Review of Human Pharmaceuticals in the Environment

Research and Development
Technical Report
P390

ENVIRONMENT AGENCY

Review of Human Pharmaceuticals in the Environment

R&D Technical Report P390

N J Ayscough, J Fawell, G Franklin and W Young

Research Contractor:
WRc–NSF Ltd

Further copies of this report are available from:
Environment Agency R&D Dissemination Centre,
c/o WRc, Frankland Road, Swindon, Wilts SN5 8YF

Tel: 01793 865138/012 Fax: 01793 514562 E-Mail: publications@wrcplc.co.uk
URL: www.wrcplc.co.uk/rdbookshop

Publishing Organisation:
Environment Agency
Rio House
Waterside Drive
Aztec West
Almondsbury
Bristol BS32 4UD

Tel: 01454 624400 Fax: 01454 624409

ISBN: 1 85705 411 3

Dissemination status
Internal: Released to Regions
External: Public Domain

Statement of use
This document reviews the release, occurrence and potential risk to the environment from pharmaceuticals. It is to be used for information by Agency staff in developing policy and future actions.

Research contractor
This document was produced under R&D Technical Service P2-T04 by:

WRc-NSF Ltd
Henley Road
Medmenham
Marlow
Buckinghamshire
SL7 2HD

Tel: 01491 571531 Fax: 01491 579094

WRc Report No.: EA 4761

Environment Agency's Project Manager
The Environment Agency's Project Manager for R&D Technical Report P390 was:
Dr Geoff Brighty, National Centre for Ecotoxicology and Hazardous Substances, Evenlode House, Howbery Park, Wallingford, Oxon. OX10 8BD.

CONTENTS

LIST OF TABLES

LIST OF FIGURES

EXECUTIVE SUMMARY

Recently, the issue of the presence and potential adverse effects of pharmaceuticals in the aquatic environment has again begun to receive increasing interest in the popular press. This is largely a result of a growing number of scientific papers published in the 1990s which have reported trace levels of pharmaceuticals detected in environmental samples, including sewage effluent, surface water, groundwater and drinking water.

In response to this, the Environment Agency commissioned the WRc-NSF's National Centre for Environmental Toxicology (NCET) to review the information available in the literature on human pharmaceuticals in the environment, their occurrence, fate and effects, to highlight any gaps in knowledge and to recommend future actions, if required. Contacts were also made with research groups active in the field and consultation with the Association of the British Pharmaceutical Industry (ABPI) and the Proprietary Association of Great Britain (PAGB) was an integral part of the process. No detailed consideration was given to veterinary drugs due to significant differences in their nature, use and pathways to the environment. Nonetheless, the Agency views the potential impact of veterinary drugs on the environment to be an important issue. In addition, no assessment was made of possible impacts on human health through drinking water as this falls outside the direct remit of the Agency.

As part of the registration process for new drugs, pharmaceutical companies are required to conduct environmental risk assessments for their products. However, guidance to industry on the environmental assessment procedure shows significant differences between the regulatory authorities in the US and Europe. Furthermore, it is of note that the EU guidance document is only draft and that final guidance is required to enable a consistent approach to the environmental assessment of pharmaceuticals in the EU.

The main routes for human pharmaceuticals to reach the environment are expected to be through use with patients in hospitals, medical centres or the community, and disposal of unused or out-of-date drugs. Following use, pharmaceutical drugs are excreted as the parent compound, water soluble conjugates or as metabolites and thus enter the sewerage system. Disposal of unused pharmaceuticals can also be a route to the environment either through disposal to sewer via the toilet or drain, or to landfill in domestic refuse by the general public or as special waste by licensed waste contractors.

There are currently no regulatory requirements for a national monitoring programme for pharmaceuticals in the environment. Where studies of pharmaceuticals in the environment have been published, these have been on an *ad hoc* basis by a relatively small number of academic research groups which are active in this field, notably in Germany and to a lesser extent in Switzerland and Denmark.

Where pharmaceuticals have been detected in sewage effluents or surface waters, the levels are in trace amounts at the ng l^{-1} or, at most, low μg l^{-1} level. The types/groups of pharmaceuticals detected are fairly broad e.g. contraceptive hormones, lipid regulators, pain killers, antibiotics, anti-cancer drugs, anti-epileptic drugs and those regulating blood pressure. The occurrence of drug metabolites has generally not been studied in detail apart from a few specific cases (e.g. clofibric acid, fenofibric acid and salicylic acid) and, therefore, current knowledge is limited.

Only a few studies were identified which have looked for the presence of pharmaceuticals in groundwater. Most often these have been associated with contamination via older landfills over vulnerable aquifers and therefore may represent isolated and rather specific circumstances. No quantitative data were located on concentrations of pharmaceuticals in sewage sludge, although this is a potential route for lipophilic substances to the terrestrial environment.

For all pharmaceuticals currently detected in surface waters, none are of significance to the aquatic environment when considering acute toxicity. Indeed, reported levels in surface water are at least three orders of magnitude below the mg l^{-1} levels which cause acute toxicity. It is more difficult to assess whether there is any environmental significance with regard to subtle long-term effects as available chronic toxicity data are lacking. Current regulatory guidance on environmental toxicity testing only requires pharmaceuticals to undergo standard acute toxicity tests unless there is good reason to believe the compound may bioaccumulate. It has been suggested that the *mode of pharmacological action* relevant to specific pharmaceuticals should be considered when planning appropriate testing to support environmental risk assessment.

The presence of oestrogenic activity in sewage effluents has been extensively studied by the Environment Agency and has been shown to impact on sexual differentiation in fish. The contribution of the contraceptive steroid 17α-ethinyloestradiol to this activity with regard its concentration appears to be small in relation to natural hormones. However, its oestrogenic potency is an order of magnitude higher than natural steroids and an additive response is important to consider given its same mode of action. 17α-Ethinyloestradiol has also been shown to be relatively persistent in the environment.

The induction of microbial resistance to antibiotics in discharges has been raised as a potential issue. However, there is no evidence that a significant proportion of resistant organisms in the environment arise as a consequence of such discharges rather than by excretion of resistant organisms by man and animals and the spread of resistance by plasmid transfer.

There are approximately 3000 active substances licensed for use in the UK. Although there has been no systematic monitoring for the presence of pharmaceuticals in the aquatic environment of the UK, the data available indicate that the concentrations in surface waters will be very low. At present, it is difficult to obtain a reliable estimate of use in tonnes within the scope of this project. Nonetheless, such data can be used as a tool for ranking priorities on the basis of high volume and high activity pharmaceuticals in the UK. Furthermore, the use of information on metabolism/excretion and environmental fate in addition to pharmaceutical use data would greatly improve assessment priorities. When risk assessment is carried out this should include consideration of the significant benefits of pharmaceuticals for human health.

The study has identified a number of gaps in knowledge and consequently a number of recommendations have been made. These include:

1. In conjunction with ABPI, further pursue with Intercontinental Medical Statistics (IMS) the possibility of providing detailed information on quantities of both prescription and over the counter pharmaceuticals used in the UK.

2. With other government departments and ABPI, consider the need for, and practicality of, central collation of readily accessible information of the quantities of prescription

and non-prescription pharmaceuticals sold. Consider information on metabolism/excretion and environmental fate in addition to pharmaceutical use data as this will improve assessment of priorities.

3. Although disposal of unused pharmaceuticals by the general public is likely to be a relatively small source of environmental contamination, it would be of benefit to minimise this possibility by encouraging the return of unwanted medicines to the pharmacy for appropriate disposal. Initiatives that the pharmaceutical industry could actively support include appropriate labelling, standard advice in safety leaflets and advertisements.

4. Using the data available on prescription quantities and over the counter sales, metabolism/excretion and environmental fate (linked to recommendation 1), carry out targeted quantitative analysis for the presence of pharmaceuticals most likely to occur in the environment, representing a range of categories, in sewage effluent and downstream of the mixing zone.

5. Carry out a desk study of the need for specialised chronic tests on aquatic organisms, incorporating pharmacological mode of action, and to determine what form such tests would take with a view to developing appropriate test guidelines. Specialised pharmacological advice and experience from the industry will be an important part of this process. However, tailoring toxicity tests to the mode of action of a parent pharmaceutical could be problematic unless the amount, nature and pharmacological activity of drug related materials reaching the environment are known

6. Consider the need for detailed laboratory and field studies on the fate of pharmaceuticals in sewage treatment and the environment. This should utilise any existing information from individual manufacturers (which may involve specialised treatment) and involve participation by sewage undertakers.

7. Consider the practicality of prioritising pharmaceuticals by structure into categories based on human metabolism and pharmacological activity, likely occurrence, persistence and risk to the environment. If possible, some comparison to the natural background of pharmacologically active compounds e.g. microbial and plant metabolites, would be useful.

8. Ensure that research and monitoring is co-ordinated with other interested parties, in the UK and the EU, in order to maximise the value of information emerging from research. To this end it would be of value to organise a selective workshop, in conjunction with other interested parties, on the risk assessment of pharmaceuticals in the environment, in order to facilitate the evaluation of the quality of existing studies and determine what research is planned or is considered necessary. Such a workshop would include researchers, regulators and manufacturers and the water industry.

9. Pursue, with the appropriate authorities, expediting the publication of the EU guidance note on the environmental assessment of pharmaceuticals.

10. Although not included in this report, the issue of veterinary drugs is considered important and their potential impact on the environment should also be addressed.

KEY WORDS

Pharmaceuticals, human, environment, surface water, groundwater, drinking water, sewage treatment, occurrence, fate, hazard, aquatic toxicity, oestrogenicity.

GLOSSARY

Acetylsalicylic acid:	The chemical name for aspirin.
Anti-epileptic/anti-convulsant:	A drug which is used to control seizures.
Anti-neoplastic:	A drug used in cancer treatment.
Analgesic:	A drug used as a pain-killer.
Anti-inflammatory:	A drug used to treat inflammation with pain relieving properties.
β-Blocker:	A drug which blocks the effects of adrenaline and noradrenaline in the body. Important in the treatment of hypertension, angina, cardiac problems and glaucoma.
Diuretic	A drug which acts on the kidney to increase urine flow and fluid loss.
EE	17α-Ethinyloestradiol, an oral contraceptive
Lipid regulator	A drug which lowers the level of cholesterol in the blood
β_2- Sympathomimetic	A drug which partially or completely mimics the effects of adrenaline and noradrenaline in the body. Important in asthma.
STW	Sewage treatment works

1. INTRODUCTION

Following studies in the 1980s (Fielding *et al.* 1981, Watts *et al.* 1983, Richardson and Bowron 1985, Aherne *et al.* 1985) there has again been a recent upsurge in interest in the discharge, presence and potential adverse effects of pharmaceuticals in the aquatic environment. In addition, a growing number of papers have appeared in the scientific literature in the 1990s which have reported trace levels of pharmaceuticals detected in the environment (including sewage effluent, surface water, groundwater and drinking water). Halling-Sørensen *et al.* (1998) and Daughton and Ternes (1999) reviewed the issue and although the concentrations detected are generally at the nanogram per litre (ng l^{-1}) level, because pharmaceuticals are biologically active agents, the authors concluded that additional research is warranted. Key research in the UK over recent years has centred on endocrine disrupters (including work on steroids such as 17α-ethinyloestradiol, oestrone and 17β-oestradiol) and oestrogenic effects on fish.

There has also been increasing coverage by the more popular press on the issue. For example, in 1998 there was an article 'Studies indicate drugs in water may come from effluent discharges' in *Water Environment and Technology* (Hun 1998) and an article 'Something in the water' appeared in the *New Scientist* which drew further attention to the issue (Pearce 1999). The issue is also gaining interest at scientific conferences, for example a presentation entitled 'Pharmaceuticals in the environment - a source of endocrine disruption' was given at an IBC conference, May 14-15th, 1999, London (Ingerslev and Halling-Sørensen 1999). More recently, an international conference was held March 9th 2000, Brussels which was wholly dedicated to the issue of pharmaceuticals in the environment (Technological Institute 2000).

In order to assess the potential environmental risk of pharmaceuticals it is important to have relevant data. This will include environmental monitoring data as well as an understanding of properties such as environmental fate and behaviour, ecotoxicity and degradation during sewage/water treatment processes. In response to this, the Environment Agency commissioned the WRc-NSF's National Centre for Environmental Toxicology (NCET) to conduct an assessment of the available data in the literature, highlight any gaps in knowledge and to recommend future actions, if required. Consultation with the Association of the British Pharmaceutical Industry (ABPI) and the Proprietary Association of Great Britain (PAGB) was an integral part of the process.

Whilst the review evaluates the environmental risks posed by human pharmaceuticals, no detailed consideration is given to veterinary drugs due to significant differences in their nature, use and pathways to the environment. Nonetheless, the Agency views the potential impact of veterinary drugs on the environment to be an important issue. In addition, no assessment was made of possible impacts on human health through drinking water as this falls outside the direct remit of the Agency. However, this topic was studied by Christensen (1998) who assessed the potential risk to human health posed by environmental exposure to three drugs:- 17α-ethinyloestradiol (an oral contraceptive), penicillin V (an antibiotic) and cyclosphosphamide (an anti-cancer drug). By using the software EUSES on worst case emission quantities, the author estimated human exposure to these drugs via the environment (drinking water, food and air) to be well below the therapeutic daily doses. It was therefore concluded that any risk to human health from environmental exposure was negligible.

This review was based on literature searches of NCET in-house sources, external databases and the internet. Contacts were also made with research groups active in the field as well as the ABPI, PAGB, the Department of Health's Pharmaceutical Price Regulation Scheme (PPRS) and various regions of the Environment Agency. The report is divided into the following sections:-

1. Introduction
2. Environmental assessment of human drugs during registration in the US and EU
3. Pharmaceutical use in the UK and other European Countries
4. Pathways of environmental contamination
5. Occurrence in the environment
6. Environmental fate
7. Environmental hazard
8. Discussion
9. Conclusions
10. Recommendations for further work - the way forward

At the end of each section, a summary has been included.

2. ENVIRONMENTAL ASSESSMENT OF HUMAN DRUGS DURING REGISTRATION IN THE US AND EU

2.1 Responsible Authorities

A pharmaceutical company is required to demonstrate the quality, safety and efficacy of a new pharmaceutical product before it can be marketed. In the United States (US), the regulatory authority is the Food and Drug Administration (FDA). The equivalent authority in the EC is the European Medicines Evaluation Authority (EMEA) for Europe-wide authorisation or the Member State's regulatory authority if individual country authorisation is sought. In the UK, the relevant authority is the Medicines Control Agency (MCA).

2.2 Environmental risk assessment in the US

In the US, an assessment of risk to the environment of manufacture, use and distribution of human drugs is required under the National Environment Policy Act of 1969. An environmental assessment procedure was developed by the FDA some years ago as part of the registration procedure for new human pharmaceutical drugs (FDA 1985, FDA 1987). In addition, in 1995, the FDA Center for Drug Evaluation and Research (CDER) issued a new guidance document '*Guidance for Industry for the Submission of an Environmental Assessment in Human drug Application and Supplements'* (FDA 1995). This document significantly reduced the previous regulatory requirements as a result of a CDER retrospective evaluation of past submissions, which showed that human pharmaceuticals generally had minimal impact on the environment. It includes guidance on the submission of detailed environmental assessments, abbreviated environmental assessments and when 'categorical exclusions' apply.

The environmental assessment procedure for new drugs is a two-stage process. First, a manufacturer is required to estimate the expected introductory concentration (EIC) entering the environment based on total fifth year production estimates. The EIC entering into the aquatic environment from patient use may include consideration of metabolism to less pharmacologically active or inactive compounds and environmental depletion mechanisms that occur in waste treatment processes (e.g. adsorption, degradation, hydrolysis), if information is available. Otherwise, the default calculation for determining the EIC for the aquatic environment is as follows:

Aquatic EIC ($mg\ l^{-1}$) = A x B x C x D (FDA 1995)

where:-

A = kg/year production
B = 1/litres per day entering publicly owned treatment works (i.e. 1.115×10^{11})
C = year/365 days
D = 10^6 $mg\ kg^{-1}$ (conversion factor)

This calculation assumes all drug substance is used, even distribution through the USA per day, with no metabolism or depletion mechanisms. If an alternative calculation is used, the basis must be clearly indicated.

If the EIC of a drug or its active metabolites at the point of entry (i.e. sewage effluent) in the aquatic environment is shown to be less than 1 $\mu g\ l^{-1}$ (1 ppb), the drug is considered to be acceptable and is given environmental 'category exclusion' and no detailed environmental risk assessment is needed. In such cases, no monitoring is conducted to confirm the environmental concentration after a drug is marketed.

If the requirement for categorical exclusion is not met (i.e. the expected introductory concentration is >1 $\mu g\ l^{-1}$), then a formal environmental assessment has to be conducted. If triggered, this will require data on environmental fate and a tiered set of ecotoxicity tests. The base set usually includes effects on microbial respiration and acute toxicity to at least one algal, invertebrate and fish species. Chronic toxicity testing only need be considered under certain circumstances, for example, if the drug has the potential to bioaccumulate. The FDA procedure is not in line with that for other chemical types because if the requirements for environmental category exclusion are met, no environmental data is required or submitted.

