fish	Schweinfurth et al. (1996a)
Isoniazid	Antibacterial	85	24h EC_{50}	*D. magna*	LiliL15 et al. (1994)
Isoniazid	Antibacterial	322	24h LC_{50}	*Artemia salina*	Calleja et al. (1994b)
Isoniazid	Antibacterial	24.4	24h LC_{50}	*Streptocepha/us probos-cideus*	Calleja et al. (1994b)
Isoniazid	Antibacterial	125.5	24h EC_{50}	*D. magna*	Calleja et al. (1994b)
Isoniazid	Antibacterial	3045	24h LC_{50}	*Brachionus calycif/orus*	Calleja et al. (1994b)
Ketorolac tromethamine	Analgesic; anti-infiammatory	1480	96h LC_{50}	*Lepomis macrochirus*	Anon (1993)
Lansoprazole	Proton pump inhibi-tor (Anti-ulcerative)	>22	EC_{50}	*Daphnia* spp,	FDA-CDER (1996)
Lansoprazole	Proton pump inhibi-tor (Anti-ulcerative)	18	LC_{50}	*Oncorhynchus mykiss*	FDA-CDER (1996)
Lincomys(c)in	Antibacterial	283.1	72h EC_{50}	*Artemia*	Migliore et al. (1997)
Lincomys(c)in	Antibacterial	379.39	72h LC_{50}	*D. magna*	Di Delupis et al. (1992)
Lithium sulfate	Antidepressant	197	24h EC_{50}	*D. magna*	Lilius et al. (1994)
Lithium sulfate	Antidepressant	4318	24h LC_{50}	*Artemia salina*	Calleja et al. (1994b)
Lithium sulfate	Antidepressant	112	24h LC_{50}	*Streptocepha/us proboscideus*	Calleja et al. (1994b)
Lithium sulfate	Antidepressant	33.1	24h EC_{50}	*D. magna*	Calleja et al. (1994b)
Lithium sulfate	Antidepressant	712	24h LC_{50}	*Brachionus ca/ycit/orus*	Calleja et al. (1994b)
Lomefioxacin	Antibacterial	130	EC_{50}	*Daphnia* spp.	FDA-CDER (1996)
Lomefioxacin	Antibacterial	170	LC_{50}	*Oncorhynchus mykiss*	FDA-CDER (1996)
Lomefioxacin	Antibacterial	2.4	EC_{50}	Unspecified green algae	FDA-CDER (1996)
Loracarbef	Anti-infective	>963	EC_{50}	*Daphnia* spp.	FDA-CDER (1996)
Losartan K	Antihypertensive	331	EC_{50}	*Daphnia* spp.	FDA-CDER (1996)
Losartan K	Antihypertensive	>929	LC_{50}	*Oncorhynchus mykiss*	FDA-CDER (1996)
Losartan K	Antihypertensive	>1000	LC_{50}	*Pimephales promelas*	FDA-CDER (1996)
Losartan K	Antihypertensive	245	MIC	Unspecified green algae	FDA-CDER (1996)

Table 1. *Continued*

Compound	Category[a]	Value ($mg l^{-1}$)	Endpoint/ Duration[b]	Species	Reference
Losartan K	Antihypertensive	949	MIC	Unspecified blue-green alage	FDA-CDER (1996)
Merthiolate (Thimerosal)	Anti-infective	60.5	24h LC_{50}	*Oncorhynchus mykiss*	Wilford (1966)
Merthiolate (Thimerosal)	Anti-infective	21.2	48h LC_{50}	*Oncorhynchus mykiss*	Wilford (1966)
Merthiolate (Thimerosal)	Anti-infective	13.0	24h LC_{50}	*Salvelinus namaycush*	Wilford (1966)
Merthiolate (Thimerosal)	Anti-infective	2.13	48h LC_{50}	*Salvelinus namaycush*	Wilford (1966)
Merthiolate (Thimerosal)	Anti-infective	110	24h LC_{50}	*Salmo trutta*	Wilford (1966)
Merthiolate (Thimerosal)	Anti-infective	54.0	48h LC_{50}	*Salmo truUa*	Wilford (1966)
Merthiolate (Thimerosal)	Anti-infective	750	24h LC_{50}	*Ictalurus punctatus*	Wilford (1966)
Merthiolate (Thimerosal)	Anti-infective	5.65	48h LC_{50}	*Ictalurus punctatus*	Wilford (1966)
Merthiolate (ThimerosiJl)	Anti-infective	895	24h LC_{50}	*Salvelinus fontinalis*	Wilford (1966)
Merthiolate (Thimerosal)	Anti-infective	745	48h LC_{50}	*Salvelinus fontinalis*	Wilford (1966)
Merthiolate (Thimerosal)	Anti-infective	110	24h LC_{50}	*Lepomis macrochirus*	Wilford (1966)
Merthiolate (Thimerosal)	Anti-infective	645	48h LC_{50}	*Lepomis macrochirus*	Wilford (1966)
Metformin HCI	Antidiabetic	>982	LC_{50}	*Lepomis macrochirus*	FDA-CDER (1996)
Metformin HCI	Antidiabetic	130	EC_{50}	*Daphnia* spp.	FDA-CDER (1996)
Methotrexate	Antineoplastic; antirheumatic	>1000	EC_{50}	*D. magna*	llenschel et al. (1997)
Methotrexate	Antineoplastic; antirheumatic	850	48h EC_{50}	*Brachydanio reria* (embryos)	Henschel et al. (1997)
Methotrexate	Antineoplastic; antirheumatic	260	72h EC_{50}	*Scenedesmus subspicotus*	Henschel et al. (1997)
Metronidazole	Antiprotozoal	>100	72h EC_{50}	*Acortia tonsa*	Lanzky and Halling-50renson (1997)
Metronidazole	Antiprotozoal	>500	96h EC_{50}	*Brachydania reria*	Lanzky and Halling-50renson (1997)
Metronidazole	Antiprotozoal	39.1	72h EC_{50}	*Selenastrum copricornutum*	Lanzky and Halling-S0renson (1997)
Metronidazole	Antiprotozoal	12.5	72h EC_{50}	*Chiarello* spp.	Lanzky and Halling-S0renson (1997)
Metronidazole	Antiprotozoal	>100	48h LC_{50}	*Oncorhynchus mykiss, Salmo trurta, Salvelinus fantinali\ Ictalurus punctatus, Lepamis macrochirus* and *Salvelinus namaycush*	Wilford (1966)
Midazolam	Anesthetic (intravenous)	0.2	EC_{50}	*D. magna*	FDA-CDER (1996)
Milrinone lactate	Cardiotonic	414	EC_{50}	*Daphnia* spp.	FDA-CDER (1996)
Moexipril HCI (pro-drug)	Antihypertensive	800	EC_{50}	*Daphnia* spp.	FDA-CDER (1996)