2.3 Environmental risk assessment in Europe

The procedure in Europe is less developed than that in the US. In the EU, from January 1 1995, a company applying for registration for a new drug must demonstrate that will not have an impact on the environment (65/65/EEC). An EU draft guidance document (CEC/III/5504/94, draft 6 version 4) was published in January 1995 which specifies the documentation required for an environmental assessment, and like the FDA system, it defines a cut-off limit for a detailed risk assessment. A simple initial estimation of the predicted environmental concentration (PEC) is conducted on the basis of statistical data such as quantity sold, number of inhabitants, waste water quantity and dilution of the material leaving the plant (i.e. 1:10) using the formula below:-

$$\text{Aquatic PEC, crude estimate } (g\ l^{-1}) = \frac{A \times (100 - R)}{365 \times P \times V \times D \times 100}$$

where:-

A [kg] = predicted amount used per year in the EU country as defined below*, or relevant value for single national applications

R [%] = removal rate (due to loss by adsorption to sludge particles by volatilisation, hydrolysis, biodegradation or other specific, naturally-occurring processes)

P = number of inhabitants of the country

V [m^3] = volume of waste water per capita and day (generally 0.15 to 0.30 m^3)

D = factor for dilution of waste water by surface water flow (average factor: 10)

100 = conversion factor for percentage

* The estimate should be conducted for the EU country with a maximum ratio A/P

Under worst case conditions i.e. no losses through degradation or adsorption, R is counted as 0 and any other chosen value should be justified.

If the PEC is <0.01 μg l^{-1}, no further evaluations or testing are required (EC 1995). If the PEC is >0.01 μg l^{-1} but <0.1 μg l^{-1}, an initial estimation of the ratio of the PEC to the predicted no-effects concentration (PNEC) is required. If this ratio is less than 1, again no further action is required. If the initial PEC >0.1 μg l^{-1} or the PEC:PNEC ratio is >1, Phase II risk assessment (III/5505/94, draft 3) will be required which will include further assessment and ecotoxicity tests on algae, *Daphnia* and fish conducted to specified OECD guidelines. However, to date these guidelines are still under discussion and have not been passed by the EU, despite calls from the industry, including the Association of the British Pharmaceutical Industry (ABPI).

Table 2.1 Summary of environmental risk assessment approach for human health drugs in US and Europe

UNITED STATES

1. If the expected introduction concentration (EIC) is <1 μg l^{-1}, no further investigations are necessary, unless toxicity or other profile of the compound warrants some environmental testing.

2. When EIC >1 μg l^{-1} evaluations or testing to show degradation and dilution will be necessary.

3. EIC - loss of drug due to degradation and dilution = Expected Environmental Concentration (EEC) (i.e. the same as a PEC)

4. If the EEC is several fold lower than no-observed effect concentration (NOEC) for aquatic and terrestrial species, a finding of no significance may be issued.

EUROPE

1. If the surface water PEC_{water} is <0.01 μg l^{-1}, no testing or evaluations will be required.

2. If the surface water PEC_{water} is >0.01 μg l^{-1} but <0.1 μg l^{-1}, the PEC:PNEC ratio should be estimated. If the ratio is <1, then no further evaluations or testing will be required.

3. If the surface water PEC_{water} is >0.1 μg l^{-1}, further testing or evaluation will be required (Phase II).

4. PECsoil and PECsediment action limits are 10 μg kg-1

References: EC (1995), FDA (1995), Velagaleti and Winberry (1998)

2.4 Concerns on regulatory testing requirements

Some concerns have been raised that a limitation to standard ecotoxicity tests would underestimate the toxicity of some pharmaceuticals. Following ecotoxicity testing of four pharmaceuticals and metabolites against a number of organisms, Henschel *et al.* (1997) indicated that the most sensitive reactions were observed for a non-standard test which incorporates relevant end points for each pharmaceutical (e.g. BF-2 fish cell line which tests for cytotoxicity and proliferation inhibition of fish cells). The researchers recommend the inclusion of a test strategy adapted to the *mode of action* for pharmaceuticals in the EU guideline. However, tailoring toxicity tests to the mode of action of a particular parent pharmaceutical could be problematic unless the amount, nature and pharmacological activity of drug-related compounds reaching the environment are known.

2.5 Summary

- Any new pharmaceutical product to be placed on the market requires authorisation by the relevant authority:

- Food and Drug Administration (FDA) in the US

- European Medicines Evaluation Agency (EMEA) in Europe

- Medicines Control Agency (MCA) in the UK

- In the US, if the expected introductory concentration (EIC) entering the environment is less than 1 μg l^{-1}, a drug is considered to be acceptable and is given 'category exclusion'. No detailed environmental assessment is then needed. If the EIC is greater than 1 μg l^{-1}, a formal environmental assessment is required with a tiered set of ecotoxicity tests.

- Compared to the US the procedure in Europe is less developed. Although a company registering a drug from January 1995 must demonstrate that it will not have an impact on the environment, the EU guidance document is still in draft. The latest version of the EU guidance is more stringent than the US in that stipulates that no testing or evaluations are required if the predicted environmental concentration (PEC) is less than 0.01 μg l^{-1} compared to the expected introductory concentration (EIC) of 1 μg l^{-1} specified by the US.

- In view of the potential for some pharmaceuticals with specific pharmacological activity to cause "effects" at doses lower than those causing toxicity, some researchers have recommended that the test strategy should be adapted to the *mode of action* for the pharmaceutical under consideration where appropriate.

3. PHARMACEUTICAL USE IN THE UK AND OTHER EUROPEAN COUNTRIES

3.1 Introduction

The use of human pharmaceuticals can be assessed from data collected by National Health Agencies in different countries. Often these data are given as annual sales of defined daily doses (DDD) of each compound. This unit states the daily drug consumption by one person receiving the dose of the compound as defined by the World Health Organization (WHO 1999) for the main indication of the drug. It is important to note that there can be significant differences in the type of drugs which are prescribed in differing countries. For example, in the UK amoxycillin is the highest prescribed drug whereas in Denmark this antibiotic is rarely used with penicillin V being the most prescribed antibiotic.

3.2 Pharmaceutical use in the UK

There are approximately 3000 active substances licensed for use in the UK, although not all of these are necessarily on the market at the current time (DOH, pers. comm). Given the large number of pharmaceuticals in use, it is impractical to monitor water samples for all the active ingredients involved. Moreover, analytical methods are not necessarily available for detecting pharmaceuticals at the extremely low levels likely to be encountered in the environment. Nonetheless, as more sophisticated analytical techniques are developed with highly sensitive limits of detection, it is likely that an increasing number of compounds will be able to be detected in the future.

In order to prioritise those pharmaceuticals most likely to be present at measurable concentrations in the UK environment, it is appropriate to establish which drugs are used to the greatest extent in the UK. This was achieved by contacting:-

(a) the PPRS (Pharmaceutical Price Regulation Scheme) branch of the Department of Health for the use of prescribed drugs dispensed in the community

(b) the Proprietary Association of Great Britain (PAGB) for use of ‘over the counter’ drugs

PPRS provided data on number of prescriptions (by active ingredient) dispensed in the community (i.e. by community pharmacists, dispensing doctors) in England in the year 1997 and it is estimated that this accounts for about 80% of use for the whole of the UK (DOH 1997). It should be noted that these figures do not include drug use in hospitals or private practice. The results of this investigation for the top ten drugs in England are summarised in Table 3.1. A complete list of drugs with over one million prescription items is given in Appendix A. The antibiotic amoxycillin was the most prescribed drug in England in 1997 followed by salbutamol (β_2-sympathomimetic), aspirin (analgesic), beclomethasone dipropionate (corticosteroid used for skin disorders) and coproxamol (dextroprop hydrogen chloride and paracetamol). Since these data are given as prescription items, rather than as defined daily doses, it was not possible in the scope of this project to derive an estimate of drug use in tonnes/year. Nonetheless, they can be used as a tool for ranking high volume drugs in the UK. Further manipulation of the data and making assumptions on therapeutic

dose could be undertaken for a better estimation, although this was unable to be done under the scope of the current review.

Table 3.1 List of top 10 prescribed pharmaceuticals in the UK for 1997

Active ingredient	Number prescription items (thousands)	Detected in sewage effluent or in the aquatic environment?
Amoxycillin	16585.4	No
Salbutamol	16167.8	Yes
Acetylsalicylic acid	11634.6	Yes
Beclomethasone dipropionate	10407.7	No
Co-Proxamol (Dextropropoxyphene HCl/ paracetamol)	10159.0	-
Paracetamol	9569.5	Yes
Atenolol	8133.0	No
Bendrofluazide	7591.5	No
Co-Codamol (codeine phosphate/paracetamol)	7345.4	-
Hydrocortisone	7147.8	No

A similar approach was undertaken in a previous UK study in order to select pharmaceuticals for investigation in biodegradability tests (Richardson and Bowron, 1985). This study obtained information from the then Department of Health and Social Security (DHSS) on drugs prescribed by general practitioners (excluding drugs administered in hospitals and private practice) for the year 1976. Similar details were sought from the Proprietary Association of Great Britain for over-the-counter medicines. The information was then translated into tonnes of active chemical ingredient by taking into account the therapeutic dose (which varies between drugs but is often in the mg to g range). At that time, approximately 170 pharmaceutical chemicals were considered to be used in excess of 1 tonne per annum. Earlier, Wood and Richardson (1980) estimated quantities of active synthetic hormones contained in prescribed drugs in England and Wales in 1976; their estimates were 0.36 tonnes per annum for norethisterone and 0.021 tonnes per annum for 17α-ethinyloestradiol.

In a smaller study, Webb (2000) estimated the UK use for 67 specific pharmaceuticals based on Intercontinental Medical Statistics (IMS) data for 1995 (see Appendix F). These drugs were selected on the basis of the availability of ecotoxicity data. Paracetamol was the highest usage drug at 2000 tonnes/annum, this being the only one used at levels >1000 tonnes/annum. The next drugs used to the greatest degree at levels above 100 tonnes were aspirin (770 tonnes/annum) and metformin (106 tonnes/annum). For the remaining 64 drugs, twelve were used at levels of >10 tonnes, fourteen at >1 - <10 tonnes, fifteen at levels of >0.1 - <1 tonne, twelve at >0.01 - <0.1 tonnes and eleven at levels of <0.01 tonne.

There is no publicly accessible central or regional record kept of drug use by hospitals and therefore it is extremely difficult to obtain an overall picture for use in the UK from this source. The PAGB could only provide some general statistical information for over the counter drug use. This information related to market trends for certain drug groups for years

1996/97. The pain relievers sector (e.g. Anadin, Solphadeine, Hedex, Calpol, Migraleve, Nurofen) dominated the market with 16 % of the market share. Skin treatments (12.2%), food supplements (9.4%), cold (8%), sore throat (7.6%) and cough remedies (5.4%) were the next groups with the largest market share.

Another source for obtaining UK pharmaceutical usage data is the Intercontinental Medical Statistics (IMS) Unit. This organisation has indicated that it could provide usage data (in tonnes) on prescription and over-the-counter drugs as well as drug use in hospitals at a national and regional level (IMS, pers. comm). However, the release of data would be subject to further discussion with the Agency on confidentiality issues and charges (estimated to be in the order of thousands of pounds).

3.2.1 Discussion

Based on the readily accessible data provided by PPRS, a number of the high use prescription drugs in the UK have been detected in the aquatic environment, although much of the monitoring data available relate to Germany (see section 5). It must be stressed that this approach should not be viewed as determining accurate use figures but more as a tool for ranking priorities. One obvious limitation is that it does not take into account use of highly biologically-active drugs which are utilised in the hospital sector. Methotrexate, which is usually only used in hospital cancer treatment, is such a drug and it is very difficult to estimate its use, although its presence in waste water from clinics with oncological departments is possible. This was confirmed by Aherne *et al.* (1985) who detected approximately 1 $\mu g\ l^{-1}$ of methotrexate in hospital effluent (only one sample was analysed) taken from a large oncology clinic (see Section 5.2). **

Another option identified for obtaining detailed usage data is from the Intercontinental Medical Statistics (IMS) Unit which can provide information on prescription drugs, over-the-counter medicines as well as drug use in hospitals. Provision of the data would be subject to further discussion with the Agency on requirements, confidentiality issues and charges; it is recommended that this option be pursued.

It is of note that for some groups of human pharmaceuticals e.g. antibiotics, there will be a seasonal variation in usage in that the number of prescriptions are higher in winter months which could have an impact on levels reaching the environment. However, this will be counteracted by the fact that there is increased flow in rivers during winter months which would result in increased dilution.

3.3 Pharmaceutical use in other European countries

A similar approach for estimating pharmaceutical use has also been conducted by German and Danish researchers.

3.3.1 Denmark

Annual consumption for the top 25 human pharmaceuticals based on use in Denmark for 1997 has been reported (see Table 3.2) (Ingerslev and Halling-Sørensen 1999; Stuer-Lauridsen *et al.* 2000). These data demonstrate that there can be a difference in the order of drugs

depending on whether it is based on number of doses (i.e. DDD) or units of weight. These same authors previously reported data for groups of drugs (e.g. antibiotics, diuretics, anti-asthmatics) for the year 1995 and this is summarised in Table 3.3.

Table 3.2 List of top 25 pharmaceuticals based on use in Denmark in 1997

Pharmaceutical	Therapeutic use	Annual consumption DDD (million)	Calculated weight (tonnes)
Frusemide	Diuretic	93.6	3.74
Paracetamol	Analgesic	82.75	248.25
Acetylsalicylic acid	Analgesic	70.93	212.79
Bendroflumethiazide	Diuretic	66.83	0.17
Gestroden and oestrogen	Contraceptive	37.14	0.045
Acetylsalicylic acid comb. excl. Psycholeptic	Analgesic	30.82	92.5
Ibuprofen	Analgesic	28.16	33.8
Lactic acid producing organisms	Antidiarrheal	27.4	-
Potassium chloride	Mineral supplement	26.7	80.1
Amlodipine	Selective potassium antagonist	26.44	0.13
Budesonide	Anti-asthmatic	25.82	0.04
Terbutaline	Anti-asthmatic	23.73	0.47
Oestradiol	Sex hormone	23.7	0.119
Nitrazepam	Anti-hypertensive	23.2	0.116
Desogestrel and oestrogen comb.	Sex hormone	45.4	0.004
Enalapril	ACE inhibitor	20.8	0.416
Diazepam	Phycholeptic agent	20.7	0.207
Zopiclone	Anti-hyptertensive	19.2	0.144
Citalopram	Physchoanaleptic	18.4	0.368
Salbutamol	Anti-asthmatic	17	0.17
Xylometazolin	Nasal sympathomimetic	16.7	0.013
Digoxin	Cardiac glycoside	16.5	0.004
Hydrochlorthiazide	Diuretic	16.0	-
Hydrogen peroxide	Stomatological anti-infective	15.3	0.916
Ketoconazole	Antifungal	14.7	-

Reference: Ingerslev and Halling-Sørensen (1999); Stuer-Lauridsen *et al.* (2000)

Table 3.3 Consumption of high-volume pharmaceuticals in Denmark in 1995

Substance/group	Defined daily doses (DDD) in 1995 (million)	DDD WHO (g)	Applied weight (tonnes)
Ibuprofen	27.2	1.2	33.2
Frusemide	91.9	0.04	3.7
Oestrogens in combination with gestoden or desorgestrel	58.3	0.000065	0.0038
Oestradiol	24.3	0.002	0.049
Therapeutic groups			
Antibiotics	25.1	1.5	37.7
Analgesics (NSAID)	56.6	0.5	28.3
Hypotensives	41	0.01	0.41
Diuretics	95.3	0.04	3.8
Anti-asthmatics	110.5	0.015	1.7
Psycholeptics	147.5	0.05	7.4

Reference:- Halling-Sørensen *et al.* (1998)

Christensen (1998) studied the therapeutic use of the 17β-oestradiol (the natural sex hormone used for replacement therapy in deficiency states e.g. primary amenorrhea, delayed onset of puberty as well as management of the menopausal syndrome) and the synthetic hormone 17α-ethinyloestradiol (an oral contraceptive). An annual use of 0.045 and 0.00364 tonnes was estimated for the year 1996. These figures reflect sales from private pharmacies; use in hospitals was not included as it is assumed that these drugs are mainly domestic use. By far the most prescribed antibiotic in the primary sector in Denmark is phenoxymethylpenicillin (penicillin V) and the author estimated a total use for this drug in the range of 19 tonnes for 1996. Cyclophosphamide was the most widely used anti-neoplastic agent (cancer treatment), with about 0.013-0.014 tonnes used in Danish hospitals and around 0.006 tonnes prescribed for sale at private pharmacies, resulting in a total use of about 0.02 tonnes for the year 1996/1997.

3.3.2 Germany

Hirsch *et al.* (1999) estimated the overall production amount of antibiotics in Germany was 1831 tonnes with 624 tonnes for the penicillins alone in 1994.

Table 3.4 summarises the amounts of drugs prescribed for Germany for which data were available in the literature.

By multiplying the amount of daily dose with the number of prescribed daily doses per year, Schwabe and Paffrath (1995) [cited in Ternes 1998] estimated that up to about 100 tonnes of individual drugs were prescribed in Germany in 1995. However, again this value does not consider ‘over the counter’ drugs and so will be an underestimation of the total consumption

of drugs. Hirsch *et al.* (1999) estimated the total amount of antibiotics used for human medication in Germany was calculated to be 37.7 tonnes in 1995.

Henschel *et al.* (1997) also estimated the use of a number of pharmaceuticals in Germany. The authors estimated that 95-315 tonnes of salicylic acid (the major metabolite of aspirin) may reach STWs with household sewage in 1994. Again, this does not include the quantities of aspirin that are freely sold over the counter. For paracetamol, the authors estimated a theoretical annual quantity reaching STWs of 292 and 585 tonnes and that between 5.6 and 7.9 tonnes of clofibric acid may have entered the wastewater. It has also been estimated that >10 tonnes per year of paracetamol and metamizol are consumed in Germany and/or Denmark (pers. comm).

Table 3.4 Consumption of prescribed pharmaceuticals in Germany 1993-1995

Compound	Calculated weight (tonnes/year) 1993[a]	Calculated weight (tonnes/year) 1994[a]	Calculated weight (tonnes/year) 1995 [b,c]
Acetylsalicylic acid	23-116		
Ibuprofen	48-96		105
Bezafibrate	38-57		30
Diclofenac	48-72		75
Clofibric acid	15-21		16
Fenofibric acid	11-15		15
Gemfibrozil	14		6
Indomethacine		3-10	6
Ketoprofen		0.7	
Metoprolol		30-60	50
Propanoprolol		2.5-5	3
Bisoprolol		0.6-1.1	
Fenoterol		0.5	
Clenbuterol		0.001	
Carbamazepine			80
Antibiotics			
Amoxycillin			25.5-127.5
Ampicillin			1.8-3.6
Penicillin V			140
Penicillin G			1.8-3.6
Sulfamethoxazole			16.6-76
Trimethoprim			3.3-15
Erythromycin			3.9-19.8
Roxithromycin			3.1-6.2
Clarithromycin			1.3-2.6
Minocycline			0.8-1.6
Doxycycline			8-16

Notes:-
[a] Stan and Heberer (1997)
[b] Ternes (1998)
[c] Hirsch *et al.* (1999)

3.3.3 Sweden

A Swedish study reported on the use of drugs for a specific large university hospital (Hartmann *et al.* 1998). Results are given in Table 3.5 and indicate that the amounts used of such highly biologically active drugs are only in the range of $4x10^{-6}$ - 0.091 tonnes which is largely a result of the low doses in which such drugs are prescribed.

Table 3.5 Hospital use of drugs in a Swedish hospital

Drug	Therapeutic use	Mean annual consumption (1992-1994) (tonnes)
Amoxycillin	Antibiotic	0.091
Ciprofloxacin	Antibiotic	0.0061
Ornidazol	Antibiotic	0.0037
Norfloxacin	Antibiotic	0.0031
Metronidazol	Antibiotic	0.0028
Fluorouracil	Anti-neoplastic	9.21×10^{-4}
Etoposide	Anti-neoplastic	2.2×10^{-4}
Dacarbazin	Anti-neoplastic	8.5×10^{-5}
Adriamycin	Anti-neoplastic/Antibiotic	3.7×10^{-5}
Cisplatin	Anti-neoplastic	3.1×10^{-5}
Bleomycin	Anti-neoplastic	6×10^{-6}
Mitomycin C	Anti-neoplastic	4×10^{-6}

Reference: Hartmann *et al.* (1998)

3.4 Metabolism of drugs

Most human pharmaceuticals are well absorbed after ingestion after which they will undergo complete or extensive Phase I followed by Phase II metabolism. Phase I reactions usually consists of oxidation, reduction or hydrolysis whereas Phase II involves conjugation (e.g. addition of glucuronic acid, sulphate, acetic acid or amino acid). These processes yield polar metabolites excreted in the urine, which normally exhibit insignificant pharmacological activity. Excretion of the free drug or a conjugate of a parent compound can occur for some drugs but is unusual. However, in a few cases, it is estimated that 50-90% can be excreted from the human body unchanged in its original or biologically active form (Ternes 1998, Hirsch *et al.* 1999). Nonetheless, it is important to emphasise that significant pharmacological activity in excreta is the exception rather than the rule.

There is evidence that conjugates (e.g. glucuronides and sulphates) entering the sewage treatment works (STWs) may be hydrolysed to the parent drug or metabolite through bacteria hydrolases (Hirsch *et al.* 1999, Ternes *et al.* 1999b, Belfroid *et al.* 1999, Panter *et al.* 1999).

One example for which this has been suggested is 17α-ethinyloestradiol (EE). The metabolism of EE is complex and involves both phase I and II metabolism. The primary phase I metabolism has been shown to be 2-hydroxylation followed by conjugation, although a significant portion of EE is directly conjugated with glucuronide and excreted in the urine

(Christensen 1998, Orme *et al.* 1983). Furthermore, a significant proportion (30%) of the metabolites are excreted by the faecal route, some of which are excreted as the unchanged form (which may be a result of deconjugation in the colon) (Orme *et al.* 1983). The rate of excretion of free EE via the urine is low, although it has been suggested that free EE may be reformed by bacterial hydrolysis in the sewer system, in waste water treatment plants, or in nature (Hirsch *et al.* 1999, Ternes *et al.* 1999b).

However, it is noteworthy that EE is a specific example that may not necessarily reflect the situation for other human pharmaceuticals. Instead, regeneration of active moieties by bacterial cleavage of conjugated parent drug or active metabolites is likely to be quite rare, due to the fact that the majority of human pharmaceuticals undergo phase I metabolism forming polar metabolites with insignificant activity.

3.5 Summary

- There are approximately 3000 active substances licensed for use in the UK.

- Based on the information readily available on UK use of prescribed pharmaceuticals (expressed as prescription items), it is difficult to obtain a reliable estimate of use in tonnes per year within the scope of this project. Further, no central or regional record of pharmaceutical use by hospitals or over-the-counter medicines is readily accessible. Together these factors make it difficult to quantify releases to the environment. Nonetheless, the data available can be used as a tool for ranking priorities on the basis of high volume pharmaceuticals in the UK.

- Further manipulation of the data and making assumptions on therapeutic dose could be undertaken for a better estimation, although this was unable to be done under the scope of the current review.

- As expected, the highest usage drugs were the analgesics (e.g. paracetamol, aspirin). In one detailed UK analysis involving a small sample of around 60 pharmaceuticals, it was estimated that paracetamol was used at 2000 tonnes per annum in 1995. [This was the only pharmaceutical used at levels >1000 tonnes in this small sample]. The antibiotic amoxycillin and salbutamol, a drug commonly used in asthma, are also highly prescribed in the UK.

- Another option identified for obtaining detailed UK usage data (in tonnes) is from the Intercontinental Medical Statistics (IMS) Unit which can provide information on prescription drugs, over the counter medicines as well as drug use in hospitals. Provision of the data would be subject to further discussion with the Agency on requirements, confidentiality issues and charges (estimated to be thousands of pounds) and it is recommended that this option be pursued.

- Similar approaches for estimating pharmaceutical use have been conducted by German and Danish researchers. These illustrate that there can be significant differences in the types and amounts of pharmaceuticals prescribed in individual countries and that data are not necessarily comparable.

- Although some pharmaceuticals may be excreted from the human body unchanged, the majority undergo significant metabolism and conjugation. These processes yield polar metabolites excreted in the urine, which normally exhibit insignificant pharmacological activity.

- There is some evidence that conjugates (i.e. glucuronides and sulphates) entering the sewage treatment works may be hydrolysed and reactivated to the parent drug or metabolite through bacterial hydrolases

4. PATHWAYS OF ENVIRONMENTAL CONTAMINATION

4.1 Introduction

Pharmaceuticals in the environment may arise from their manufacture, formulation, distribution, use and disposal. The manufacture of pharmaceutical products in the UK is controlled by Good Manufacturing Practice (GMP) regulations. Sites are inspected by the MCA to confirm that quality systems and production procedures are appropriate in order to ensure the quality and safety of products. 'Pharmaceutical processes' are also prescribed for integrated pollution control (IPC) under the Prescribed Processes and Substances Regulations[1]. Although human pharmaceuticals are not prescribed substances it is of note that 'non-prescribed substances from a prescribed process must be minimised and rendered harmless'.

Wastage from manufacturing units (to landfill, incinerators or sewage treatment works (STWs)) will be minimal compared to other chemical industry discharges due to the careful handling and packaging of expensive pharmaceutical products, often in controlled environments such as sterile packaging areas. For example, it has been estimated that a manufacturer or packer of a pharmaceutical will only incur 1-5% wastage of their product (Richardson and Bowron 1985, EC 1993). Similarly, the distribution of pharmaceutical products is likely to lead to releases to the environment only in exceptional circumstances (e.g. an accident).

4.2 Sources

An outline of the sources of pharmaceuticals is given in Figure 4.1. Veterinary products are not discussed in detail in this report as they vary considerably from human pharmaceuticals in their nature, use and pathways to the environment. For example, fish farm chemicals pass directly to water and are not subject to STW processes; antibiotics are added to cattle feed as growth enhancers which are then excreted and dispersed on fields in manure (Hirsch *et al.* 1999). The fate of veterinary products is discussed in more detail in several papers (Halling-Sørensen *et al.* 1998, Henschel *et al.* 1997, Hirsch *et al.* 1999).

The major routes of pharmaceuticals into the environment are from their use by individuals either dispersed throughout the community or concentrated in medical centres of hospitals, and the disposal of unwanted or out of date drugs by users. After use, a medical substance will be excreted in urine or faeces as a mixture of unchanged substance, metabolites or conjugated with an inactivating substituent attached to the molecule (Halling-Sørensen *et al.* 1998). The substances then enter the sewerage system and pass through sewage treatment before release via sludge, or effluent discharge to surface waters. STWs therefore serve as an important pathway of pharmaceutical contaminations. In order to identify human pharmaceuticals that are most likely to reach surface water from these sources, use patterns (see Section 3) and their biodegradability in STWs (See section 6) will need to be taken into account.

[1] The Environmental Protection (Prescribed Processes and Substances) Regulations (1991) SI 462. ISBN 0-11-013472-9.

4.3 Fate during sewage treatment

In sewage treatment, a pharmaceutical compound and its metabolites can follow one of three patterns in behaviour:

(a) Partial or complete mineralisation (e.g. aspirin) transformation into water and carbon dioxide (Richardson and Bowron 1985).

(b) Lipophilic substances (e.g. penicillins) bind to solid sludge and may undergo slow biodegradation (Halling-Sørensen et al. 1998).

(c) Hydrophilic substances, often formed by metabolism (e.g. clofibric acid), remain in the aqueous phase and may pass though the STW (Halling-Sørensen et al. 1998).

In general, there is a potential for biological (aerobic and anaerobic biodegradation by micro-organisms) and chemical (hydrolysis or photolysis in water) degradation that leads to the reduction of the drug substance or its metabolites leaving the STW (Velagaletti and Winberry 1998). Although biodegradation could lead to complete mineralisation to carbon dioxide and water, more commonly it leads to biotransformation into smaller molecular entities and some mineralisation. The fate of pharmaceuticals is discussed in more detail in section 6.

4.4 Disposal

The disposal of waste pharmaceuticals is subject to control in the cases of manufacturers, wholesalers and retailers of such products, and hospitals. With regard to disposal of unused drugs by the general population, the correct procedure is to return these to the pharmacy which is then responsible for disposal. This is done through the use of special containers to be collected by licensed waste disposal contractors. Depending on the nature of the waste, it may then undergo incineration, go to STWs or be taken to designated landfill sites. In the case of hospitals, disposal will be also through the use of licensed disposal contractors as for pharmacies. Although householders are encouraged to return unused or life-expired medicines to pharmacists for safe disposal they are under no obligation to do so. Furthermore, such action is dependent on whether clear advice is given, for example, in any accompanying patient information leaflet. In practice, the majority of people will either flush unused drugs down the toilet (ultimately passing to STW) or dispose of them in domestic refuse which ultimately will enter domestic waste landfill sites or, to a lesser extent, be incinerated.

4.5 Summary

- The major routes of human pharmaceuticals into the environment are expected to be from their use by individuals either in the home or under medical supervision in hospitals and medical centres, and to a lesser extent by the disposal of unwanted or out of date drugs by users or providers.

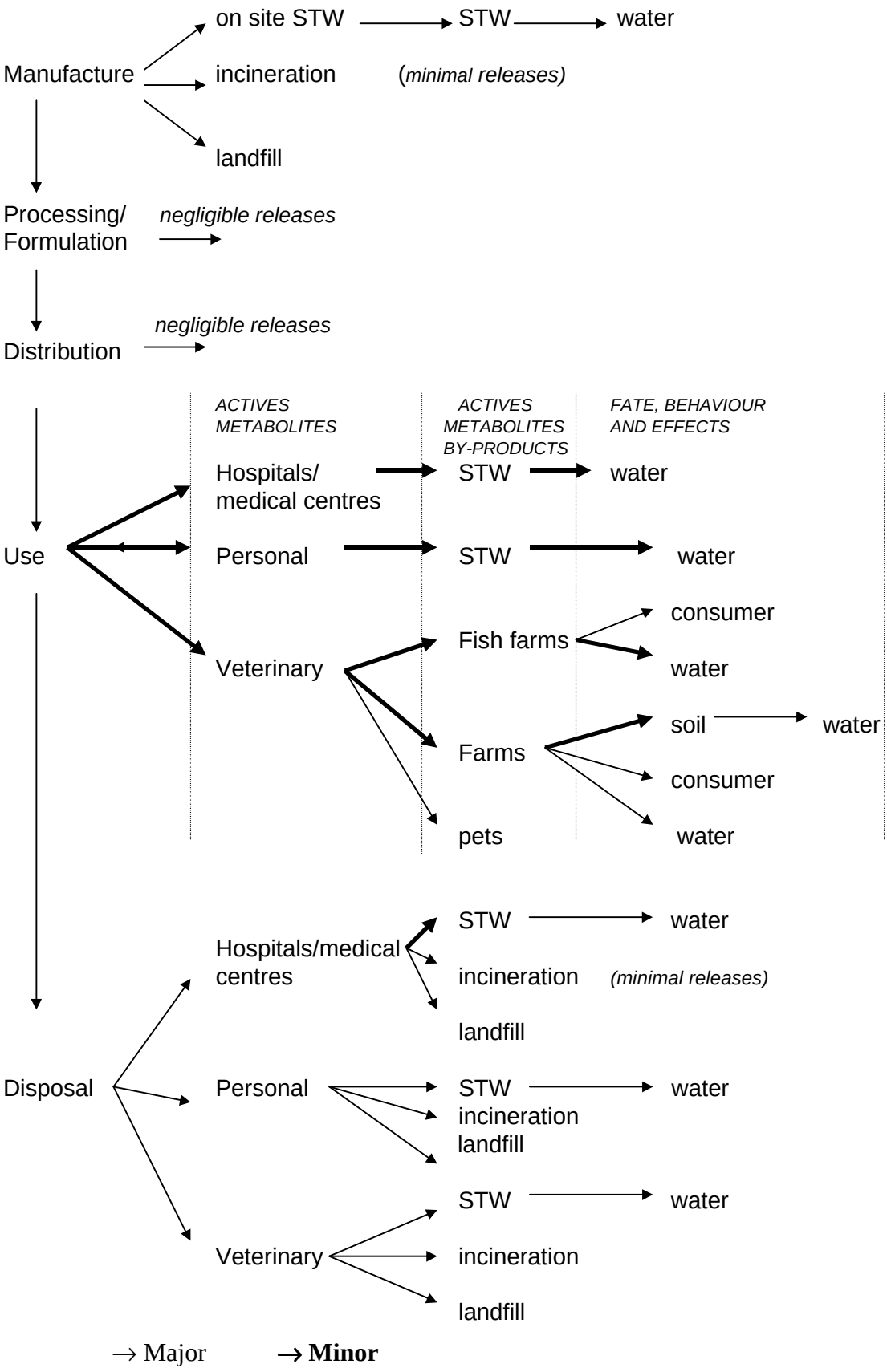

Figure 4.1 Pathways of pharmaceuticals in the environment

- Ingested, topically applied or parenterally administered pharmaceuticals will be excreted as the parent compound, metabolite or conjugate and will be transported to sewage treatment works. In sewage treatment, the compound may be degraded or partially degraded, adsorbed to sludge if lipophilic, be deconjugated or pass through sewage treatment unchanged. Once in the environment the substance will be subject to further degradation processes.

- The disposal of waste pharmaceuticals is subject to control in the cases of manufacturers, wholesalers and retailers of such products, and hospitals. Although householders are encouraged to return unused or life-expired medicines to pharmacists for safe disposal they are under no obligation to do so. Furthermore, such action is dependent on whether clear advice is given, for example, in any accompanying medical safety leaflet. In practice, the majority of people will either flush unused drugs down the toilet (ultimately passing to STW) or dispose of them in domestic refuse which ultimately will enter domestic waste landfill sites or, to a lesser extent, be incinerated.

5. OCCURRENCE IN THE ENVIRONMENT

5.1 Introduction

Like many other organic micropollutants, pharmaceutical drugs have been measured in surface water, groundwater and in drinking water, albeit at trace levels which are generally less than 1 $\mu g\ l^{-1}$. Most of the monitoring data available are from Germany where research has been particularly active in the 1990s, and to a lesser extent the UK, Switzerland, Netherlands, US and Canada. In other countries it is also likely that pharmaceuticals will be present in surface water but analyses are either absent, scarce or not available in the open literature. With the increasing improvements in analytical capabilities, it is likely that further pharmaceuticals will be detected in the future at even lower limits of detection.

Early investigations of drug residues in the environment often focused on clofibric acid, the major metabolite of the three blood lipid regulators (etofibrate, etofyllinclofibrate and clofibrate) (Stan and Linkerhägner 1992). This was largely a consequence of its structural similarity to the chlorophenoxy herbicide, mecoprop, meaning that it is relatively easily detected during routine analysis for acidic pesticides (Stan and Heberer 1997). In Germany, clofibric acid has been found on numerous occasions in surface water, groundwater and tap water (Stan *et al.* 1994). However, more recently, researchers have extended their analysis and detected a much broader range of pharmaceuticals.