Table 1. *Continued*

Compound	Category[a]	Value ($mg1^{-1}$)	Endpoint/ Duration[b]	Species	Reference
Moexiprilat (active metabolite)	Antihypertensive	>1000	EC_{50}	*Daphnia* spp.	FDA-CDER (1996)
Naproxen sodium	Anti-inflammatory; analgesic; antipyretic	140	24h EC_{50}	*D. magna*	Rodriguez et al. (1992)
Naproxen sodium	Anti-inflammatory; analgesic; antipyretic	383	96h LC_{50}	*Hya/ella azteea*	Rodriguez et al. (1992)
Naproxen sodium	Anti-inflammatory; analgesic; antipyretic	560	96h LC_{50}	*Lepomis macroehirus*	Rodriguez et al. (1992)
Naproxen sodium	Anti-inflammatory; analgesic; antipyretic	690	96h LC_{50}	*Oncorhynchus mykiss*	Rodriguez et al. (1992)
Nefazodone HCI	Antidepressant	7	EC_{50}	*Daphnia* spp.	FDA-CDER (1996)
Nicotine sulfate	Cholinergic agonist	13.8	96h EC_{50}	*Pimepha/es prome/as*	Russom et al. (1997)
Nicotine	Cholinergic agonist	3.0	EC_{50}	*D. magna*	FDA-CDER (1996)
Nicotine	Cholinergic agonist	7.0	LC_{50}	*Oncorhynchus mykiss*	FDA-CDER (1996)
Nicotine	Cholinergic agonist	20.0	LC_{50}	*Pimepha/es prome/as*	FDA-CDER (1996)
Nicotine	Cholinergic agonist	4.0	LC_{50}	*Lepomis macroehirus*	FDA-CDER (1996)
Nicotine	Cholinergic agonist	13	LC_{50}	"Goldfish"	FDA-CDER (1996)
Nisoldipine	Antihypertensive; antianginal	33	EC_{50}	*Daphnia* spp.	FDA-CDER (1996)
Nisoldipine	Antihypertensive; antianginal	3	EC_{50}	Unspecified fish	FDA-CDER (1996)
Nitrofurazone	Topical anti-infective	1.45	EC_{50}	*Sefenastrum capricornutum*	Macri and Sbardella (1984)
Nitrofurazone	Topical anti-infective	28.7	LC_{50}	*D. magna*	Macri and Sbardella (1984)
Nitrofurazone	Topical anti-infective	10	96h LC_{50}	*Morone saxatilis* (larvae)	Hughes (1973)
Nitrofurazone	Topical anti-infective	>5	24h LC_{50}	*Penaeus setirerus*	Johnson (1976)
Omeprazole	Anti-ulcerative	88	EC_{50}	*Daphnia* spp.	FDA-CDER (1996)
Ondansetron HCI	Antiemetic	28	EC_{50}	*Daphnia* spp.	FDA-CDER (1996)
Orphenadrine HCI (mephenamin)	Relaxant; antihistaminic	8.9	24h EC_{50}	*D. magna*	Lilius et al. (1994)
Orphenadrine HCI (mephenamin)	Relaxant; antihistaminic	45	24h LC_{50}	*Artemia salina*	Calleja et al. (1994b)
Orphenadrine HCI (mephenamin)	Relaxant; antihistaminic	4.3	24h LC_{50}	*Streptocephafus proboscideus*	Calleja et al. (1994b)
Orphenadrine HCI (mephenamin)	Relaxant; antihistaminic	10.	24h EC_{50}	*D. magna*	Calleja et al. (1994b)
Orphenadrine HCI (mephenamin)	Relaxant; antihistaminic	5.4	24h LC_{50}	*Brachianus*	Calleja et al. (1994b)
Oxytetracycline	Antibacterial	>5	24h LC_{50}	*Penaeus setiferus*	Johnson (1976)
Oxytetracycline HCI	Antibacterial	62.	24/48/72/ 96h LC_{50}	*Morone saxati/is* (larvae)	Hughes (1973)

Table 1. *Continued*

Compound	Category[a]	Value ($mg1^{-1}$)	Endpoint/ Duration[b]	Species	Reference
Oxytetracycline HCI	Antibacterial	150	24h LC_{50}	*Morone saxatilis* (fingerling)	Hughes (1973)
Oxytetracycline HCI	Antibacterial	125	48h LC_{50}	*Morone saxatilis* (fingerling)	Hughes (1973)
Oxytetracycline HCI	Antibacterial	100	72h LC_{50}	*Morone saxat/lis* (fingerling)	Hughes (1973)
Oxytetracycline HCI	Antibacterial	75	96h LC_{50}	*Morone saxatilis* (fingerling)	Hughes (1973)
Oxytetracycline HCI	Antibacterial	<200	24/96h LC_{50}	*Salvelinus namaycush*	Marking et al. (1988)
Oxytetracycline	Antibacterial	0.231	EC_{50}	*Microcystis aeruginosa*	Holten LOtzh0ft et al. (1998)
Oxytetracycline	Antibacterial	50	EC_{50}	*Se/enastrum copricornutum*	Holten Lutzh0ft et al. (1998)
Oxytetracycline	Antibacterial	1.7	EC_{50}	*Rhadomonas*	Holten Lutzh0ft et al. (1998)
Paclitaxel	Antineoplastic	>0.74	LC_{50}	*Daphnia* spp.	FDA-COER (1996)
Paracetamol/ Acetaminophen	Analgesic; antipyretic	577	24h LC_{50}	*Artemia salina*	Calleja et al. (1994b)
Paracetamol! Acetaminophen	Analgesic; antipyretic	29.6	24h LC_{50}	*Streptocephalus praboscideus*	Calleja et al. (1994b)
Paracetamol/ Acetaminophen	Analgesic; antipyretic	555	24h EC_{50}	*D. magno*	Calleja et al. (1994b)
Paracetamol! Acetaminophen	Analgesic; antipyretic	5306	24h LC_{50}	*Brochionus cofyciflorus*	Calleja et al. (1994b)
Paracetamol/ Acetaminophen	Analgesic; antipyretic	13	24h EC_{50}	*D. magna*	Kuhn et al (1989)
Paracetamol/ Acetaminophen	Analgesic; antipyretic	92	48h EC_{50}	*D. magna*	Kuhn et al. (1989)
Paracetamol/ Acetaminophen	Analgesic; antipyretic	293	24 EC_{50}	*D. magna*	Henschel et al. (1997)
Paracetamol/ Acetaminophen	Analgesic; antipyretic	50.0	48 EC_{50}	*D. magna*	Henschel et al. (1997)
Paracetamol/ Acetaminophen	Analgesic; antipyretic	378	48h EC50	*Brachydanio rerio* (embryos)	Henschel et al. (1997)
Paracetamol/ Acetaminophen	Analgesic; antipyretic	134	72h EC_{50}	*Scenedesrnus subspicotus*	Henschel et al. (1997)
Paroxetine HCI	Antidepressant	3.0	EC_{50}	*Daphnio* spp	FDA-COER (1996)
Paroxetine HCI	Antidepressant	2.0	LC_{50}	*Lepomis macrochirus*	FDA-COER (1996)
Paroxetine HCI	Antidepressant	3.29	4h LOEC	*Sphaeriurn* spp.	Fong et al. (1998)
Perindopril Erbumine	Antihypertensive	>1000	EC_{50}	*Daphnia* spp.	FDA-COER (1996)
Perindopril Erbumine	Antihypertensive	>990	LC_{50}	*Lepomis macrochirus*	FDA-COER (1996)
Pentobarbital	Sedative; hypnotic	49.S	96h EC_{50}	*Pimephales promefas*	Russom et al. (1997)