In Europe, some of the most active research groups are located at the:-

(a) Institute of Food Chemistry, Berlin University, Germany (principle researchers include Thomas Heberer and Hans-Jürgen Stan);

(b) ESWE-Institut for Water Research Water Technology, Wiesbaden, Germany (principle researchers include Thomas Ternes, Marcus Stumpf, Roman Hirsch and Klaus Haberer);

(c) Royal School of Pharmacy, Copenhagen, Denmark (principle researchers include Halling-Sørensen and Flemming Ingerslev);

(d) Swiss Federal Research Station, Switzerland (principle researchers include Hans-Rudolf Buser, Marcus Müller);

(e) Swiss Federal Institute for Environmental Science and Technology (EAWAG) (principle researcher Alfredo Alder);

(f) In the UK, analytical work conducted in the 1980s was carried out by a number of researchers including WRc and Surrey University. A large UK research programme in the 1990s has focused on endocrine disruption (which has included work on natural and synthetic hormones) and has been supported by the Environment Agency and the Department of the Environment, Transport and the Regions (DETR) and conducted by the Centre for Environmental, Fisheries and Aquaculture Science (CEFAS) and Brunel University.

5.2 Overview of analytical data

A number of issues must be considered when looking at the occurrence data collected by various research groups. These can be divided into two major categories: sampling and analysis.

5.2.1 Sampling

Although a substance may be detected in a single sample, it is important to assess the nature of the sampling programme in order to obtain a view of environmental concentrations in the wider context. The discussion in this section highlights a number of difficulties which need to be addressed.

A number of specialist drugs, such as the highly active anti-cancer drugs, may only be used in a small number of specialist hospitals, isolating their release to a specific localities and routes (Aherne *et al.* 1985). Factories producing or processing pharmaceuticals may also give rise to localised areas of high drug concentrations (Stan and Heberer 1997). In order to avoid such anomalies, research groups have investigated a number of sources in the same location and have shown that concentrations can vary in a relatively small area (Ternes 1998, Stumpf *et al.* 1999).

Single environmental samples taken from flowing sources (such as STW or rivers) may also be affected by sudden releases. These problems can be avoided by longer monitoring periods, such as the work of Hirsch *et al.* (1999) which showed that only a few compounds are found regularly in STW effluent. Indeed, the flow in rivers and STWs can vary depending on rainfall, this can cause variations in concentrations detected, even though the rate of release may be constant (Shore *et al.* 1993). This can only be avoided by longer monitoring periods possibly coupled with collection of rainfall data.

5.2.2 Analysis

Various analytical techniques are available to allow most organic chemicals to be determined at low levels in aqueous matrices. Each technique has its own characteristics which can give rise to different sensitivities and selectivities.

Basic analysis usually consists of a number of steps: extraction; concentration; detection and quantification. In some cases steps may be combined or omitted. A concentration step is normally required because levels of interest for many compounds including pharmaceuticals, are often below 1 $\mu g\ l^{-1}$.

The more important factors influencing the analysis of pharmaceuticals in the environment are outlined below.

Matrix

Organic chemicals can be analysed in most matrices using modern techniques. One important consideration should be the possible absorption of organic material onto solid matter in the sample. In the case of waters from most rivers, boreholes or the mains supply a record should

be kept of whether a sample was filtered prior to extraction. Waters with a very large proportion of solid matter, for example raw sewage, sewage treatment works liquors or some rivers, may require special attention, such as separation of the solids from the aqueous phase followed by analysis of both components or sample homogenisation followed by analysis of the resultant slurry.

Extraction

Many pharmaceuticals are highly substituted with ionizible groups. Generally, for this type of compound, there are two possible extraction strategies. The first involves partitioning of the compound into an organic solvent or onto a hydrophobic solid phase material. In these cases the efficiency of the extraction can be very pH dependent. The second strategy is to use ion exchange resins to absorb the compounds of interest and again this is pH dependent. Methods using solid phase resins are generally unsuitable for samples containing solid or colloidal material.

Some compounds can be derivatised by adding a reagent to the sample which will react with the compound of interest and make it easier to extract.

Compounds may be extracted from solid matrixes using Accelerated Solvent Extraction (ASE) or Soxhlet extraction, which removes the analyte from the solid using hot organic solvent.

However, no single extraction method will remove all types of pharmaceuticals from a sample because of their widely varying physico-chemistry properties.

Analysis

In order to obtain a high degree of selectivity, which is important when the sample (e.g. river water, sewage effluent) may contain a large number of closely-related compounds, chromatography followed by mass spectrometry allows many compounds to be identified and quantified with a high degree of certainty.

Volatile compounds can be analysed using GCMS (gas chromatography - mass spectrometry). Non-volatile compounds can be analysed using LCMS (liquid chromatography - mass spectrometry). However this may require different ionisation techniques for different compounds.

Quantification of detected compounds can be carried out by calibrating the detector with solutions of known concentration. However in the case of environmental samples, where the efficiency of the extraction may vary, an internal standard should be required, which, if added before extraction will also compensate for the losses incurred during sample preparation. Isotopically labelled versions of compounds of interest are available for many commonly occurring environmental contaminants, but for pharmaceuticals it may be necessary to approach the manufacturer to obtain such standards.

Reliable quantitative data requires the use of a method with a known performance (*e.g.* Blue Book Methods). However, almost none of the reported data has been produced using such methods, so values in the literature should be taken as estimates of the true concentration.

Care must therefore be taken in the interpretation of any of the occurrence data given in the following section. Many data may relate to worst case or isolated samples and only be approximations or estimations of the true concentrations present.

5.3 Hospital effluent

A number of pharmaceuticals have been detected in hospital effluents at the low μg l^{-1} level. Aherne *et al.* (1985) detected approximately 1 μg l^{-1} of methotrexate in a sample of hospital effluent taken from a large oncology clinic. Other pharmaceuticals have also been detected in hospital effluents, for example, Richardson and Bowron (1985) detected approximately 1 μg l^{-1} of methaqualone (a hypnotic/sedative) in sewage originating from a hospital. Hartmann *et al*. (1998) detected 3-87 μg l^{-1} of the antibiotic ciprofloxacin in the wastewater from a large university hospital. Steger-Hartmann *et al.* (1996) detected the anti-neoplastic drug, cyclophosphamide in hospital effluent at levels of 0.146 μg l^{-1} and, more recently, at levels of 0.019-4.5 μg l^{-1} (Steger-Hartmann *et al.* 1997). Another anti-neoplastic drug, ifosfamide, has been detected in hospital effluent at levels of 0.024 μg l^{-1} (Steger-Hartmann *et al.* 1996) and <0.006-1.914 μg l^{-1} (median 0.109 μg l^{-1}) (Kümmerer *et al.* 1997).

5.4 Sewage effluent

A variety of pharmaceuticals have been detected in sewage effluent with levels generally ranging from below detection limits up to the low μg l^{-1} range (see Appendix B, Table B1).

The first study that detected drugs in sewage effluent was at the Big Blue River sewage treatment plant in Kansas City, USA in 1976 (Garrison *et al.* 1976, Hignite and Azarnoff, 1977). Garrison *et al.* (1976) measured clofibric acid at concentrations up to 2 μg l^{-1} in raw and treated sewage waters. Hignite and Azarnoff (1977) confirmed these results and measured up to 10 μg l^{-1} of clofibric acid and salicylic acid up to 95.62 μg l^{-1} in sewage effluent, although the latter result would seem rather high in view of more recent data. Since then, a number of other studies have measured clofibric acid as well as other human pharmaceuticals in sewage effluent (see **Table B1**).

One of the more extensive studies is that reported by Ternes (1998) who investigated the occurrence of 32 pharmaceuticals (including analgesics, lipid regulators, psychiatric drugs, β-blockers, β_2-sympathomimetics as well as five drug metabolites) in German sewage effluents. For most of the human pharmaceuticals detected in sewage effluent, concentrations were less than 1 μg l^{-1}. However, there are some for which up to a few μg l^{-1} were detected which include:- acetylsalicylic acid, bezafibrate, carbamazepine, clofibric acid, diclofenac, fenofibric acid, fenoprofen, gemfibrozil, ibuprofen and metoprolol.

Stumpf *et al.* (1999) examined 11 drugs and 2 metabolites in 10 sewage treatment plant effluents in Brazil. The median concentration in the effluents ranged from 0.l to 1 μg l^{-1}, the highest median values being for bezafibrate at concentrations of 1 μg l^{-1}. Compounds for which a maximum concentration of >1 μg l^{-1} was detected included acetylsalicylic acid, bezafibrate, clofibric acid, diclofenac, gemfibrozil, ibuprofen and naproxen (the latter compound is both a human and veterinary drug). The authors estimated that the removal rates

of the individual drugs in the STWs varied from 12 to 90%, with the activated sludge treatment step being more effective for removal than the biological filter.

Hirsch *et al.* (1999) analysed sewage effluents for 18 antibiotics and only five of the compounds investigated could be detected frequently in sewage effluents. These included dehydrated erythromycin, roxithromycin, clarithromycin, sulfamethoxazole and trimethoprim. The highest concentrations in STW effluents were for the erythromycin degradation product with a median value of 2.5 μg l^{-1}, and a maximum of 6 μg l^{-1}. Roxithromycin, sulfamethoxazole, trimethoprim and clarithromycin exhibited median values below 1 μg l^{-1}. Only 5 sewage effluents were analysed for tetracyclines and penicillins and none of them showed any detectable amount of these analytes. Due to the chemically unstable β-lactam ring, penicillins are readily susceptible to hydrolysis and are easily eliminated and therefore their absence was not unexpected.

One particular group of compounds which have received interest, particularly in the UK, are the natural female steroid hormones (17β-oestradiol, oestrone) and the synthetic hormone, 17α-ethinyloestradiol (EE). Recently, Johnson *et al.* (1999) estimated sewage influent concentrations for 17β-oestradiol for six UK STWs based on population equivalents and excretion rates. The authors calculated 17β-oestradiol influent concentrations of between 13.6-24 ng l^{-1} and estimated percentage removals of 33-81% depending on the particular STW (these were based on previous measured concentrations in the STW by Desbrow *et al.* 1998). Previously, Rathner and Sonneborn (1979) estimated normal natural oestrogen secretion per day in the wastewater of West Berlin to be 806 ng l^{-1}. Extrapolating from calculations undertaken on potential levels of steroids in UK rivers some twenty years ago (Wilson 1978), it has also been estimated that up to 1000 ng l^{-1} of naturally occurring oestrogens may enter sewage treatment works (H James, pers. comm.).

Ternes *et al.* (1999a) reported on concentrations of oestrone and oestradiol in the liquid phase (following filtration through 1 μm filters) of sewage influent in Brazil and Germany. The average concentrations found were 21 ng l^{-1} for 17β-oestradiol and 40 ng l^{-1} for oestrone in the Brazilian raw sewage, and 15 ng l^{-1} and 27 ng l^{-1}, respectively, for the German raw sewage. It should be emphasised that these concentrations only relate to the liquid influent, and the only validation data reported are for two raw sewage samples spiked at 50 ng l^{-1} after filtration. Concentrations of oestrone and 17β-oestradiol in German and Canadian treated sewage effluents (again after filtration) were up to 70 ng l^{-1} and 3 ng l^{-1}, respectively (Germany) and up to 48 ng l^{-1} and 64 ng l^{-1}, respectively (Canada). Belfroid *et al.* (1999) measured oestrone and 17β-oestradiol in 5 STWs (3 domestic, 2 industrial) in the Netherlands and reported levels of up to 47 ng l^{-1} and 1-12 ng l^{-1}, respectively. The concentrations were higher in the domestic effluents when compared to the industrial effluents. These results compare with UK studies in which oestrone and 17β-oestradiol were measured in treated domestic sewage effluents at concentrations of around 1-80 and 1-50 ng l^{-1}, respectively (Desbrow *et al.* 1998).

Oestrogen concentrations (17β-oestradiol plus oestrone) have been determined during sewage treatment and in treated sewage effluents in Israel (Shore *et a.l* 1993). Levels were dependent on the treatment processes and water availability (higher concentrations were found either during periods of drought or when there was little rainfall). For example, concentrations of 27-55 ng l^{-1} were found in effluents when the treatment comprised anaerobic and aerobic

digestion. However, concentrations of 24-184 ng l^{-1} and 145-427 ng l^{-1} were also measured in other treated effluent samples.

Although 17β-oestradiol is used therapeutically for hormone replacement, it will be metabolised and excreted in the same way as endogenous 17β-oestradiol (i.e. to oestrone and oestriol). Of the two, natural excretion of endogenous hormones will be the greatest source of these compounds to the environment. Indeed, Christensen (1998) estimated that the extra load to the environment due to the therapeutic use of 17β-oestradiol would contribute less than 5% when compared to the natural excretion.

In contrast, EE is a synthetic hormone and will occur in the environment only through use as a contraceptive. Extrapolating from theoretical calculations undertaken on potential levels of steroids in UK rivers some time ago (Wilson, 1978), it was estimated that up to 5-10 ng l^{-1} of synthetic steroids may enter STWs. Similarly, Rathner and Sonneborn (1979) estimated average EE concentrations of 15 ng l^{-1} would be produced in wastewater in West Berlin based on calculations involving contraceptive use and wastewater yield. Kalbfus (1995) suggests that EE concentrations in effluents from Bavarian sewage treatment works are in the range 0.3-0.5 ng l^{-1}. In contrast, Tabak *et al.* (1981) reported much higher concentrations (between 500-2300 ng l^{-1}) in wastewater before treatment in the USA, although these values are considered to be of dubious quality as the selectivity of the analytical determination is considered to be suspect (Schweinfurth *et al.* 1996).

In a UK survey, low ng l^{-1} levels (up to 7 ng l^{-1}) of EE were detected in some STW effluents (Aherne and Briggs, 1989), although it was not clear how specific the measurement technique (radioimmunoassay) was, or whether both the free steroid and its conjugates were determined.

More recent UK studies in which seven STWs effluents were assessed on three separate occasions found that EE was below the limit of detection (<0.2 ng l^{-1}) for 14 of the 21 samples. When identified, concentrations ranged from 0.2$\pm$0.1 to 7$\pm$3.7 ng l^{-1}, with levels <1 ng l^{-1} for 4 of the samples (Desbrow *et al.* 1998). This compares well with calculations carried out by Schweinfurth *et al.* (1996) in which estimates of 5-10 ng l^{-1} were reported for EE and metabolites in treated sewage effluents. Ternes *et al.* (1999a) have also measured EE in treated sewage effluents in Canada and Germany. The reported concentrations were surprisingly high (Canadian samples up to 42 ng l^{-1}; German samples up to 15 ng l^{-1}) bearing in mind that the highest reported level of this steroid in UK treated sewage effluents was 7 ng l^{-1}, with most being below the level of detection (0.2 ng l^{-1}). Similarly, Stumpf *et al.* (1996b) surveyed German sewage effluents and detected EE above the quantification limit of 1 ng l^{-1} in all 20 STWs investigated; the median concentration being 17 ng l^{-1} with a maximum value of 62 ng l^{-1}. Belfroid *et al.* (1999) found EE below the level of detection (0.3-1.8 ng l^{-1}) for 8 of 10 samples taken from 5 STWs in the Netherlands. When identified levels were 7.5 ng l^{-1} (domestic effluent) and 2.6 ng l^{-1} (industrial), which are similar to those levels reported in the UK. It is of note that although the natural hormones have been detected at greater concentrations than EE, the synthetic hormone is more potent at inducing vitellogenesis (see section 7.2) and is also likely to be more persistent (see section 6).

For those STWs which receive hospital waste water effluents, drugs of high biological activity may be present. For example, Steger-Hartmann *et al.* (1997) report cyclophosphamide in influent and effluent of a municipal STW which received waste water from 6 hospitals. Influent levels of below the detection limit (<6 ng l^{-1}) to up to 143 ng l^{-1} were reported, whereas treated sewage effluent levels ranged from <6-17 ng l^{-1}. However, the authors

indicate a high degree of analytical uncertainty with these data, particularly to those relating to the influent samples, and considered the data too unreliable for calculating a balance for cyclophosphamide. Similarly, for a STW which received hospital waste, Kümmerer *et al.* (1997) measured ifosfamide in influent samples of <6-29 ng l^{-1} and in effluent at levels of <6-43 ng l^{-1}.

5.5 Sewage sludge

No quantitative data relating specifically to pharmaceuticals in sewage sludge were located, which is likely to be due to analytical difficulties associated with this matrix particularly for trace contaminants. In a previous review, Rogers (1996) concluded that there was no evidence to suggest that pharmaceutical residues are present at significant levels in sewage sludges.

5.6 Surface water

5.6.1 Freshwaters

The available data on concentrations of human pharmaceuticals detected in surface waters are summarised in Appendix B, Table B2. Concentrations are usually less than 100 ng l^{-1}, although in some rivers concentrations of up to 3 μg l^{-1} have been detected.

Most monitoring data on pharmaceuticals in surface water has been produced in Germany, particularly in the Berlin area. In 1992, whilst monitoring for herbicides, German researchers detected clofibric acid as a result of its structural similarity to chlorophenoxy herbicides (Stan and Linkerhägner, 1992). Since that time, clofibric acid has been found in a number of investigations of German surface waters at various locations at concentrations up to 220 ng l^{-1}, indicating that a more widespread contamination rather than a local phenomenon (Stan *et al.* 1994, Heberer *et al.* 1998, Stumpf *et al.* 1996a, Stan and Heberer 1997). The Danube River in Germany and the Po River in Italy have also measured measurable quantities of clofibric acid at 17 and 30 ng l^{-1}, respectively (Heberer and Stan 1997).

Two of the more extensive German studies which have screened surface waters are by Ternes (1998) and Heberer *et al.* (1998).

Ternes (1998) screened German surface waters for 32 pharmaceuticals as well as five metabolites and found 20 different drugs including bezafibrate, carbamazephine, diclofenac, gemfibrozil, ibuprofen, indomethacine, metoprolol, naproxen, phenazone, propranol and the metabolites clofibric acid, fenofibric acid and salicylic acid to be ubiquitously present in the rivers and streams, mostly in the ng l^{-1} range. However, maximum concentrations were determined up to 3100 ng l^{-1}, and median values as high as 350 ng l^{-1}, both for bezafibrate.

Heberer *et al.* (1998) screened 30 representative surface water samples collected from rivers, lakes and canals in Berlin. Residues or pharmaceuticals were found at maximum concentrations at up to 1000 ng l^{-1} level and the pharmaceuticals most frequently detected in the surface water included clofibric acid, diclofenac, ibuprofen, propylphenazone. Clofibric acid and diclofenac were often detected at levels above 100 ng l^{-1} whereas the levels detected for ibuprofen and propylphenazone were generally below 100 ng l^{-1}.

Diclofenac, a drug used as an analgesic and anti-inflammatory drug, has also been detected in rivers and lakes in Switzerland (Buser *et al.* 1998a). The concentrations in the lakes ranged from <1 - 12 ng l^{-1}, with higher concentrations of 5-370 ng l^{-1} were observed in the river Aabach or its tributaries.

Stumpf *et al.* (1999) examined 11 drugs and 2 metabolites in 18 Brazilian surface waters and found that clofibric acid, diclofenac and naproxen were frequently detected; the median concentration of these residues was in the low ng l^{-1} (20-40 ng l^{-1}). The median values for all the other drugs investigated were found to be lower than the limit of detection (10 ng l^{-1}). By contrast, maximum concentrations often exceeded 100 and were up to 500 ng l^{-1} (e.g. for fenofibric acid, ibuprofen, ketoprofen, diclofenac, bezafibrate, naproxen).

UK studies conducted in the 1980s detected a few human pharmaceuticals in surface water at concentrations up to approximately 1 µg l^{-1} when measured by chemical analysis (Waggott 1981, Watts *et al.* 1983, Crathorne *et al.* 1984, Richardson and Bowron 1985). For example, Watts *et al.* (1983) identified erythromycin, tetracycline and theophylline at approximately 1 µg l^{-1} and Fielding *et al.* (1981) qualitatively identified clofibric acid in surface waters.

Using immunoassay techniques, Aherne *et al.* (1985) detected progesterone (6 ng l^{-1}) and norethisterone (17 ng l^{-1}) in a few UK river samples, but found that the majority of results were below the limits of detection (5 and 10 ng l^{-1}, respectively). EE (detection limit 5 ng l^{-1}) and the anti-cancer drug, methotrexate (detection limit 6.25 ng l^{-1}) were not found in any of the samples. A later study by Aherne and Briggs (1989) measured EE concentrations of 2-15 ng l^{-1} in surface water.

More recently, Ternes *et al.* (1999a) also reported monitoring data for oestrone, 17β-oestradiol and EE in 15 German rivers and streams. Oestrone was detected at very low levels of 0.7-1.6 ng l^{-1} in only three of the rivers. Other natural oestrogens and contraceptives (including 17β-oestradiol and EE) were not detected in any of the rivers, the reported limit of detection being 0.5 ng l^{-1}. Similarly, Belfroid *et al.* (1999) could only detect very low concentrations (generally below the level of detection up to about 5 ng l^{-1}) of 17β-oestradiol, oestrone and EE in surface waters in the Netherlands and the glucuronide conjugates were not detected. Oestrone was detected the most frequently (7 of 11 locations) whereas EE was detected only at 3 locations.

5.6.2 Saltwater

There are only a limited number of studies which have detected human pharmaceuticals in the marine environment (Stumpf *et al.* 1999, Buser *et al.* 1998b). Stumpf *et al.* (1999) detected clofibric acid, diclofenac and naproxen up to 100 ng l^{-1} in Guanabara Bay, Brazil. Buser *et al.* (1998b) detected clofibric acid in the central region of North Sea at levels of 1-2 ng l^{-1}; a level of 7.8 ng l^{-1} was also detected at a North Sea sampling station in the plume of the River Elbe.

5.7 Groundwater

There are a few reports of metabolites of pharmaceuticals occurring in groundwater (Hirsch *et al.* 1999, Heberer and Stan 1997, Heberer *et al.* 1997, Holm *et al.* 1995, Eckel *et al.* 1993) with most significant contamination being associated with landfills (Holm *et al.* 1995, Eckel

et al. 1993). Table B3 (Appendix B) summarises the concentrations of pharmaceuticals which have been found in groundwaters.

Hirsch *et al.* (1999) conducted an extensive study investigating the presence of antibiotics in groundwater in Germany and, in nearly all cases, levels were below the limit of detection (20 or 50 ng l^{-1}). In contrast, Heberer *et al.* (1997) analysed 17 water samples from groundwater wells in the catchment of a drinking water treatment plant and found that clofibric acid, phenazone and propylphenazone were all detected at levels above 1 μg l^{-1}.

Eckel *et al.* (1993) confirmed pentobarbitol (sedative), meprobamate (sedative) and phensuximide (anti-convulsant) in a groundwater well in Florida in samples taken in 1984. The source was concluded to be a nearby landfill (300 m) which had received wastes from a naval base hospital during the period 1968-1969. In 1991, the authors re-analysed the well and confirmed the presence of phenobarbitol and tentatively identified four sulfonamide drugs. In all cases, the identification was only qualitative.

Holm *et al.* (1995) described findings and distributions of organic compounds originating from waste from the pharmaceutical industry in the downgradient of a landfill site in Denmark. During the period 1962-1975, the landfill was used for household waste and the disposal of waste from pharmaceutical production. The estimated amount of chemical waste from the pharmaceutical production was 85 000 tonnes. Groundwater samples for the study originated from 23 sampling points at nine distances from the landfill. The authors identified a number of compounds which included six sulfonamide derivatives (antibiotics), propylphenazone (mild analgesic) and 5,5-diallybarbituric acid (sleeping tablets and other uses) and 2-methyl-2-*n*-propyl-1,3-propanediol (a hydrolysis intermediate of the sedative meprobamate). At the sampling points closest to the landfill, 2-methyl-2-*n*-propyl-1,3-propanediol was present at an extremely high concentration of 18,000 μg l^{-1}. In one sample sulfanilic acid and propylphenazone were also generally >1000 μg l^{-1} at this point. As would be expected with greater distance from the landfill concentrations decreased, and at a distance of 150 m downgradient of the landfill none of the pharmaceutical compounds could be detected.

5.8 Drinking water

There is currently no regulatory requirement for monitoring pharmaceuticals in drinking water. Based on the limited available data (see Appendix B, Table B4), human pharmaceuticals have only occasionally been detected in drinking water with concentrations generally being less than 10 ng l^{-1}. An exception is for clofibric acid for which Heberer and Stan (1996) quantified a maximum concentration of up to 170 ng l^{-1} in drinking water samples collected from one of 14 waterworks in Germany. For drinking water samples taken from the remaining 13 water works, values were below 75 ng l^{-1} with samples for 2 waterworks being below the level of detection of 1 ng l^{-1}. Clofibric acid has also been qualitatively detected in UK drinking water samples (Fielding *et al.* 1981). However, it is of note that the source of clofibric acid in Berlin drinking water is thought to be from recharged groundwaters contaminated by sewage and is not a considered to be a general problem in Germany (Daughton and Ternes 1999, DVGW 1999). Since the 1980s clofibrate has rarely prescribed in the UK and other drugs have replaced its use (IARC 1996). In 1995, it was reported that UK tonnage was 1.5 tonnes/year (Webb 2000) which compares with 16 tonnes/annum reported for Germany for the same year (Ternes 1998).

Due to the widespread use of oral contraceptives, work has been conducted on the presence of steroids in drinking water samples. Research by WRc on behalf of UKWIR and DWI has not, so far, identified human hormones in drinking water (James *et al.* 1997). This work involved measuring oestrone, 17β-oestradiol and 17α-ethinyloestradiol in drinking water (involving six water treatment works, each sampled on three separate occasions). Each works employed different water treatment methods including chlorination, ozonation and granular activated carbon (GAC). In all cases, the concentrations of steroids were below the limits of detection (0.2 ng l^{-1} for oestrone and 17β-oestradiol and 0.4 ng l^{-1} for ethinyloestradiol). Laboratory scale studies of water treatment showed that chlorination, ozonation and powdered activated carbon were all very effective in reducing the concentrations of these three steroids, with 95% removal in each case. However, coagulation and filtration were found to be ineffective.

Previous experiments studied the effects of oestrogens on fish in water sources used for drinking water production (Harries *et al.* 1995). The fish were placed in cages for up to six weeks, at the end of which they were examined for induction of vitellogenesis which was not observed. The conclusion was that "there is no evidence of a risk to drinking water supplies and for the present there is no need for further research".

In addition, Christensen (1998) assessed the potential risk to human health posed by environmental exposure to three drugs:- 17α-ethinyloestradiol (an oral contraceptives), penicillin V (an antibiotic) and cyclosphosphamide (an anti-cancer drug). By using the software EUSES on worst case emission quantities, the author estimated human exposure to these drugs via the environment (drinking water, food and air) to be well below the therapeutic daily doses. It was therefore concluded that any risk to human health from environmental exposure was negligible.

5.9 Summary

- There are studies published in the open literature which have reported the occurrence of pharmaceuticals in the environment (e.g. hospital effluent, sewage effluent, surface waters, saltwater, groundwater and drinking water) at trace levels.

- Where reports of pharmaceuticals in the environment have been published, these have been on an *ad hoc* basis by a relatively small number of academic research groups which are active in this field, notably in Germany and to a lesser extent by Switzerland and Denmark.

- The UK Government has been highly active in the area of endocrine disrupters and conducted key research on the oestrogenic activity of natural steroid hormones, including 17α-ethinyloestradiol, the synthetic contraceptive pill. Other UK studies date back to the 1980s during which time there have been improvements in analytical techniques and changes in the treatment of sewage and drinking water which may mean that some of the data may be no longer relevant.

- Where pharmaceuticals have been detected in sewage effluents or surface waters, the levels are at trace amounts at the ng l^{-1} or at most low μg l^{-1} level. The types/groups of drugs detected are fairly broad e.g. hormones, lipid regulators, pain killers, antibiotics, anti-cancer drugs, anti-epileptic drugs and those regulating blood pressure.

- Analysis for drug metabolites has generally not been carried out apart from a few specific cases (e.g. clofibric acid, fenofibric acid and salicylic acid) and is identified as one area for which current knowledge is limited.

- Only a few studies were located which have analysed for the presence of pharmaceuticals in groundwater, none of which were in the UK. Most often these have been associated with contamination via landfills and therefore may represent isolated and rather specific circumstances.

- Human pharmaceuticals have only occasionally been detected in drinking water with concentrations generally being less than 10 ng l^{-1}. On the rare occasion when detected above this level, notably in Berlin, this has been traced to specific contamination and represents a localised situation.

- No quantitative data were located on concentrations of pharmaceuticals in sewage sludge, although for lipophilic substances which will bind to sludge, this is a potential route into the environment.

6. ENVIRONMENTAL FATE

6.1 Introduction

Research into the fate of pharmaceuticals in the environment is still in its preliminary phase and further information is still required before any firm conclusions can be made (Stumpf *et al.* 1999). In addition, much of the research has been directed to fate of parent drugs rather excreted metabolites which are more likely to be present in sewage and enter the environment. An overview of the systematic study of the fate of pharmaceuticals in the environment is given in Table 6.1

Table 6.1 Major routes of degradation, depletion and dilution in various environmental compartments and the profile of environmental fate for human pharmaceuticals

DOMESTIC SEWAGE	AQUATIC COMPARTMENT
Processes	Processes
Hydrolysis	Hydrolysis, photolysis
Biodegradation (aerobic and anaerobic)	Aerobic degradation in surface water
Adsorption	Anaerobic degradation in surface water and sediment
	Volatilisation
Results	Results
Degradation	Degradation
Depletion	Depletion
Partitioning	
STW	TERRESTRIAL COMPARTMENT
Processes	Processes
Adsorption	Aerobic and anaerobic biodegradation
Hydrolysis	Soil photolysis, adsorption/desorption
Direct photodegradation in water	Run-off and leaching
I ndirect photodegradation in water	Volatilisation
Aerobic biodegradation in water	
Anaerobic biodegradation in sludge	
Results	Results
Degradation	Degradation
Depletion	Depletion
Partitioning	Partitioning
	Dissipation

Reference: Velagaleti and Winberry, 1998

6.2 Sewage treatment

Most human pharmaceuticals are released by excretion from the patient or, to a lesser extent, in aqueous waste produced by manufacturing. Sewage treatment works (STWs), are therefore expected to be the main point of collection and subsequent release into the environment.

There are three possible fates for pharmaceuticals in a STW:

(a) Mineralisation (e.g. aspirin) and rapid transformation into water and carbon dioxide (Richardson and Bowron 1985);

(b) Lipophilic substances (e.g. penicillins) bind to solid sludge and may undergo slow biodegradation (Halling-Sørensen et al. 1998);

(c) Hydrophilic substances, often formed by metabolism (e.g. clofibric acid), remain in the aqueous phase and may pass though the STW (Halling-Sørensen et al. 1998).

Surveys into the fate of pharmaceuticals in STW have been conducted by Richardson and Bowron (1985), Ternes (1998) and Stumpf *et al.* (1999). However, none of these studies systematically analysed for degradation products and the lack of such information is considered to be an important knowledge gap (Halling-Sørensen *et al.* 1998).

Data located in the published scientific literature on fate of pharmaceuticals during sewage treatment is given in Table C1 (Appendix C). However, it is of note that the data available refer to parent drug rather than metabolites which are more likely to occur in sewage. Much of the recent data available relate to rates of removal during activated sludge and biological filter treatment steps in municipal sewage treatment works (Stumpf *et al.* 1999, Ternes 1998). Such studies involved measuring pharmaceuticals levels in sewage influent and effluents and calculating the percentage removal.

Stumpf *et al.* (1999) reported on the removal of 7 drugs and two drug metabolites during passage through a Brazilian STW. Concentrations in the raw sewage were between 0.3-1.2 $\mu g\, l^{-1}$ depending on the individual drug. The authors found that effluents from the activated sludge treatment step contained significantly lower levels of the pharmaceuticals than effluents from the biological gravel filter. Removal rates for activated sludge treatment ranged from 34% (clofibric acid) to 83% (indomethacine). Indeed, clofibric acid, fenofibric acid and gemfibrozil were the only compounds to exhibit less than 50% removal by the activated sludge treatment step. In contrast, removal rates by biological filter treatment were less than 30% other than for indomethacine (71% removal) and ketoprofen (48% removal). The lowest removal rates were 6% for fenofibric acid, 9% for diclofenac, 15% of clofibric acid and 15% for naproxen. It was uncertain whether removal was a result of adsorption or degradation although, due to the high polarities of the drugs under investigation, adsorption to sludge was expected to be low.

Ternes (1998) similarly measured a variety of pharmaceuticals in sewage influent and final effluents in a German municipal STW. The elimination rates of the investigated drugs during passage through the STW ranged from 7% (cabamazepine) to greater than 99% (salicylic acid). Generally more than 60% of the drug residues detected in the influent were removed. Only carbamazepine, clofibric acid, phenazone and dimethylphenazone showed lower average

removal rates. Fenofibrate, acetaminophen (paracetamol) and metabolites of acetylsalicylic acid (aspirin) which include salicylic acid, *o*-hydroxyhippuric acid, gentisic acid were not detectable in the effluent, even though up to 54 μg l^{-1} of salicylic acid were determined in the influent.

Other studies have investigated the fate of pharmaceuticals in laboratory-scale sewage treatment plants (Kümmerer *et al.* 1997, Steger-Hartmann *et al.* 1997) or involved laboratory testing for biodegradability (Richardson and Bowron 1985, Kümmerer *et al.* 1997, Steger-Hartmann *et al.* 1997, Henschel *et al.* 1997).

Richardson and Bowron (1985) found that acetylsalicylic acid (aspirin) was readily biodegradable as was acetaminophen (paracetamol) after a period of acclimation, although a number of compounds belonging to diverse groups of pharmaceuticals were also identified as being 'non-biodegradable' (see Table C1). No other details such as percentage removal were reported in the paper.

Henschel *et al.* (1997) investigated the biodegradability of paracetamol and methotrexate and the two drug metabolites, salicylic acid and clofibric acid according to OECD Guideline 301F ('monometric respiration test'). In agreement with other studies, salicylic acid and, to a lesser extent, paracetamol were considered to be readily biodegradable whereas clofibric acid and methotrexate (an anti-cancer drug) were found to be persistent. Two other anti-cancer drugs which have also been investigated for their biodegradability include ifosfamide and cyclophosphamide (Kümmerer *et al.* 1996, Kümmerer *et al.* 1997, Steger-Hartmann *et al.* 1997). Both these drugs proved to be of poor biodegradability in the Closed Bottle Test (OECD 301D), the Zahn-Wellens/EMPA test for inherent biodegradability (OECD 302B) and in a laboratory scale sewage treatment plant.

An attempt to model the removal of pharmaceuticals by a STW is given in Appendix E. However, no correlation between the model output and the experiment values could be found within the scope of the project. The only conclusion that could be drawn was that in all cases except two (gemfibrozil and ifosfamid), the model underestimated removal.