Table 1. *Continued*

Compound	Category[a]	Value ($mg l^{-1}$)	Endpoint/ Duration[b]	Species	Reference
Phenobarbital	Anticonvulsant; sedative; hypnotic	484	96h EC_{50}	*Pimephales promelas*	Russom et al. (1997)
Phenobarbital (phenobarbitone)	Anticonvulsant; sedative; hypnotic	> 10	24h LC_{50}	*Artemia salina*	Calleja et al. (1994b)
Phenobarbital (phenobarbitone)	Anticonvulsant; sedative; hypnotic	1212	24h LC_{50}	*Streptocephalus proboscideus*	Calleja et al. (1994b)
Phenobarbital (phenobarbitone)	Anticonvulsant; sedative; hypnotic	1463	24h EC_{50}	D. *magna*	Calleja et al. (1994b)
Phenobarbital (phenobarbitone)	Anticonvulsant; sedative; hypnotic	5179	24h LC_{50}	*Brachionus calyciflorus*	Calleja et al. (1994b)
Porfirmer sodium	Photosensitiser	>994	EC_{50}	*Daphnia* spp.	FDA-CDER (1996)
Propranolol HCI	Antihypertensive; antianginal; antiarrhythmic	2.7	24h EC_{50}	*D. magna*	Lilius et al. (1'994)
R-(±) Propranolol	Antihypertensive; antianginal; antiarrhythmic	407	24h LC_{50}	*Artemia salina*	Calleja et al. (1994b)
R-(±) Propranolol	Antihypertensive; antianginal; antiarrhythmic	1.87	24h LC_{50}	*Streptocephalus proboscideus*	Calleja et al. (1994b)
R-(±) Propranolol	Antihypertensive; antianginal; antiarrhythmic	15.87	24h EC_{50}	*D. magna*	Calleja et al. (1994b)
R-(±) Propranolol	Antihypertensive; antianginal; antiarrhythmic	2.59	24h LC_{50}	*Brachionus calyciflorus*	Calleja et al. (1994b)
Quinacrine HCI	Anthelminthic; antimalarial	122	48h LC_{50}	*Oncorhynchus mykiss*	Willford (1966)
Quinacrine HCI	Anthelminthic; antimalarial	25.0	24h LC_{50}	*Solvelinus namaycush*	Willford (1966)
Quinacrine HCI	Anthelminthic; antimalarial	21.0	48h LC_{50}	*Salvelinus namaycush*	Willford (1966)
Quinacrine HCI	Anthelminthic; antimalarial	300	24h LC_{50}	*Salmo trutta*	Willford (1966)
Quinacrine HCI	Anthelminthic; antimalarial	230	48h LC_{50}	*Salmo trurta*	Willford (1966)
Quinacrine HCI	Anthelminthic; antimalarial	196	24h LC_{50}	*Ictalurus punctatus*	Willford (1966)
Quinacrine HCI	Anthelminthic; antimalarial	70	48h LC_{50}	*Ictalurus punctatus*	Willford (1966)
Quinacrine HCI	Anthelminthic; antimalarial	230	48h LC_{50}	*Salvelinus fontinalis*	Willford (1966)
Quinacrine HCI	Anthelminthic; antimalarial	120	24h LC_{50}	*Lepomis macrochirus*	Willford (1966)

Table 1. *Continued*

Compound	Category[a]	Value ($mg1^{-1}$)	Endpoint/ Duration[b]	Species	Reference
Quinacrine HCI	Anthelminthic; antimalarial	79	48h LC_{50}	*Lepomis maaochirus*	Willford (1966)
Quinacrine HCI	Anthelminthic; antimalarial	7.7	24h LC_{50}	*Penaeus setiferus*	Johnson (1976)
Quinidine sulfate	Cardiac depressant (antiarrhythmic)	60	24h EC_{50}	*D. magna*	Lilius et al. (1994)
Quinidine sulfate	Cardiac depressant (antiarrhythmic)	274	24h LC_{50}	*Artemia salina*	Calleja et al. (1994b)
Quinidine sulfate	Cardiac depressant (antiarrhythmic)	8.3	24h LC_{50}	*Streptocephafus proboscideus*	Calleja et al. (1994b)
Quinidine sulfate	Cardiac depressant (antiarrhythmic)	60	24h EC_{50}	*D. magna*	Calleja et al. (1994b)
Quinidine sulfate	Cardiac depressant (antiarrhythmic)	8.7	24h LC_{50}	*Brachionus cafyciflorus*	Calleja et al. (1994b)
Quinine bisulfate	Antimalarial; oral sclerosing agent	13.1	24h LC_{50}	*Penaeus setiferus*	Johnson (1976)
Quinine HCI	Antimalarial	>100	48h LC_{50}	*Oncorhynchus mykiss, Salmo trurta, Salvelinlls fontinalis, fctafurus punctatus, Lepomis maaochirlls* and *Salvelinus namaycush*	Willford (1966)
Quinine sulfate	Antimalarial; muscle relaxant	13.8	24h LC_{50}	*Penaeus setiferus*	Johnson (1976)
Ranitidine HCI	Anti-ulcerative	650	EC_{50}	*Daphnia* spp.	FDA-CDER (1996)
Risperidone	Antipsychotic	6.0	LC_{50}	*Lepomis maaachirus*	FDA-CDER (1996)
Risperidone	Antipsychotic	6.0	EC_{50}	*Daphnia* spp.	FDA-CDER (1996)
Salicylic acid	Topical keratolytic	> 1440	24h EC_{50}	*D. magna*	Bringmann and Kuhn (1982)
Salicylic acid	Topical keratolytic	230	24h EC_{50}	*D. magna*	Wang and Lay (1989)
Salicylic acid·	Topical keratolytic	118	EC_{50}	*D. magna*	Henschel et al. (1997)
Salicylic acid	Topical keratolytic	37.0	48h EC_{50}	*Brachydanio rerio* (embryos)	Henschel et al. (1997)
Salicylic acid	Topical keratolytic	>100	72h EC_{50}	*Scenedesmus subspicatus*	Henschel et al. (1997)
Simethicone	Antifiatulent	44.5	48h TL_{50}	*D. magna*	Hobbs (1975)
Salmeterol	Antiasthmatic)	20	EC_{50}	*Daphnia* spp.	FDA-CDER (1996)
Secobarbital,	Sedative; hypnotic	23.6	96h EC_{50}	*Pimephafes promelas*	Russom et al. (1997)
Spirapril HCI	Antihypertensive	>930	EC_{50}	*Daphnia* spp.	FDA-CDER (1996)
Spirapril HCI	Antihypertensive	>970	LC_{50}	*Lepomis maaochirus*	FDACDER (1996)
Stavudine	Anti(retro)viral	>980	LC_{50}	*Daphnia* spp.	FDA-CDER (1996)
Sulfadimethoxine	Antibacterial	1866	24h LC_{50}	*Artemia salina* (nauplii)	Brambilla et al. (1994)