6.2.1 Oestrogens

It has been reported that synthetic oestrogen components of oral contraceptives exhibit greater overall resistance to breakdown by micro-organisms isolated from activated and primary settled sewage than the natural steroids (Tabak and Bunch 1970). Under laboratory conditions, the biodegradation of 17α-ethinyloestradiol (EE) in a modified CO_2 evolution test according to an FDA test guideline was found to be slow and only 3% mineralisation of a 10 mg l^{-1} solution was observed within 28 days (Schweinfurth *et al.* 1996). Earlier reports are contradictory, with one reporting no reduction in concentration of EE during incubation with activated sewage sludge over a five day period (Norpoth *et al.* 1973), while another reported 79-95% primary degradation over a 28 day period (Tabak and Bunch 1970). D'Haese *et al.* (2000) tested 17β-oestradiol and ethinyloestradiol in the ISO 9888 test; a standardised batch test that examines aerobic biodegradability of organic compound and found that 17β-oestradiol was biodegradable but that EE was persistent.

Other more recent work has examined the behaviour of oestrogens in municipal STWs (Ternes *et al.* 1999a, Ternes *et al.* 1999b, Johnson and Williams 1999).

Ternes *et al.* (1999a) measured the levels of oestrogens in sewage influent and corresponding effluents in a German and Brazilian municipal STW. In the Brazilian STW, the observed removal rates for EE and oestrone were 78 and 83%, respectively, indicating relatively effective removal. The activated sludge treatment step removed the oestrogens with a higher level of efficiency than the biological filter. However, in the German STW, the loads of oestrone and EE were not appreciably removed and no elimination rate could be established. The authors considered that the low temperatures might cause the differences in the removal rates in the German sampling period (with -2 ^{o}C on average compared to 20 ^{o}C in Brazil). For both STWs, 17β-oestradiol was eliminated with a higher efficiency than EE and oestrone.

Johnson *et al.* (1999) estimated sewage influent concentrations for 17β-oestradiol for six UK STWs based on population equivalents and excretion rates. The authors calculated 17β-oestradiol influent concentrations of between 13.6-24 ng l^{-1} and estimated percentage removals of 33-81% depending on the particular STW (these were based on previous measured concentrations in the STW by Desbrow *et al.* 1998). Based on these calculations, there was no evidence that the activated sludge systems were more efficient than the biological filter systems which is in contrast to other authors (Ternes *et al.* 1999a).

Ternes *et al.* (1999b) recently conducted batch experiments involving STW activated sludge and examined the persistence of oestrogens under aerobic conditions (see Table 6.2). These results indicate that 17β-oestradiol was oxidised to oestrone, which was further eliminated in the batch experiment in an approximate linear time dependence. Further degradation products of oestrone were not observed. EE was relatively stable under these conditions which could account for its detection in STW effluent and the aquatic environment. In addition, two glucuronides of 17β-oestradiol were cleaved when in contact with the activated sludge and 17β-oestradiol was released. It was also noted that concentrations of oestrogens in water rise after primary clarification in STW, possibly due to the breakdown of oestrogen-glucuronide metabolites in the settling tanks (Ternes *et al.* 1999b).

Table 6.2 The fate of oestrogens and their metabolite when spiked into STW sludge

Compound	Length of test	Removal (%)	Products	Reference
17β-Oestradiol-17-(β-D-glucuronide)	5 min	80	17β-Oestradiol and Oestrone	Ternes *et al.* 1999b
17β-Oestradiol	1-3 h	95	Oestrone	Ternes *et al.* 1999b
16α-Hydroxyoestrone	5 h	60	Unknown	Ternes *et al.* 1999b
Oestrone	24 h	50	Unknown	Ternes *et al.* 1999b
17α-Ethinyloestradiol	24 h	20	Unknown	Ternes *et al.* 1999b
17α-Ethinyloestradiol	120 h	0	Unknown	VonRathner and Sonneborn 1979
Norethisterone	24 h	100	Unknown	VonRathner and Sonneborn 1979
Menstranol	24 h	80	17α-Ethinyloestradiol (7%) and Unknown	Ternes *et al.* 1999b

Panter *et al.* (1999) also recently studied the breakdown of oestradiol-3-glucuronide in laboratory simulations of the activated sludge process ('porous pots') and in a high flow rate degradation system with comparatively low microbial activity. The authors found that oestradiol-3-glucuronide had no detectable inherent oestrogenic activity (as measured by

plasma vitellogenesis and gonadosomatic index) when fish were exposed to microbially clean, continuous-flow system. However, when fish were tested exposed to the effluent generated from the porous pots to which oestradiol-3-glucuronide had been added, oestrogenic activity was observed suggesting microbial activity was capable of degrading the steroid metabolite into a more potent oestrogen.

6.3 Groundwater

Holm *et al.* (1995) studied the degradation processes in a groundwater which had been contaminated by pharmaceuticals leaching from a landfill. The landfill site was used between 1930 and 1977, and a total of 85,000 tonnes of pharmaceutical plant waste, mostly composed of used activated carbon filter media and distillation waste entered the site from 1962 to 1975. The landfill was on a 10 m deep sandy aquifer above clay and the sand close to the site was found to be highly reducing.

Samples of ground water were taken from wells in 1995 and a summary of the results shown in Table 6.3. 2-Methyl-2-n-propyl-1,3-propanediol, 5,5-diallybarbituric acid, aniline, o-chloroaniline, p-chloroaniline, propyphenazone, sulfadiazine, sulfadimidine, sulfaguanidine, sulfametizole, sulfanilamide, sulfanilic acid and tris(2-methylpropyl)phosphate were all detected.

Concentrations of organic compounds leaching from landfill may be reduced by dilution, degradation or absorption. All of the pharmaceuticals observed had disappeared to below the analytical limits of detection within 150 m of the landfill. Using chloride as a tracer, dilution did not appear to be a factor and as all of the compounds studied had low water/octanol partition coefficients and high water solubilities, adsorption was also considered unlikely. The authors considered that degradation in the highly reducing anaerobic region was the most likely route of removal.

In another study in Florida, pentobarbital was found 300 m from a landfill site which had been used for the disposal of hospital waste, 21 years after the site was closed. The ground water conditions were similar to those in the previous study, a strongly reducing sand aquifer on clay (Eckel *et al.* 1993).

Clofibric acid has been found at depths of more than 70 m underground beneath STWs indicating that it is not absorbed by the subsoil or biologically degraded (Herberer and Stan 1997).

Table 6.3 Concentration of pharmaceuticals found in groundwater from landfill

Compound	Depth (m)	Distance from landfill (m)								
		0	15	37	50	82	115	150	237	260
Total Pharmaceutical (µg l^{-1})	5.5	2180	<181	<181	<181	<181	<181	<181	<181	<181
	7	32995	8840	1360	100	50	<181	<181	<181	<181
	8.5	3070	13615	7090	420	<181	<181	<181	<181	<181
	10	12660	<181	4350	3003	<181	115	<181	<181	<181
Chloride (mg l^{-1})	5.5	163	-	-	-	-	119	-	-	-
	7	96	129	185	124	98	-	-	71	60
	8.5	89	135	256	94	-	21	43	42	56
	10	114	-	189	149	-	40	29	-	117
Non-volatile Organic Carbon (NVOC) (mg l^{-1})	5.5	32.9	-	-	-	-	4.3	-	-	-
	7	79.1	74.0	45.4	39.2	47.8	-	-	1.3	1.2
	8.5	69.9	91.4	55.6	34.8	-	14.8	2.2	1.5	1.3
	10	82.9	-	65.3	44.3	-	15.3	3.7	-	1.3
Percentage of NVOC found as Pharmaceutical [a]	5.5	13	-	-	-	-	0	-	-	-
	7	83	24	6	1	0	-	-	0	0
	8.5	9	30	26	2	-	0	0	0	0
	10	31	-	13	14	-	2	0	-	0

Notes: - Result not given
a The percentage pharmaceutical figure calculated is based on 50% of the total pharmaceutical being NVOC

6.4 Surface water

The environmental fate of pharmaceuticals in surface water has not been well studied, with only very limited data being located for clofibric acid and diclofenac.

6.4.1 Clofibric acid

Levels of clofibric acid found in the North Sea and various Swiss lakes and compared with use indicate that it is highly mobile and very persistent (with an estimated half-life of 1-2 years) (Buser and Müller 1998).

6.4.2 Diclofenac

Diclofenac has been shown to disappear rapidly from lake water in Switzerland, with the major route of removal being photodegradation (Buser and Müller 1998). It was not detected in sediments of the lake (limit of detection 10 ng g^{-1}) and in a laboratory experiment, a concentration of 500 ng l^{-1} showed negligible adsorption onto sediment particles. A concentration of 100 ng l^{-1} in lake water which was periodically analysed for 37 days showed no degradation in the dark, suggesting minimal chemical and biodegradation. However, when exposed to sunlight, rapid photodegradation was observed with less than 1% of an initial concentration of 100 ng l^{-1} present within 4 days. The fast photodegradation was confirmed in a second experiment in which aqueous solutions of diclofenac (1 μg l^{-1}) were exposed to sunlight for 0, 2 and 4 hours. Diclofenac was reduced to a level of approximately 4% of the initial concentration in only 4 hours, with a half-life of less than 1 hour.

6.4.3 Oestrogens

Jurgens *et al.* (1999) recently reported on the fate and behaviour of steroid oestrogens in river waters. Firstly, this comprised of laboratory studies in which river waters were spiked with steroids at relatively high concentrations (200-400 μg l^{-1}). These studies demonstrated that under aerobic conditions, 17β-oestradiol was degraded in all river waters tested (half-lives <3, 4, 6 and 27 days depending on the river water tested). In addition, 17β-oestradiol was shown to convert to oestrone, which was then further degraded at a similar rate. However, EE was shown to be much more persistent with a half-life of 46 days compared to 4 days for 17β-oestradiol under the same experimental conditions. Under anaerobic conditions, degradation of 17β-oestradiol in river water was still relatively rapid, although oestrone was more persistent. EE showed no degradation under anaerobic conditions over 46 days.

In an effort to examine whether 17β-oestradiol would actually be degraded at more realistic concentrations, 0.3 μg l^{-1} of 17β-oestradiol was added to samples of River Thames water. No change was seen in the sterile controls, whereas 17β-oestradiol was degraded to below detection limits (<0.15 μg l^{-1}) within 3 days in the Thames river water.

D'Haese *et al.* (2000) similarly dosed EE and 17β-oestradiol to surface waters at environmentally relevant concentrations (1 μg l^{-1}). After 33 days of incubation, the oestrogenic activity measured with the recombinant yeast screen was significantly decreased

i.e. 65% and 56% for 17β-oestradiol and EE. However, the rate of decline was very different for the two compounds in that the oestrogenic activity of 17β-oestradiol diminished substantially after 2 days and then reached a steady phase. The vessels with EE supplementation showed a lag phase of approximately 15 days after which the oestrogenic activity decreased.

6.5 Summary

- A limited number of studies have investigated the fate and removal of pharmaceuticals during municipal sewage treatment. These have reported removal rates of between 6% up to >95% depending on the individual pharmaceutical and the treatment processes involved. In general, it would appear that removal by the activated sludge treatment step is more effective at removal compared with biological filters.

- Although removal rates are highly dependent on an individual STW, clofibric acid and fenofibric acid (two lipid regulator metabolites) have been consistently shown to be poorly removed and these have also been detected in sewage effluents (see section 5).

- Laboratory scale biodegradability studies have confirmed that clofibric acid is persistent as are a number of anti-cancer drugs (ifosfamide, cyclophosphamide and methtrexate). By contrast, high usage drugs such as acetylsalicylic acid (aspirin) and its metabolites, paracetamol and ibuprofen are biodegradable.

- The few studies investigating the removal of oestrogens (17β-oestradiol, oestrone and 17α-ethinyloestradiol) during municipal sewage treatment have given mixed results, with some STWs indicating high percentage removal (≈80% or more) and others showing no appreciable removal. The activated sludge treatment step appears to be more efficient at removal than biological filter, and 17β-oestradiol is generally eliminated with a higher efficiency than oestrone and 17α-ethinyloestradiol.

- There is increasing evidence that excreted conjugates of oestrogens can be deconjugated by bacterial enzymes present in sewage treatment or in the environment, thereby reforming the parent compound.

- Data on the fate and behaviour of pharmaceuticals in surface and groundwaters are lacking. Clofibric acid has been found in the North Sea and various Swiss lakes and appears to be highly mobile and persistent whereas diclofenac was found to rapidly disappear from lake water in Switzerland as a result of photodegradation. Laboratory and modelling studies on fate of steroids in river waters suggest that 17α-ethinyloestradiol is relatively persistent in the environment.

7. ENVIRONMENTAL HAZARD

7.1 Aquatic toxicity

Although pharmaceutical chemicals receive considerable pharmacological and clinical testing, information on the ecotoxicity of these biologically active substances is generally more limited. This is largely due to current regulatory guidance which only requires pharmaceuticals to undergo standard acute toxicity tests (often for algae, *Daphnia* and fish) unless there is good reason to believe the compound may bioaccumulate. Indeed, this aspect has been highlighted by a number of researchers (Halling-Sørenson *et al.* 1998, Henschel *et al.* 1997) who have considered that the use of conventional acute ecotoxicity tests may be inappropriate when assessing the environmental risks of pharmaceuticals. They suggest that environmental toxicity testing should consider the mode of action relevant to specific pharmaceuticals e.g. endocrine activity, genotoxicity.

Data on the aquatic toxicity of pharmaceuticals located in the scientific literature are given in Table D1 (Appendix D). [The scope of the review did not allow assessment of registration packages submitted to the US Food and Drug Administration for individual drugs].

Aquatic toxicity data were located for seventeen individual human pharmaceuticals, nearly all of which related to acute exposure. The available data related to a number of taxonomic groups including algae, bacteria, invertebrates and fish.

Acute toxicity values are in the mg l^{-1} range for all the pharmaceuticals listed in Table D1 other than an LC_{50} of 0.106 mg l^{-1} for clofibrate which was based on reproduction effects in *Daphnia magna* (no further details are available). By comparison, environmental levels (which are generally in the ng l^{-1} to low μg l^{-1} range) are at least three orders of magnitude below these levels.

It is more difficult to assess the environmental significance of pharmaceuticals with regard to subtle long-term effects as chronic toxicity data are generally lacking. 17α-Ethinyloestradiol was the only pharmaceutical for which chronic data were available (a 4 week study in three life-stages of fish) and these are discussed in greater detail in Section 7.2.

Two studies have recently been published which have conducted environmental risk assessments (ERAs) for human pharmaceuticals (Stuer-Lauridsen *et al.* 2000, Webb 2000).

Stuer-Lauridsen *et al.* (2000) presented ERAs for 25 highly used human pharmaceuticals in Denmark by comparing predicted environmental concentrations (PECs) (and measured concentrations where available) with predicted no-effect concentrations (PNECs). PECs for the aquatic environment were derived as specified in the draft EU (1994) guidance document for medicinal products for human use (see section 2.3 for calculation). Assumptions included: population and volume of wastewater per day per capita in Denmark, % removal during wastewater treatment as zero and a dilution factor in the environment of 10. However, due to lack of aquatic data, derivation of PNECs based on aquatic ecotoxicity data was only possible for six of the pharmaceuticals. In all cases, a default safety factor of 1000 was used to derive the PNECs. The majority of PECs were between 0.001 and 0.1 μg l^{-1} with only paracetamol, acetylsalicylic acid, ibuprofen, diazepam and digoxin being above 1 μg l^{-1}. The PEC:PNEC

ratio exceeded one for paracetamol, acetylsalicylic acid and ibuprofen only. However, when taking account of measured concentrations in the environment, all the ratios were below one. For 'oestrogens', the use of a non-standard test (increased growth in *M. sativa* at 5 μg l^{-1}) yielded a risk quotient approaching 1. However, when a standard acute toxicity test in *Daphnia magna* was used to derive the PNEC, the PEC:PNEC ratio was well below 1. However, it is note that these authors did not make reference to the extensive UK research available on oestrogenicity nor the chronic life-stage test in fathead minnow (Schweinfurth *et al.* 1996).

Webb (2000) also conducted an environmental risk assessment for 67 drugs (see Appendix F). Sewage influent concentrations were calculated based on a UK population of 57.6 million and a water consumption of 259 litres/capita/day. The assumption of no human metabolism, passage of all material to drain, no removal during wastewater treatment (via biodegradation, soprtion or volatilisation) and no surface water dilution of effluent were used to calculate the PEC. These assumptions are all conservative and considered worst case. The PNEC values were derived using an assessment factor of 1000 with relevant acute data. The PEC:PNEC ratio was <1 in all but eight of the cases (paracetamol, aspirin, detropropoxyphene, fluoxetine, oxytetracycline, propanolol, amitripyline and thioridazine). Further refinement was conducted for these drugs which was based on improving the PEC (e.g. taking into account removal during wastewater treatment) and/or surface water dilution of sewage effluent. No further refinement (with the exception of fluoxetine) could be made to the PNEC as no chronic data were available to justify a lower safety factor. For aspirin, dextropropoxyphene, oxytetracycline, propanol, amitriptyline and thioridazine, consideration of surface water dilution alone (assumed as 10) was sufficient to ensure a PEC:PNEC ratio of <1. For fluoxetine following consideration of biodegradation, surface water dilution and chronic toxicity data, a revised PEC:PNEC of 0.3 was derived. For paracetamol, once biodegradation and dilution were taken into account, the PEC:PNEC ratio reduced to 0.08.