Table 1. *Continued*

Compound	Category[a]	Value ($mg1^{-1}$)	Endpoint/ Duration[b]	Species	Reference
Sulfadimethoxine	Antibacterial	851	48h LC_{50}	*Artemia salina* (nauplii)	Brambilla et al. (1994)
Sulfadimethoxine	Antibacterial	537	72h LC_{50}	*Artemia salina* (nauplii)	Brambilla et al. (1994)
Sulfadimethoxine	Antibacterial	19.5	96h LC_{50}	*Artemia salina* (nauplii)	Brambilla et al. (1994)
Sulfadimethoxine	Antibacterial	1866	24h LC_{50}	*Artemia salina* (nauplii)	Migliore et al. (1993)
Sulfadimethoxine	Antibacterial	851	48h LC_{50}	*Artemia salina* (nauplii)	Migliore et al. (1993)
Sulfadimethoxine	Antibacterial	537	72h LC_{50}	*Artemia salina* (nauplii)	Migliore et al. (1993)
Sulfadimethoxine	Antibacterial	19.5	96h LC_{50}	*Artemia salina* (nauplii)	Migliore et al. (1993)
Sulfamerazine	Antibacterial	>100	48h LC_{50}	*Oncorhynchus mykiss, Salmo trutta, Salvelinus fontinalis,lctalurus punctatus, Lepomis macrochirus* and *Salvelinus namaycush*	Willford (1966)
Sulfamethazine	Antibacterial	>100	48h LC_{50}	*Oncorhynchus mykiss, Salmo trutta, Salvelinus fontinalis,lctalurus punctatus, Lepomis macrochirus* and *Salvelinus namaycush*	Willford (1966)
Sulfisoxazole	Antibacterial	>100	48h LC_{50}	*Oncorhynchus mykiss, Salmo trutta, Salvelinus fontinalis,lctalurus punctatus, Lepomis macrochirus* and *Salvelinus namaycush*	Willford (1966)
Sumatriptan succinate	Antimigraine	290	EC_{50}	*Daphnia* spp.	FDA-COER
Tetracycline	Antiamebic; antibacterial; antiricketettsial	16	72h EC_{50}	*Nitzschia closterium*	Peterson et al. (1993)
Tetracycline HCI	Antiamebic; antibacterial; antiricketettsial	220	24/96h LC_{50}	*Salvelinus namaycush*	Marking et al. (1988)
Tetracycline HCI	Antiamebic; antibacterial; antiricketettsial	>182	24/48/96h LC_{50}	*Morane saxatilis*	Welborn (1969)
Theophylline	Bronchodilator	155	24h EC_{50}	*D. magna*	Lilius et al. (1994)
Theophylline	Bronchodilator	8247	24h LC_{50}	*Artemia salina*	Calleja et al. (1994b)
Theophylline	Bronchodilator	425	24h LC_{50}	*Streptocephalus proboscideus*	Calleja et al. (1994b)
Theophylline	Bronchodilator	483	24h EC_{50}	*D. magna*	Calleja et al. (1994b)
Theophylline	Bronchodilator	3926	24h LC_{50}	*Brachionus calycif/orus*	Calleja et al. (1994b)
Thiopental, sodium	Anesthetic	26.2	96h EC_{50}	*Pimephales promelas*	Russom et al. (1997)
Thiotepa	Antineoplastic	546	EC_{50}	*Daphnia* spp.	FDA-COER (1996)
Thioridazine HCI	Antipsychotic	069	24h EC_{50}	*D. magna*	Lilius et al. (1994)

Table 1. *Continued*

Compound	Category[a]	Value ($mg1^{-1}$)	Endpoint/ Duration[b]	Species	Reference
Thioridazine HCI	Antipsychotic	14.5	24h LC_{50}	*Artemia salina*	Calleja et al. (1994b)
Thioridazine HCI	Antipsychotic	0.33	24h LC_{50}	*Streptocephalus proboscideus*	Calleja et al. (1994b)
Thioridazine HCI	Antipsychotic	4.56	24h EC_{50}	*D. magna*	Calleja et al. (1994b)
Thioridazine HCI	Antipsychotic	0.30	24h LC_{50}	*Brachionus calyciflorus*	Calleja et al. (1994b)
Tiludronate disodium	Metabolic Bone Disease	562	24h EC_{50}	*D. magna*	Sanofi (1996)
Tiludronate disodium	Metabolic Bone Disease	320	48h EC_{50}	*D. magna*	5anofi (1996)
T olazoline HCI	Antiadrenergic	354	96h EC_{50}	*Pimephales pramelas*	Russom et al. (1997)
Tramadol HCI	Analgesic	130	LC_{50}	Unspecified fish	FDA-CDER (1996)
Tramadol HCI	Analgesic	73	EC_{50}	*Daphnia spp*	FDA-CDER (1996)
Verapamil HCI	Antianginal; antiarrhythmic	327	24h EC_{50}	*D. magna*	Liliuset al. (1994)
Verapamil HCI	Antianginal; antiarrhythmic	356	24h LC_{50}	*Artemia salina*	Calleja et al. (1994b)
Verapamil HCI	Antianginal; antiarrhythmic	6.24	24h LC_{50}	*Streptocephafus proboseideus*	Calleja et al. (1994b)
Verapamil HCI	Antianginal; antiarrhythmic	55.5	24h EC_{50}	*D. magna*	Calleja et al. (1994b)
Verapamil HCI	Antianginal; antiarrhythmic	10.90	24h LC_{50}	*Brachionus calyeiflorus*	Calleja et al. (1994b)
Warfarin	Anticoagulant	12	96h LC_{50}	*Rasbora heteromorpha*	Tooby et al. (1975)
Warfarin	Anticoagulant	89	24h EC_{50}	*D. magna*	Lilius el al. (1994)
Warfarin	Anticoagulant	3638	24h LC_{50}	*Artemia salina*	Calleja et al. (1994b)
Warfarin	Anticoagulant	342	24h LC_{50}	*Streptoeephafus proboscideus*	Calleja et al. (1994b)
Warfarin	Anticoagulant	475	24h EC_{50}	*D. magna*	Calleja et al. (1994b)
Warfarin	Anticoagulant	444	24h LC_{50}	*Brachionus calyeiflarus*	Calleja et al. (1994b)
Zalcitabine	Anti(retro)viral	>1790	EC_{50}	*Daphnia* spp.	FDA-CDER (1996)

[a] Therapeutic category is as detailed in the Merck Index (Budavari 1989).

[b] LC_{50} values relate to lethality in all organisms. EC_{50} values in *Daphnia* typically relate to immobilisation.ln the case of algae, EC_{50} values relate to effects upon growth (i.e. biomass or cell number). US FDA test guidelines include: 4.01 Algal assay, 4.08 *Daphnia* acute toxicity (48 h), 4.09 *Daphnia* chronic testing, 4.10 *Hyalella azteca* acute toxicity, and 4.11 Freshwater fish acute toxicity.

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APPENDIX D- CHRONIC TOXICITY DATA FOR PHARMACEUTICALS

Table 2. Chronic toxicity data for aquatic organisms exposed to human pharmaceuticals

Therapeutic class	Substance	Taxonomic group	Species	Long-term exposure result (mg l^{-1})*	Acute to chronic ratio (if available)	Reference
Androgen	Methyltestosterone	Fish	*Carassius carassius*	0.00001		Fujioka
Androgen	Methyltestosterone	Fish	*Oryzias latipes*	<10.0 ng/l	>1000000	Hutchinson et al. (2003b)
Androgen	Methyltestosterone	Fish	*Pimepha/es prome/as*	0.01		Zerulla et al. (2002)
Androgen	Methyltestosterone	Invertebrate (snail)	*Lymnaea stagnalis*	1.0 ng/I		Czech et al. (2001)
Androgen	Methyltestosterone	Invertebrate (snail)	*Marisa cornuarietis*	<100 ng/I		Schulte-Oehlmann et al. (2004)
Anti-androgen (non-steroidal)	Flutamide	Fish	*Oryzias latipes*	1.0	3.6	Hutchinson et al. (2003b)
Anti-bacterial	Trimethoprim	Plant (duckweed)	*Lemna gibba*	>1.0 (EC1 0)		Brain et al. (2004b)
Anti-bacterial (aminoglycoside)	Neomycin	Plant (duckweed)	*Lemna gibba*	>1.0 (EC10)		Brain et al. (2004b)
Anti-bacterial (aminoglycoside)	Streptomycin	Plant (duckweed)	*Lemna gibba*	>1.0 (EC10)		Brain et al. (2004b)
Anti-bacterial (cephalosporin)	Cephalexin	Plant (duckweed)	*Lemna gibba*	>1.0 (EC1 0)		Brain et al. (2004b)
Anti-bacterial (fluoroquinolone)	Ciprofloxacin	Plant (duckweed)	*Lemna gibba*	0.106 (EC10)		Brain et al. (2004b)
Anti-bacterial	Levofloxacin	Plant (duckweed)	*Lemna gibba*	0.013 (EC10)		Brain et al.

Therapeutic class	Substance	Taxonomic group	Species	Long-term exposure result (mg l^{-1})*	Acute to chronic ratio (if available)	Reference
(fluoroquinolone)						(2004b)
Anti-bacterial (fluoroquinolone)	Lomefloxacin	Alga (green)	Unspecified	2.0		FDA-(1996)
Anti-bacterial (fluoroquinolone)	Lomefloxacin	Plant (duckweed)	*Lemna gibba*	0.008 (EC10)		Brain et al. (2004b)
Anti-bacterial (fluoroquinolone)	Norfloxacin	Plant (duckweed)	*Lemna gibba*	0.206 (EC10)		Brain et al. (2004b)
Anti-bacterial (fluoroquinolone)	Ofloxacin	Alga (blue-green)	*Synechococcus leopo/ensis*	0.005		Ferrari et al. (2004)
Anti-bacterial (fluoroquinolone)	Ofloxacin	Alga (diatom)	*Cye/otella meneghiniana*	0.0312		Ferrari et al. (2004)
Anti-bacterial (fluoroquinolone)	Ofloxacin	Alga (green)	*Pseudokifchneriella subcapitata*	2.5		Ferrari et al. (2003,2004)
Anti-bacterial (fluoroquinolone)	Ofloxacin	Invertebrate (rotifer)	*Brachionus calyciflorus*	12.5		Ferrari et al. (2003
Anti-bacterial (fluoroquinolone)	Ofloxacin	Invertebrate (waterflea)	*Ceriodaphnia dubia*	10.0		Ferrari et al. (2003,
Anti-bacterial (fluoroquinolone)	Ofloxacin	Plant (duckweed)	*Lemna gibba*	0.121 (EC10)		Brain et al. (2004b)
Anti-bacterial (macrolide antibiotic)	Erythromycin	Plant (duckweed)	*Lemna gibba*	>1.0 (EC1 0)		Brain et al. (2004b)
Anti-bacterial (macrolide antibiotic)	Lincomycin	Plant (duckweed)	*Lemna gibba*	>1.0 (EC10)		Brain et al. (2004b)
Anti-bacterial	Roxithromycin	Plant (duckweed)	*Lemna gibba*	>1.0 (EC10)		Brain et al.

Therapeutic class	Substance	Taxonomic group	Species	Long-term exposure result (mg l^{-1})*	Acute to chronic ratio (if available)	Reference
(macrolide antibiotic)						(2004b)
Anti-bacterial (macrolide antibiotic)	Tylosin	Plant (duckweed)	*Lemna gibba*	>1.0 (EC10)		Brain et al. (2004b)
Anti-bacterial (penicillin)	Amoxicillin	Invertebrate (cnidarian)	*Hydra vulgaris*	>0.01		Pascoe et al. (2003)
Anti-bacterial (penicillin)	Amoxicillin	Plant (duckweed)	*Lemna gibba*	>1.0 (EC10)		Brain et al. (2004b)
Anti-bacterial (sulfonamide)	Sulfadimethoxine	Plant (duckweed)	*Lemna gibba*	0.044 (EC10)		Brain et al. (2004b)
Anti-bacterial (sulfonamide)	Sulfamethazine	Plant (duckweed)	*Lemna gibba*	>1.0 (EC1 0)		Brain et al. (2004b)
Anti-bacterial (sulfonamide)	Sulfamethoxazole	Alga (blue-green)	*Syneehoeoeeus /eopo/ensis*	0.0059		Ferrari et al. (2004)
Anti-bacterial (sulfonamide)	Sulfamethoxazole	Alga (diatom)	*Cye/otella meneghiniana*	1.25		Ferrari et al. (2004)
Anti-bacterial (sulfonamide)	Sulfamethoxazole	Alga (green)	*Pseudokifehneriella subeapitata*	0.09		Ferrari et al. (2003,
Anti-bacterial (sulfonamide)	Sulfamethoxazole	Invertebrate (rotifer)	*Braehionus ea/yeiflorus*	25.0		Ferrari et al. (2003
Anti-bacterial (sulfonamide)	Sulfamethoxazole	Invertebrate (waterflea)	*Ceriodaphnia dubia*	0.25		Ferrari et al. (2003,
Anti-bacterial (sulfonamide)	Sulfamethoxazole	Plant (duckweed)	*Lemna gibba*	0.011 (EC10)		Brain et al. (2004b)
Anti-bacterial	Sulfochlorpyridazin	Plant (duckweed)	*Lemna minor*	2.33 (EC50)		Pro et al.