Webb (2000) did emphasise, however, that for 17α-ethinyloestradiol, taking into account chronic data could alter the risk assessment. Based on acute toxicity end-points the PEC:PNEC ratio was below 1, but if chronic toxicity end-points were considered along with a low dilution factor (i.e. <1-in-2 where effluent concentrations are above the detection limit of 0.2 ng l^{-1}), a PEC:PNEC ratio above 1 could be derived.

7.2 Oestrogenic activity

A number of compounds and environmental effluents have been associated with potential reproductive and developmental anomalies in fish. Hermaphrodite fish (i.e. those which exhibit both male and female characteristics) have been observed in rivers below sewage treatment plants in a number of countries including the UK (Purdom *et al.* 1994, Harries *et al.* 1995, 1996, 1997, Jobling *et al.* 1998) and the USA (Folmar *et al.* 1996). This phenomenon has also been shown in marine populations of flounder (Lye *et al.* 1997, Matthiessen *et al,* 1998). In recent years, UK government agencies have been highly active in researching the effects of oestrogenic compounds on aquatic life. Recently, the Environment Agency published a review of the scientific evidence and strategic response to endocrine-disrupting substances in wildlife (Environment Agency 1998).

For human pharmaceuticals, as expected, the natural hormones 17β-oestradiol and oestrone and the synthetic hormone ethinyloestradiol exhibit oestrogenic activity. This activity has

been demonstrated in a variety of *in vitro* and *in vivo* test assays which have utilised both non-mammalian and mammalian species (Shelby *et al.* 1996).

One assay of particular relevance to the aquatic environment is the induction of vitellogenesis in male fish. In these experiments, male rainbow trout are placed either in undiluted effluent from sewage treatment works (STWs) or downstream from STWs and periodically sampled for the presence of vitellogenin in blood serum. Vitellogenin is an egg yolk protein that is normally only found in sexually mature female fish but exposure to oestrogenic substances can induce its production in male fish. It is well established that the induction of vitellogenin in the female is under oestrogenic control, specifically by the natural hormone 17β-oestradiol. Much of the work has been conducted on rainbow trout which has been shown to be a more sensitive species in comparison to carp and roach (Purdom *et al.* 1994, Routledge *et al.* 1998). The threshold at which 17β-oestradiol induces vitellogenesis in male rainbow trout is around 1-10 ng l^{-1} and 50-100 ng l^{-1} in roach. For oestrone, the threshold for vitellogenin induction in rainbow trout is around 25-50 ng l^{-1} (Routledge *et al.* 1998). Ethinyloestradiol can induce vitellogenesis at 0.1 ng l^{-1} (Purdom *et al.* 1994) and 2 ng l^{-1} has been shown to inhibit testicular growth in male rainbow trout (Jobling *et al.* 1996). Routledge *et al.* (1998) also found that when male rainbow trout were exposed simultaneously to oestrone and 17β-oestradiol, a highly significant vitellogenin response was stimulated which indicated an additive response to these hormones.

Fractionation studies directed at identifying the oestrogenic substances in domestic sewage effluent have showed that natural and synthetic oestrogenic hormones derived from conjugated material excreted by women are responsible for the oestrogenic activity of most domestic sewage effluents (Environment Agency 1996). 17β-Oestradiol and oestrone have been detected in STW effluents in the UK at levels ranging from 1 to 50 ng l^{-1} and 80 ng l^{-1}, respectively (Desbrow *et al.* 1998). Ethinyloestradiol, although generally below the level of detection, was measured in STW effluent at levels up to 7 ng l^{-1} (Desbrow *et al.* 1998). These environmental levels are within the range of concentrations which can induce vitellogenesis in male fish.

In addition, studies on the long-term toxicity of ethinyloestradiol in fathead minnow have been conducted. Schweinfurth *et al.* (1996) reported on a preliminary study in which 3 life-stages of fish (embryo larvae, juvenile and adult) were exposed over a period of 4 weeks to graduated concentrations of 0, 10, 100, 1000 and 10,000 ng l^{-1} under flow-through conditions. Observations included mortality, growth, morphology, egg deposition of adult fish and histopathological examinations. An increase in mortality in all 3 life-stages was seen at concentrations of 1000 ng l^{-1} or above. Growth was reduced in the larvae at concentration of >100 ng l^{-1} (this only occurred at 10,000 ng l^{-1} in juveniles). Histopathological changes in the kidney and liver were noted in larvae and juvenile fish at concentrations as low as 10 ng l^{-1}. In adult fish there appeared to be reduced deposition of eggs at all test concentrations. A subsequent nine month study revealed a nine month reproduction NOEC of 1 ng l^{-1} (Länge *et al.* 1997).

In its recent review, the Agency concluded that there is a sufficient weight of evidence for the link between natural and synthetic hormones and a range of effects in freshwater fish populations in UK rivers (Environment Agency 1998).

7.3 Genotoxicity

The use of *in vitro* assays for genotoxicity in studying environmental samples remains controversial since the tests do not indicate the likely activity *in vivo* and can only be used as a relatively coarse indicator. Risk assessment requires identification of the substances responsible for the activity. The impact of genotoxic substances on aquatic organisms also remains largely uncertain (Mohn and De Raat 1993, Würgler and Kramers 1992).

Although there are a few studies in which genotoxic activity of hospital waste water has been demonstrated (Guiliani *et al.* 1996, Gartiser *et al.* 1994, 1996, Steger-Hartmann *et al.* 1997, Hartmann *et al.* 1998), it is likely to undergo significant dilution on passage to the STW, thereby reducing any genotoxic potential to negligible levels as demonstrated by Guiliani *et al.* (1996).

In one study, Giuliani *et al.* (1996) found that 13% of over 800 hospital effluent samples from a large hospital applying chemotherapy proved to be genotoxic in the umuC assay. The highest genotoxic activity occurred in the morning hours, but genotoxic samples were detected throughout the day and night. Most of the genotoxic waste water samples (96%) revealed a genotoxic potential without detectable cytotoxic effects. The authors considered that anti-neoplastic agents were the possible causative agents. It is of note that no genotoxic activity was detected in the influx of the municipal STW which received the waste water of the hospital. Consequently, the authors concluded that there was no obvious pollution hazard attributable to the waste. Gartiser *et al.* (1994, 1996) also demonstrated genotoxicity of hospital effluent with the chromosome aberration test (hamster cell line V79) and the Ames test system. However, none of these studies could attribute the observed genotoxic effects to a specific substance or group of substances.

More recently, some workers have tried to identify the causal agents of genotoxicity activity in hospital effluent (Steger-Hartmann *et al.* 1997, Hartmann *et al.* 1998).

Steger-Hartmann *et al.* (1997) investigated the effects of cyclophosphamide, one of the oldest known cytostatics which is frequently used in cancer chemotherapy, in the bacterial genotoxicity umuC assay. No genotoxic effects of cyclophosphamide were found up to concentrations of 1 g l^{-1}. This is in agreement with the SOS chromotest in which Hellmér and Bolcsfoldi (1992) could not detect a genotoxic effect of cyclophosphamide at concentrations of up to 4.6 g l^{-1}. As would be expected, levels of cyclosphosphamide in hospital effluent samples which were in the ng l^{-1} did not exhibit a positive response in this test. Hartmann *et al.* (1998) found evidence to suggest that one single class of antibiotic drug, the fluoroquinolone antibiotics (e.g. especially ciprofloxacin), were responsible for the genotoxic activity for a specific hospital under investigation.

7.4 Microbial resistance

The induction of microbial resistance to antibiotics by exposure to environmental concentrations is a subject which remains controversial. Many antibiotic resistant isolates of micro-organisms can be found in the environment but the most likely source is excretion of resistant organisms by humans and animals receiving antibiotics. Studies of antibiotic resistant organisms in water and wastewater show a significant occurrence of resistant strains

(Cooke 1976, Campeau *et al.* 1996, Jazrawi *et al.* 1988, Alvero 1986, Malik and Ahmad 1994).

Hartmann *et al.* (1998) claimed that antibiotics in hospitals would be significant to induce resistance but other authors do not support this view. Grabow and van Zyl (1976) found that conventional sewage treatment had a limited effect on the incidence of drug resistance in bacteria when studying coliform bacteria resistant to ampicillin, chloramphenicol, streptomycin, kanamycin and tetracycline. Similar results were determined by Bell (1978) in bacteria isolated from domestic sewage before and after treatment in an aerobic lagoon in Canada.

7.5 Summary

- The aquatic acute toxicity data available for human pharmaceuticals indicate effects above the mg l^{-1} level, whereas environmental concentrations are orders of magnitude lower at the ng l^{-1} or, at most, low μg l^{-1} levels. Consequently, none are of environmental significance when considering acute toxicity in the aquatic environment.

- It is more difficult to assess the environmental significance of pharmaceuticals with regard to subtle long-term effects as the available chronic toxicity data are lacking. This is largely due to current regulatory guidance which only requires pharmaceuticals to undergo standard acute toxicity tests unless there is good reason to believe the compound may bioaccumulate. This has been highlighted by a number of researchers who have considered that the use of conventional acute ecotoxicity tests may be inappropriate when assessing the environmental risks of some pharmaceuticals and that the *mode of action* relevant to a specific pharmaceutical should be considered.

- Currently, the only human pharmaceutical for which subtle effects have been demonstrated in laboratory studies at environmentally relevant concentrations is 17α-ethinyloestradiol.

- Although endocrine disrupting activity associated with sewage effluents is known to cause intersex in fish, the contribution of pharmaceuticals e.g. 17α-ethinyloestradiol in terms of concentration appears to be small compared to that from natural hormones. However, the oestrogenic potency of 17α-ethinyloestradiol is at least an order of magnitude higher than natural steroids and an additive response is important to consider given its same mode of action.

- Microbial resistance to antibiotics has been noted in surface water and sewage effluent. Levels of antibiotics in the environment are at the ng l^{-1} level and the source of antibiotic resistant organisms is likely to be from humans and animals given antibiotics. Nonetheless, a number of researchers have concluded that additional research is warranted.

8. DISCUSSION

The issue of the presence and potential adverse effects of pharmaceuticals in the aquatic environment has begun to receive increasing interest in the popular press. This is largely a result of a growing number of scientific papers published in the 1990s which have reported trace levels of pharmaceuticals detected in environmental samples, including sewage effluent, surface water, groundwater and drinking water.

As part of the registration process for new drugs, pharmaceutical companies are required to conduct environmental risk assessments for their products. However, guidance to industry on the environmental assessment procedure shows significant differences between the regulatory authorities in the US and Europe. There are similarities in that both systems have a two stage process in which a 'trigger' concentration is specified before a detailed environmental assessment is required. However, the concentration specified by the US Food and Drug Administration is 1 $\mu g\ l^{-1}$ (based on the *expected introductory concentration* to the aquatic environment) compared to the value of 0.01 $\mu g\ l^{-1}$ (based on *predicted environmental concentration*) currently specified by the EU. Furthermore, it is of note that the EU guidance document is still only draft and that final guidance is required to enable a consistent approach to the environmental assessment of pharmaceuticals in the EU.

There are approximately 3000 active substances licensed for use in the UK. The information readily available on use of prescription drugs is held by the Department of Health's Prescription Price Regulation Scheme (PPRS). However, the PPRS does not hold information on quantities of use but could provide number of prescription items. Although this can gives an indication of the highly prescribed drugs, the therapeutic dose (which can range from μg to g depending on biological activity) needs to be considered in order to calculate quantities of pharmaceutical use. In addition, no readily accessible information of use of drugs in hospitals or over-the-counter medicines was available and it is therefore difficult to obtain a reliable estimate of use in tonnes per year within the scope of this project.

However, another option identified for obtaining detailed UK usage data (in tonnes) is from the Intercontinental Medical Statistics (IMS) Unit which can provide data on prescription drugs, over the counter medicines as well as drug use in hospitals. Provision of the information would be subject to further discussion with the Agency on requirements, confidentiality issues and charges (estimated to be thousands of pounds) and it is recommended that this option be pursued.

Based on the data available, the highest usage drugs were the analgesics (e.g. paracetamol, aspirin). In one detailed UK analysis involving a small sample of 64 pharmaceuticals, it was estimated that paracetamol was used at 2000 tonnes per annum in 1995. [This was the only pharmaceutical used at levels >1000 tonnes in this small sample]. The antibiotic amoxycillin and salbutamol, a drug commonly used in asthma, are also highly prescribed in the UK.

Estimates of the quantities of use of prescribed pharmaceuticals have been conducted by German and Danish researchers. Analgesics again feature as a high use group as do antibiotics and lipid regulators. However, the data also illustrate that there can be significant differences in the types and amounts of pharmaceuticals prescribed in individual countries and that data are not necessarily comparable. For example, in the UK amoxycillin is the highest prescribed drug whereas in Denmark this antibiotic is rarely used.

The main routes for human pharmaceuticals to reach the environment are expected to be through use with patients in hospitals, medical centres or the community, and disposal of unused or out-of-date drugs. Following use, pharmaceutical drugs are excreted as the parent compound, water soluble conjugates (e.g. glucuronides, sulphates) or as metabolites and thus enter the sewerage system. Disposal of unused drugs can also be a route to the environment either to sewer via the toilet or drain, or to landfill via domestic refuse by the general public or as special waste by licensed waste contractors. Although householders are encouraged to return unused or life-expired medicines to pharmacists for safe disposal they are under no obligation to do so. Furthermore such action is dependent on whether clear, consistent advice is give, for example, in any accompanying medical safety leaflet.

A limited number of studies have investigated the fate and removal of pharmaceuticals during municipal sewage treatment. These have reported removal rates of between 6% up to >95% depending on the individual pharmaceutical and the treatment processes involved. In general, it would appear that removal by the activated sludge treatment step is more effective at removal compared with biological filters.

Although removal rates are highly dependent on an individual STW, clofibric acid and fenofibric acid (two lipid regulator metabolites) have consistently been shown to be poorly removed and have also been detected in sewage effluents. Laboratory scale biodegradability studies have confirmed that clofibric acid is persistent as are a number of anti-cancer drugs (ifosfamide, cyclophosphamide and methotrexate). By comparison, the high use analgesic drugs such as acetylsalicylic acid (aspirin) and its metabolites, paracetamol and ibuprofen are readily biodegradable, particularly after acclimation.

The few studies investigating the removal of oestrogens (17β-oestradiol, oestrone and 17α-ethinyloestradiol) during municipal sewage treatment have given mixed results, with some STWs indicating high percentage removal (≈80% or more) and others showing no appreciable removal. The reason for these differences in efficiencies may be due to a number of factors e.g. microbial activity, rain events and temperature, all of which can influence the efficiency of a particular sewage treatment works. Nonetheless, it would appear that the activated sludge treatment step is more efficient at removal than biological filters and that 17β-oestradiol is generally eliminated with a higher efficiency than oestrone and 17α-ethinyloestradiol. In addition, there is increasing evidence that excreted conjugates of 17β-oestradiol (considered to be biologically inactive) can be deconjugated by bacterial enzymes present in sewage treatment or in the environment, thereby reforming the parent compound.

Data on the fate and behaviour of pharmaceuticals in surface and groundwaters are lacking. In relation to surface waters, clofibric acid has been found in the North Sea and various Swiss lakes and appears to be highly mobile and persistent, whereas diclofenac was found to rapidly disappear from lake water in Switzerland as a result of photodegradation.

There are currently no regulatory requirements for a national monitoring programme for pharmaceuticals in the environment. Where studies of pharmaceuticals in the environment have been published, these have been on an *ad hoc* basis by a relatively small number of academic research groups which are active in this field, notably in Germany and to a lesser extent in Switzerland and Denmark.

A wide range of pharmaceuticals (representing broad groups) has been detected in the environment e.g. contraceptive hormones, lipid regulators, pain killers, antibiotics, anti-cancer drugs, anti-epileptic drugs and those regulating blood pressure. Where pharmaceuticals have been detected in sewage effluents or surface waters, the levels are in trace amounts at the ng l^{-1} or, at most, low μg l^{-1} level. The occurrence of drug metabolites has generally not been studied in detail apart from a few specific cases (e.g. clofibric acid, fenofibric acid and salicylic acid) and, therefore, current knowledge is limited.

Pharmaceuticals have been found in groundwater but this is a limited dataset. Most often these have been associated with contamination via older landfills over vulnerable aquifers and therefore may represent isolated and rather specific circumstances. No quantitative data were located on concentrations of pharmaceuticals in sewage sludge, although this is a potential route for lipophilic substances to the terrestrial environment.

Acute toxicity data for the aquatic environment indicate effects above the mg l^{-1} level, whereas environmental concentrations are orders of magnitude low at the ng l^{-1} or, at most, low μg l^{-1} levels. Consequently, none are of environmental significance when considering acute toxicity.

It is more difficult to assess whether there is any environmental significance with regard to subtle long-term effects as available chronic toxicity data are lacking. Current regulatory guidance only requires pharmaceuticals to undergo standard acute toxicity tests unless there is good reason to believe the compound may bioaccumulate. It has been suggested the mode of action relevant to specific pharmaceuticals should be considered when planning appropriate testing to support environmental risk assessment. Currently, the only human pharmaceutical for which subtle effects have been demonstrated in laboratory studies at environmentally relevant concentrations is 17α-ethinyloestradiol.

The presence of oestrogenic activity in sewage effluents has been extensively studied and has been shown to impact on sexual differentiation in fish. The contribution of the contraceptive steroid 17α-ethinyloestradiol to this activity appears to be small in relation to natural hormones. However, its oestrogenic potency is an order of magnitude higher than the natural hormones and an additive response is important to consider given its same mode of action.