Therapeutic class	Substance	Taxonomic group	Species	Long-term exposure result (mg l^{-1})*	Acute to chronic ratio (if available)	Reference
(sulfonamide)	e					(2003)
Anti-bacterial (tetracycline)	Chlortetracycline	Plant (duckweed)	*Lemna gibba*	0.036 (EC10)		Brain et al. (2004b)
Anti-bacterial (tetracycline)	Doxycycline	Plant (duckweed)	*Lemna gibba*	0.055 (EC10)		Brain et al. (2004b)
Anti-bacterial (tetracycline)	Oxytetracycline	Plant (duckweed)	*Lemna gibba*	0.788 (EC10)		Brain et al. (2004b)
Anti-bacterial (tetracycline)	Oxytetracycline	Plant (duckweed)	*Lemna minor*	4.92 (EC50)		Pro et al. (2003)
Anti-bacterial (tetracycline)	Tetracycline	Plant (duckweed)	*Lemna gibba*	0.23 (EC10)		Brain et al. (2004b)
Anti-depressant (SSRI)	Citalopram	Invertebrate (waterflea)	*Ceriodaphnia dubia*	0.8	4.9	Henry et al. (2004)
Anti-depressant (SSRI)	Fluoxetine	Alga (green)	Unspecified	0.001		FDA- (1996)
Anti-depressant (SSRI)	Fluoxetine	Invertebrate (amphipod)	*Hyalella azteca*	>43 mg/kg		Brooks et (2003)
Anti-depressant (SSRI)	Fluoxetine	Invertebrate (waterflea)	*Ceriodaphnia dubia*	0.056		Brooks et (2003)
Anti-depressant (SSRI)	Fluoxetine	Invertebrate (waterflea)	*Ceriodaphnia dubia*	0.089	5.7	Henry et al. (2004)
Anti-depressant (SSRI)	Fluoxetine	Plant (duckweed)	*Lemna gibba*	>1.0 (EC10)		Brain et al. (2004b)
Anti-depressant (SSRI)	Fluvoxamine	Alga (green)	Unspecified	31		FDA- (1996)
Anti-depressant	Fluvoxamine	Invertebrate	*Ceriodaphnia dubia*	0.366	2.3	Henry et al.

Therapeutic class	Substance	Taxonomic group	Species	Long-term exposure result (mg l^{-1})*	Acute to chronic ratio (if available)	Reference
(SSRI)		(waterflea)				(2004)
Anti-depressant (SSRI)	Paroxetine	Invertebrate (waterflea)	*Ceriodaphnia dubia*	0.22	2.8	Henry et al. (2004)
Anti-depressant (SSRI)	Sertraline	Invertebrate (waterflea)	*Ceriodaphnia dubia*	0.009	13.3	Henry et al. (2004)
Anti-depressant (SSRI)	Sertraline	Plant (duckweed)	*Lemna gibba*	>1.0 (EC10)		Brain et al. (2004b)
Anti-diabetic (biguanide)	Metformin	Alga (green)	*Desmodesmus subspieatus*	>320.0 (EC50)		Cleuvers (2003)
Anti-diabetic (biguanide)	Metformin	Plant (duckweed)	*Lemna minor*	110.0 (EC50)		Cleuvers (2003)
Anti-epileptic	Carbamazepine	Alga (blue-green)	*Syneehoeoeeus /eopo/ensis*	17.0		Ferrari et al. (2004)
Anti-epileptic	Carbamazepine	Alga (diatom)	*Cye/otella meneghiniana*	10.0		Ferrari et al. (2004)
Anti-epileptic	Carbamazepine	Alga (green)	*Desmodesmus subspieatus*	74.0 (EC50)		Cleuvers (2003)
Anti-epileptic	Carbamazepine	Alga (green)	*Pseudokirehneriella subeapitata*	>100.0		Ferrari et al. (2003, 2004)
Anti-epileptic	Carbamazepine	Fish	*Danio rerio*	25		Ferrari et al. (2003)
Anti-epileptic	Carbamazepine	Invertebrate (midge larva)	*Chironomus riparius*	0.625 mg/kg		Nentwig et (2004)
Anti-epileptic	Carbamazepine	Invertebrate (01 igochaete worm)	*Lumbrieu/us variegatus*	>10 mg/kg		Nentwig et (2004)

Therapeutic class	Substance	Taxonomic group	Species	Long-term exposure result (mg l^{-1})*	Acute to chronic ratio (if available)	Reference
Anti-epileptic	Carbamazepine	Invertebrate (rotifer)	*Brachionus calyciflorus*	0.377		Ferrari et al. (2003,
Anti-epileptic	Carbamazepine	Invertebrate (waterflea)	*Ceriodaphnia dubia*	0.025	3108	Ferrari et al. (2003,
Anti-epileptic	Carbamazepine	Plant (duckweed)	*Lemna gibba*	>1.0 (EC10)		Brain et al. (2004b)
Anti-epileptic	Carbamazepine	Plant (duckweed)	*Lemna minor*	25.5 (EC50)		Cleuvers (2003)
Anti-(3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor)	Atorvastatin	Plant (duckweed)	*Lemna gibba*	0.085 (EC10)		Brain et al. (2004b)
Anti-hyperlipoproteinemic	Clotibric acid	Alga	Unspecified	5.4 (EC10)		Kopt (1995)
Anti-hyperlipoproteinemic	Clofibric acid	Alga (blue-green)	*Synechococcus leopolensis*	23.5		Ferrari et al. (2004)
Anti-hyperlipoproteinemic	Clofibric acid	Alga (diatom)	*Cye/otella meneghiniana*	>100.0		Ferrari et al. (2004)
Anti-hyperlipoproteinemic	Clofibric acid	Alga (green)	*Oesmodesmus subspicatus*	115.0 (EC50)		Cleuvers (2003)
Anti-	Clofibric acid	Alga (green)	*Pseudokirchneriella*	75.0		Ferrari et al.

Therapeutic class	Substance	Taxonomic group	Species	Long-term exposure result (mg l^{-1})*	Acute to chronic ratio (if available)	Reference
hyperlipoproteinemic			*subcapitata*			(2003, 2004)
Anti-hyperlipoproteinemic	Clofibric acid	Fish	*Danio rerio*	70		Ferrari et al. (2003)
Anti-hyperlipoproteinemic	Clofibric acid	Invertebrate (midge larva)	*Chironomus riparius*	*>8 mg/kg*		Nentwig et (2004)
Anti-hyperlipoproteinemic	Clofibric acid	Invertebrate (oligochaete worm)	*Lumbriculus variegatus*	*>8 mg/kg*		Nentwig et (2004)
Anti-hyperlipoproteinemic	Clofibric acid	Invertebrate (rotifer)	*Brachionus calyciflorus*	0.246		Ferrari et al. (2003
Anti-hyperlipoproteinemic	Clofibric acid	Invertebrate (waterflea)	*Ceriodaphnia dubia*	0.64	>312	Ferrari et al. (2003, 2004)
Anti-hyperlipoproteinemic	Clofibric acid	Invertebrate (waterflea)	*Daphnia magna*	0.01	1428	Kopf (1995)
Anti-hyperlipoproteinemic	Clofibric acid	Plant (duckweed)	*Lemna minor*	12.5 (EC50)		Cleuvers (2003)
Anti-hypertensive	Losartan K	Alga (blue-green)	Unspecified	556		FDA-COER (1996)
Anti-hypertensive	Losartan K	Alga (green)	Unspecified	143		FDA-COER

Therapeutic class	Substance	Taxonomic group	Species	Long-term exposure result (mg l^{-1})*	Acute to chronic ratio (if available)	Reference
						(1996)
Anti-hypertensive (angiotensin-converting enzyme inhibitor)	Captopril	Alga (green)	*Desmodesmus subspicatus*	168.0 (EC50)		Cleuvers (2003)
Anti-hypertensive (angiotensin-converting enzyme inhibitor)	Captopril	Plant (duckweed)	*Lemna minor*	25.0 (EC50)		Cleuvers (2003)
Anti-i nfective	Lorcabef	Alga (green)	Unspecified	13		FDA-(1996)
Anti-inflammatory (corticosteroid)	Budesonide	Alga (green)	Unspecified	10		FDA-(1996)
Anti-protozoal	Metronidazole	Alga (green)	*Chlorella* sp.	2.03 (EC10)		Lanzky & Halling-S0rensen (1997)
Anti-protozoal	Metronidazole	Alga (green)	*Pseudoklfchneriella subcapitata*	19.9 (EC10)		Lanzky & Halling-S0rensen (1997)
Anti-psychotic	Riseperidone	Alga (blue-green)	Unspecified	<100.0		FDA-(1996)
Anti-psychotic	Riseperidone	Alga (green)	Unspecified	<10.0		FDA-(1996)
Anxiolytic; muscle	Diazepam	Invertebrate	*Hydra vulgaris*	<0.01		Pascoe et

Therapeutic class	Substance	Taxonomic group	Species	Long-term exposure result (mg l^{-1})*	Acute to chronic ratio (if available)	Reference
relaxant (benzodiazepine)		(cnidarian)				(2003)
Aromatase inhibitor	Fadrozole	Fish	*Pimephales promelas*	0.002		Ankley et al. (2002)
Benign prostatic hypertrophy drug (Sa-reductase inhibitor)	Finasteride	Alga (green)	Unspecified	>49		FDA-COER (1996)
Bone resorption inhibitor	Alendronate	Alga (green)	Unspecified	0.5		FDA-COER (1996)
Bone resorption inhibitor	Etidronic acid	Alga (green)	*Pseudokirchneriella subcapitata*	1.3 - 13.2		Gledhill & Feijtel
Bone resorption inhibitor	Etidronic acid	Invertebrate (waterflea)	*Daphnia magna*	>12.0	43.9	Gledhill & Feijtel
Bone resorption inhibitor	Tiludronate	Alga (blue-green)	*Microcystis aeruginosa*	13.3 (EC50)		Sanofi
Bone resorption inhibitor	Tiludronate	Alga (green)	*Pseudokirchneriella subcapitata*	36.6 (EC50)		Sanofi
Calcium channel blocker	Amlodipine	Invertebrate (cnidarian)	*Hydra vulgaris*	<0.01		Pascoe et al. (2003)
Cardiotonic (digitalis medicine)	Digoxin	Invertebrate (cnidarian)	*Hydra vulgaris*	<0.01		Pascoe et al. (2003)
Central nervous system stimulant	Caffeine	Plant (duckweed)	*Lemna gibba*	>1.0 (EC10)		Brain et al. (2004b)
Cholinergic agonist	Nicotine	Invertebrate (waterflea)	*Daphnia pulex*	<0.07	42.9	FDA-CER (1996)

Therapeutic class	Substance	Taxonomic group	Species	Long-term exposure result (mg l^{-1})*	Acute to chronic ratio (if available)	Reference
Diuretic	Bendroflumethiazide	Invertebrate (cnidarian)	*Hydra vulgaris*	>0.01		Pascoe et al. (2003)
Diuretic (loop)	Furosemide	Invertebrate (cnidarian)	*Hydra vulgaris*	>0.01		Pascoe et al. (2003)
Nicotine metabolite	Cotinine	Plant (duckweed)	*Lemna gibba*	>1.0 (EC10)		Brain et al. (2004b)
Non-steroid anti-inflammatory drug	Acetaminophen (paracetamol)	Plant (duckweed)	*Lemna gibba*	>1.0 (EC10)		Brain et al. (2004b)
Non-steroid anti-inflammatory drug	Acetylsalicylic acid (aspirin)	Invertebrate (cnidarian)	*Hydra vulgaris*	>0.01		Pascoe et al. (2003)
Non-steroid anti-inflammatory drug	Diclofenac	Alga (blue-green)	*Syneehoeoeeus leopo/ensis*	10.0		Ferrari et al. (2004)
Non-steroid anti-inflammatory drug	Diclofenac	Alga (diatom)	*Cyelotella meneghiniana*	10.0		Ferrari et al. (2004)
Non-steroid anti-inflammatory drug	Diclofenac	Alga (green)	*Desmodesmus subspieatus*	72.0 (EC50)		Cleuvers (2003)
Non-steroid anti-inflammatory drug	Diclofenac	Alga (green)	*Pseudokirehneriella subeapitata*	10.0		Ferrari et al. (2003,
Non-steroid anti-inflammatory drug	Diclofenac	Fish	*Danio rerio*	4		Ferrari et al. (2003)
Non-steroid anti-inflammatory drug	Diclofenac	Invertebrate (rotifer)	*Braehionus ealyeiflorus*	12.5		Ferrari et al. (2003
Non-steroid anti-inflammatory drug	Diclofenac	Invertebrate (waterflea)	*Ceriodaphnia dubia*	1.0	22.7	Ferrari et al. (2003,
Non-steroid anti-inflammatory drug	Diclofenac	Plant (duckweed)	*Lemna minor*	7.5 (EC50)		Cleuvers (2003)

Therapeutic class	Substance	Taxonomic group	Species	Long-term exposure result (mg l^{-1})*	Acute to chronic ratio (if available)	Reference
Non-steroid anti-inflammatory drug	Ibuprofen	Alga (green)	*Desmodesmus subspicatus*	315.0 (EC50)		Cleuvers (2003)
Non-steroid anti-inflammatory drug	Ibuprofen	Invertebrate (cnidarian)	*Hydra vulgaris*	>0.01		Pascoe et al. (2003)
Non-steroid anti-inflammatory drug	Ibuprofen	Invertebrate (snail)	*Planorbis carinatus*	1.02	1.68	Pounds et al. (2004)
Non-steroid anti-inflammatory drug	Ibuprofen	Plant (duckweed)	*Lemna gibba*	>1.0 (EC10)		Brain et al. (2004b)
Non-steroid anti-inflammatory drug	Ibuprofen	Plant (duckweed)	*Lemna minor*	22.0 (EC50)		Cleuvers (2003)
Non-steroid anti-inflammatory drug	Naproxen	Alga (green)	*Desmodesmus subspicatus*	>320.0 (EC50)		Cleuvers (2003)
Non-steroid anti-inflammatory drug	Naproxen	Plant (duckweed)	*Lemna minor*	24.2 (EC50)		Cleuvers (2003)
Non-steroid anti-inflammatory drug	Paracetamol (acetaminophen)	Invertebrate (cnidarian)	*Hydra vulgaris*	>0.01		Pascoe et al. (2003)
Non-steroid anti-Inflammatory drug (metabolite of aspirin)	Gentisic acid	Invertebrate (waterflea)	*Daphnia longispina*	0.32	1070	Marques et (2004)
Non-steroid anti-Inflammatory drug (metabolite of aspirin)	Gentisic acid	Invertebrate (waterflea)	*Daphnia magna*	0.32	1258	Marques et (2004)
Non-steroid anti-Inflammatory drug	o-hydroxyhippuric acid	Invertebrate (waterflea)	*Daphnia longispina*	84.5	>21	Marques et (2004)

Therapeutic class	Substance	Taxonomic group	Species	Long-term exposure result (mg l^{-1})*	Acute to chronic ratio (if available)	Reference
(metabolite of aspirin)						
Non-steroid anti-Inflammatory drug (metabolite of aspirin)	o-hydroxyhippuric acid	Invertebrate (waterflea)	*Daphnia magna*	186.0	>9.7	Marques et (2004)
Non-steroid anti-Inflammatory drug (metabolite of aspirin)	Salicylic acid	Invertebrate (waterflea)	*Daphnia longispina*	5.6	205	Marques et (2004)
Non-steroid anti-Inflammatory drug (metabolite of aspirin)	Salicylic acid	Invertebrate (waterflea)	*Daphnia magna*	>10.0	<195	Marques et (2004)
Non-steroidal anti-androgen	Bicalutamide	Alga (blue-green)	Unspecified	1		FDA-COER (1996)
Non-steroidal anti-androgen	Bicalutamide	Alga (green)	Unspecified	1		FDA-COER (1996)
Oestrogen	17B-oestradiol	Fish	*Oryzias latipes*	10 ng/l	390000	Hutchinson et al. (2003b)
Oestrogen	Diethylstilbestrol	Fish	*Oryzias latipes*	10 ngll	140000	Hutchinson et al. (2003b)
Oestrogen	Diethylstilbestrol	Invertebrate (copepod)	*Nitocra spinepes*	0.003	97	Breitholtz & Bengtsson (2001)
Oestrogen	Diethylstilbestrol	Invertebrate	*Tisbe battaqliai*	0.01	<10	Hutchinson et

Therapeutic class	Substance	Taxonomic group	Species	Long-term exposure result (mg l^{-1})*	Acute to chronic ratio (if available)	Reference
		(cope pod)				al. (1999)
Oestrogen	Diethylstilbestrol	Invertebrate (waterflea)	*Daphnia magna*	0.062	17.6	Baldwin et al. (1995)
Oestrogen	Ethinylestradiol	Alga	Unspecified	0.054 (EC10)		Kopf (1995)
Oestrogen	Ethinyloestradiol	Fish	*Oncorhynchus mykiss*	<0.1 ng/L		Purdom et al. (1994)
				<0.3 ng/L		Sheahan et al. (1994)
Oestrogen	Ethinyloestradiol	Fish	*Oryzias latipes*	10 ng/I	150000	Hutchinson et al. (2003b)
Oestrogen	Ethinyloestradiol	Fish	*Pimepha/es prome/as*	1 ng/L		Lange et al. (2001)
Oestrogen	Ethinyloestradiol	Invertebrate (amphipod)	*Hya/ella azteca*	0.0001		Vandenburg et al. (2003)
Oestrogen	Ethinyloestradiol	Invertebrate (copepod)	*Nitocra spinepes*	0.05	10.2	Breitholtz & Bengtsson (2001)
Oestrogen	Ethinyloestradiol	Invertebrate (snail)	*Bithynia tentaculata*	<0.125 ng/I		Belfoid & Leonards (1996)
Oestrogen	Ethinyloestradiol	Invertebrate (snail)	*Lymnaea stagnalis*	<1.25 ng/I		Belfoid & Leonards (1996)
Oestrogen	Ethinyloestradiol	Invertebrate (snail)	*Marisa comuarietis*	<1.0 ng/I		Schulte-Oehlmann et al. (2004)

Therapeutic class	Substance	Taxonomic group	Species	Long-term exposure result (mg l^{-1})*	Acute to chronic ratio (if available)	Reference
Oestrogen	Ethinyloestradiol	Invertebrate (waterflea)	*Daphnia magna*	0.01	570	Kept (1995)
Oestrogen	Oestradiol	Invertebrate (copepod)	*Nitocra spinepes*	0.16	10	Breitholtz & Bengtsson (2001)
Peristaltic stimulant	Cisapride	Alga (green)	Unspecified	320 ('Effects')		FDA-COER (1996)
Peristaltic stimulant	Cisapride	Blue-green alga	Unspecified	100 ('Effects')		FDA-COER (1996)
Topical keratolytic	Salicylic acid	Invertebrate (waterflea)	*Daphnia magna*	<20.0	5.9	Wang & 1989
X-ray contrast medium	lopromide	Alga (blue-green)	Unspecified	68		FDA-COER (1996)
X-ray contrast medium	lopromide	Invertebrate (waterflea)	*Daphnia magna*	>1000.0	1	Schweinturt et al. (1996)
p-adrenergic receptor blocker	Atenolol	Invertebrate (cnidarian)	*Hydra vulgaris*	>0.01		Pascoe et al. (2003)
p-adrenergic receptor blocker	Metoprolol	Alga (green)	*Desmodesmus subspicatus*	7.3 (EC50)		Cleuvers (2003)
p-adrenergic receptor blocker	Metoprolol	Plant (duckweed)	*Lemna minor*	>320.0 (EC50)		Cleuvers (2003)
p-adrenergic receptor blocker	Propranolol	Alga (blue-green)	*Synechococcus leopo/ensis*	0.35		Ferrari et al. (2004)
p-adrenergic receptor blocker	Propranolol	Alga (diatom)	*Cye/otella meneghiniana*	0.094		Ferrari et al. (2004)
p-adrenergic receptor blocker	Propranolol	Alga (green)	*Desmodesmus subspicatus*	5.8 (EC50)		Cleuvers (2003)

Therapeutic class	Substance	Taxonomic group	Species	Long-term exposure result (mg l^{-1})*	Acute to chronic ratio (if available)	Reference
B-adrenergic receptor blocker	Propranolol	Alga (green)	*PseudokifchnerieHa subcapitata*	5.0		Ferrari et al. (2003, 2004)
l3-adrenergic receptor blocker	Propranolol	Fish	*Oryzias latipes*	<0.0005	>48600	Huggett et (2002)
l3-adrenergic receptor blocker	Propranolol	Invertebrate (amphipod)	*HyaleHa azteca*	0.001	29800	Huggett et (2002)
l3-adrenergic receptor blocker	Propranolol	Invertebrate (rotifer)	*Brachionus calyciflorus*	0.18		Ferrari et al. (2003
l3-adrenergic receptor blocker	Propranolol	Invertebrate (waterflea)	*Ceriodaphnia dubia*	0.009		Ferrari et al. (2003, 2004)
l3-adrenergic receptor blocker	Propranolol	Invertebrate (waterflea)	*Ceriodaphnia dubia*	0.125	6.8	Huggett et (2002)
l3-adrenergic receptor blocker	Propranolol	Plant (duckweed)	*Lemna minor*	114.0 (EC50)		Cleuvers (2003)

* (NOEC in mg l^{-1} unless otherwise)

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