The induction of microbial resistance to antibiotics in discharges has been raised as a potential issue. However, there is no evidence that a significant proportion of resistant organisms in the environment arise as a consequence of such discharges rather than by excretion of resistant organisms by man and animals and the spread of resistance by plasmid transfer.

Although there has been no systematic monitoring for the presence of pharmaceuticals in the aquatic environment of the UK, the data available indicate that the concentrations in surface waters will be very low (at the ng l^{-1} levels). When environmental risk assessment is carried out this should include consideration of the significant benefits of pharmaceuticals for human health.

9. CONCLUSIONS

1. A reliable estimate of UK use of pharmaceutical in tonnes per year is not readily accessible. Detailed usage information could be available from the Intercontinental Medical Statistics (IMS), although provision of the data would be subject to further discussion with the Agency on requirements, confidentiality issues and charges.

2. As part of the registration process for new drugs, pharmaceutical companies are required to conduct environmental risk assessments for their products. However, guidance to industry on the environmental assessment procedure shows significant differences between the regulatory authorities in the US and Europe. Furthermore, the EU guidance document is still only draft. Final guidance is therefore required to enable a consistent approach to the environmental assessment of pharmaceuticals in the EU.

3. The main routes for human pharmaceuticals to reach the environment are expected to be through use with patients in hospitals, medical centres or the community, and to a lesser extent, disposal of unused or out-of-date drugs. Following use, pharmaceutical drugs are excreted as the parent compound, water soluble conjugates or as metabolites and thus enter the sewerage system. Disposal of unused drugs can also be a route to the environment either to sewer via the toilet or drain, or to landfill via domestic refuse by the general public or as special waste by licensed waste contractors.

4. There are currently no regulatory requirements for a national monitoring programme for pharmaceuticals in the environment. Where studies of pharmaceuticals in the environment have been published, these have been on an *ad hoc* basis by a relatively small number of academic research groups which are active in this field, notably in Germany and to a lesser extent in Switzerland and Denmark.

5. A wide range of pharmaceuticals (representing broad groups) has been detected in the environment e.g. contraceptive hormones, lipid regulators, pain killers, antibiotics, anti-cancer drugs, anti-epileptic drugs and those regulating blood pressure. When detected in sewage effluents or surface waters, the levels are in trace amounts at the ng l^{-1} or at most low $\mu g\ l^{-1}$ level.

6. The occurrence of drug metabolites has generally not been studied in detail apart from a few specific cases (e.g. clofibric acid, fenofibric acid and salicylic acid) and current knowledge is therefore limited.

7. Pharmaceuticals have been found in groundwater but this is a limited dataset. Most often these have been associated with contamination via older landfills over vulnerable aquifers and therefore may represent isolated and rather specific circumstances.

8. No quantitative data were located on concentrations of pharmaceuticals in sewage sludge, although this is a potential route for lipophilic substances to the terrestrial environment.

9. For all pharmaceuticals currently detected, none are of significance to the aquatic environment when considering acute toxicity. Reported levels in surface water are at least three orders of magnitude below the mg l^{-1} levels which cause acute toxicity.

10. It is more difficult to assess whether there is any environmental significance with regard to subtle long-term effects as the available chronic toxicity data are much more limited. Current regulatory guidance on environmental toxicity testing only requires pharmaceuticals to undergo standard acute toxicity tests unless there is good reason to believe the compound may bioaccumulate. It has been suggested the mode of action relevant to specific pharmaceuticals should be considered when planning appropriate testing to support environmental risk assessment. Currently, the only human pharmaceutical for which subtle effects have been demonstrated in laboratory studies at environmentally relevant concentrations is 17α-ethinyloestradiol.

11. The presence of oestrogenic activity in sewage effluents has been extensively studied and has been shown to impact on sexual differentiation in fish. The contribution of the contraceptive steroid 17α-ethinyloestradiol to this activity with regard its concentration appears to be small in relation to natural hormones. However, its oestrogenic potency is an order of magnitude higher than natural steroids and an additive response is important to consider given its same mode of action. 17α-Ethinyloestradiol has also been shown to be relatively persistent in the environment. Since the Agency has an extensive research programme underway on endocrine-disrupters, no further recommendations have been made on this issue.

12. Studies of the behaviour of pharmaceuticals, excreted as conjugates (e.g. glucuronides and sulphates), in sewage treatment and in the environment need to consider reactivation to the parent drug compound by bacterial enzymes.

13. The induction of microbial resistance to antibiotics in discharges has been raised as a potential issue. However, there is no evidence that a significant proportion of resistant organisms in the environment arise as a consequence of such discharges rather than by excretion of resistant organisms by man and animals and the spread of resistance by plasmid transfer.

14. Although there has been no systematic monitoring for the presence of pharmaceuticals in the aquatic environment of the UK, the data available indicate that the concentrations in surface waters will be very low. However, it is difficult to assess the environmental significance with regard to subtle chronic effects due to the lack of appropriate toxicity data (see 10). When environmental risk assessment is carried out this should include consideration of the significant benefits of pharmaceuticals for human health.

15. The future evaluation of the potential risks of pharmaceuticals in the environment would be much improved by publication of a final EU guidance document on the environmental assessment of pharmaceuticals for human use.

10. RECOMMENDATIONS FOR FURTHER WORK

1. Pharmaceutical usage data in UK

- In conjunction with ABPI, further pursue with Intercontinental Medical Statistics (IMS) the possibility of providing detailed information on quantities of both prescription and over the counter pharmaceuticals used in the UK.

- With other government departments and ABPI, consider the need for, and practicality of, central collation of readily accessible information of the quantities of prescription and non-prescription pharmaceuticals sold.

- Consider information on metabolism, form of excreted drugs and environmental fate in addition to pharmaceutical use data to improve assessment of priorities.

2. Minimising pathways of environmental contamination

- Although disposal of unused pharmaceuticals by the general public is likely to be a relatively small source of environmental contamination, it would be of benefit to minimise the quantity reaching the environment by encouraging the return of unwanted medicines to the pharmacy for appropriate disposal. Initiatives which the pharmaceutical industry could actively support include appropriate labelling, standard advice in safety leaflets and advertisements.

3. Risk assessment

- Consider the practicality of prioritising human pharmaceuticals by structure into categories based on human metabolism and pharmacological activity, likely occurrence, persistence and risk to the environment. If possible, some comparison to the natural background of pharmacologically active compounds e.g. microbial and plant metabolites, would be useful.

- Ensure that research and monitoring is co-ordinated with other interested parties, in the UK and the EU, in order to maximise the value of information emerging from research. To this end it would be of value to organise a selective workshop, in conjunction with other interested parties, on the risk assessment of pharmaceuticals in the environment, in order to facilitate the evaluation of the quality of existing studies and determine what research is planned or is considered necessary. Such a workshop would include researchers, regulators and manufacturers and the water industry.

- Pursue, with the appropriate authorities, expediting the publication of the EU guidance note on the environmental assessment of pharmaceuticals.

- Although not included in this report, the issue of veterinary drugs is considered important and their potential impact on the environment should also be addressed.

4. Environmental monitoring data

- Using the data available on prescription quantities and over the counter sales, metabolism/excretion and environmental fate (linked to recommendation 1), carry out a limited but targeted quantitative analysis for the presence of pharmaceuticals most likely to occur in the environment, representing a range of categories, in sewage effluent and downstream of the mixing zone.

5. Toxicity and fate test data

- Carry out a desk study of the need for specialised chronic tests on aquatic organisms, incorporating pharmacological mode of action, and to determine what form such tests would take with a view to developing appropriate test guidelines. Specialised pharmacological advice and experience from the industry will be an important part of this process. Tailoring toxicity tests to the mode of action of a parent pharmaceutical could be problematic unless the amount, nature and pharmacological activity of drug related materials reaching the environment are known.

- Consider the need for detailed laboratory and field studies on the fate of pharmaceuticals in sewage treatment and the environment. This should utilise any existing information from individual manufacturers (which may involve specialised treatment) and involve participation by sewerage undertakers.

REFERENCES (REVIEWS UNDERLINED)

Aherne, G.W. (1984) The use and significance of immunoassays in the analysis of water. *Proc. Anal. Dir. Royal Soc. Chem*. **21**, 177-179.

Aherne, G.W. and Briggs, R. (1989). The relevance of the presence of certain synthetic steroids in the aquatic environment. *J. Pharm. Pharmacol*. **41**, 735-736.

Aherne, G.W., English, J. and Marks, V. (1985) The role of immunoassay in the analysis of microcontaminants in water samples. *Ecotoxicological Environmental Safety* **9**, 79-83.

Aherne, G.W., Hardcastle, A. and Nield, A.H. (1990) Cytotoxic drugs and the aquatic environment; estimation of bleomycin in river and water samples. *J. Pharm. Pharmacol*. **42**, 741-42.

Alvero C.C. (1987) Antibiotic resistance of heterotrophic bacterial flora of two lakes. *System Applied Microbiology* **9**,169-172.

Belfroid. A.C., Van der Horst, A., Vethaak, A.D., Schäfer, A.J., Rijs, G.B.J., Wegener, J. and Cofino, W.P. (1999) Analysis and occurrence of estrogenic hormones and their glucuronides in surface water and waste water in The Netherlands. *The Science of the Total Environment* **225**, 101-108.

Bell, RB. (1978) Antibiotic resistance patterns of faecal coliforms isolated from domestic sewage before and after treatment in an aerobic lagoon. *Canadian Journal of Microbiology* **24**,886-888.

Berger, K., Peterson, B and Buening-Pfauc, H., (1986) Persistence of drugs occurring in liquid manure in the food chain. *Archiv fuer Lebensmittelhygiene*. **37**(4), 99-102 [In German]

Björnerot, L., Franklin, A. and Tysen. E. (1996) Usage of antibacterial and antiparasitic drugs in animals in Sweden between 1988 and 1993. *The Veterinary Record*. **139,** 282-286.

Brambilla, G., Givitareale, C. and Migliore, L. (1994) Experimental toxicity and analysis of bacitracin, flumequine and sulphadimethoxine in terrestrial and aquatic organisms as a predictive model for ecosystem damage. *Quimica analitica* 13 (supp 1), 114-118.

Burridge R, Warren C, Philips I. (1986) Macrolid, lincosamide and streptogramin resistance in campylobacter jejeuni/coli. *J Antimicrob Chemother* **17**, 3115-3221.

Buser, H.R., Poiger, T. and Müller, M.D. (1998a) Occurrence and fate of the pharmaceutical drug diclofenac in surface waters: rapid photodegradation in a lake. *Environmental Science and Technology* **32**(22), 3449-3456.

Buser, H.R. and Müller, M.D. (1998b) Occurrence of the pharmaceutical drug clofibric acid and the herbicide mecoprop on various Swiss lakes and in the North Sea. *Environmental Science and Technology* **32**(1), 188-192.

Butz, S., Heberer T., and Stan, H.J. (1994) Determination of phenoxyalkanoic acids and other acidic compounds at the low ppt level in water applying solid-phase extraction with RP-C_{18} material. *Journal of Chromatography* A. **677**, 63-74

Calleja, M.C., Persoone, G. and Geladi, P. (1993) The predictive potential of a battery of ecotoxicological tests for human acute toxicity, as evaluated with the first 50 MEIC chemicals. *ALTA - Alternatives to Laboratory Animals*. **21**, 330-349.

Campeau, R.C., Gulli, L.F. and Graves, J.F. (1996). Drug resistance in Detroit River Gram-negative bacilli. *Microbios* **88**, 205-212.

Christen, K. (1998) Human estrogen could be causing adverse effects in fish. *Water Environment and Technology*, July 1998.

Christensen, F.M. (1998) Pharmaceuticals in the environment - a human risk*? Regulatory Toxicology and Pharmacology* **28**, 212-221.

Coats, J.R., Metcalfe, R.L., LU. P-Y, Brown, D.D., Williams, J.F. and Hansen, L.G. (1976) Model Ecosystem Evaluation of the Environmental Impacts of the Veterinary Drugs Phenothiazine, Sulfametazine, Clopidol and Diethylstilbestrol. *Environmental Health Perspectives* **18**, 167-179.

Conor, H.A. Strockel, M., Evrard. J and Legator, M.S. (1997) The contribution of metronidazole and two metabolites to the mutagenic activity detected in urine of treated humans and mice. *Cancer Research*. **37**, 629-633.

Cooke MD (1976). Antibiotic resistance in coliform and faecal coliform bacteria from natural waters and effluents. *NZ Journal of Marine and Freshwater Research* **10**, 391-397.

Crathorne, B., Fielding, M., Steel, C.P. and Watts, C.D. (1984) Organic compounds in water; Analysis using coupled-column high performance liquid chromatography and soft-ionization mass spectrometry. *Environmental Science and Technology*, **18**, 797-802.

Daughton, C.G. and Ternes T.A. (1999) Pharmaceuticals and personal care products in the environment: agents of subtle change? *Environmental Health Perspectives*, **107**(Supplement 6), 907-938.

Department of Health (DOH) (1997) Prescription Cost Analysis Statistics. England 1997.

Desbrow, C., Routledge, E.J., Brighty, G.C., Sumpter, J.P. and Waldock, M. (1998) Identification of estrogenic chemicals in STW effluent. 1. Chemical fractionation and *in vitro* biological screening. *Environmental Science and Technology* **32**, 1549-1558.

D'Haese, I., Kozak, A., Huysmans A., Van Malderen, V., Dhooge, W., Weemases, M. and Verstraete, W. (2000) Pharmaceuticals in the environment: focus on the estrogen 17α-ethinyloestradiol. In: Proceedings of *International Seminar on Pharmaceuticals in the Environment*. March 9th 2000, Brussels, Tecnological Institute.

DVGW (1999) Residues of phrmaceuticals in water sample: results and their assessment from the point of view of drinking water supply. DVGW – Schriftenreiche Wasser Nr. 94. ISSN-Nr 0342-5630. [In German].

EC (1993) Technical and economic study on the reduction (based on Best Available Technology not Entailing Excessive Costs) of industrial emissions from the pharmaceuticals and cosmetics industry. ISBN 928 265 8929.

Eckel, W.P., Ross, B. and Isensee, R.K. (1993) Pentobarbitol found in ground water. *Groundwater* **31**, 801-804.

Elvers, K.T. and Wright, S.J.L. (1995) Antibacterial Activity of the Anti-inflammatory Compound Ibuprofen. *Letters in Applied Microbiology* **20**, 82-84.

Environment Agency (1998) Endocrine disrupting substances in wildlife. A review of the scientific evidence and strategic response, Environment Agency, Bristol, UK, 80 pp.

EU (1994) Phase II ecotoxicity assessment of human and veterinary medicinal products (III/5505/94 Draft 3), European Commission, Brussels.

EU (1995) Ad hoc working group on environmental risk assessment for non GMO containing medicinal products. Assessment of potential risks to the environment posed by medicinal products for human use (excluding products containing live genetically modified organisms). Phase I: Environmental risk assessment. III/5504/94. Draft 6, version 4, European Commission, Brussels.

Fielding, M., Gibson, T.M., James, H.A., McLoughlin, K. and Steel, C.P. (1981) Organic micropollutants in drinking water. WRc Report No. TR159.

Folmar, L.C., Denslow, N.D., Rao, V., Chow, M., Crain, D.A., Enblom, J., Marcino, J. and Guillette, L.J. (1996) Vitellogenin induction and reduced serum testosterone concentrations in feral male carp (*Cyprinus carpio*) captured near a major metropolitan sewage treatment plant. *Environmental Health Perspectives* **104**, 1096-1101.

Food and Drug Administration (1985) FDA Final Rule for Compliance with National Environmental Policy Act: Policy and Procedures, Federal Register 50 FR 16636, 21 CFR 25, 26 April 1985.

Food and Drug Administration (1987) Environmental Assessment Technical Assistance Handbook (FDA Centre for Food safety and Applied Nutrition, Environmental Impact section, March 1987). NTIS PB87-175345.

Food and Drug Administration (1995) Center for Drug Evaluation and Research (CDER). Guidance for industry for the submission of an environmental assessment in human drug applications and supplements. Food and Drug Administration. November, CMC 6.

Franke, S., Hildebrandt, S., Schwarzbauer, J., Link, M. and Franke, W. (1995) Organic compounds as contaminants of the Elbe river and its tributaries. Part II: GC/MS screening for contaminants of the Elbe water. *Fresenius Journal of Analytical. Chemistry* **353**, 39-49.

Garrison, A.W., Pope, J.D. and Allen, F.R. (1976) In: Identification and analysis of organic pollutants in water. ed. Keith, C.H., Ann Arbor Science Publishers Inc, Ann Arbor, 517-566.

Gartiser, S., Brinker, L., Erbe, T., Kümmerer, K. and Willmund, R. (1996) Belstung von Krankenhausabwasser mit gefährlichen Stoffen im Sinne 7a WHG. *Acta Hydrochim. Hydrobiol*. **24**, 90-97.

Gartiser, S., Brinker, L., Uhl, A., Willmund, R., Kümmerer, K. and Dachner, F. (1994) Investigation of hospital effluents - the example of the Frieburg University hospital. *Industrieabwässer* **9**, 1618-1624.

Gavalchin, J. and Katz. S.E. (1994) The persistence of faecal-borne antibiotics in soil. *J. of AOEC international* **77**(2), 481-485.

Giuliani, F., Koler, T., Würgler, F.E. and Widmer, R.M. (1996) Detection of genotoxic activity in native hospital waste water by the umuC test. *Mutation Research* **368**, 49-57.

Grabow WOK, Van Zyl M, Prozesky OW (1976). Behavior in conventional sewage purification processes of coliform bacteria with transferable or non-transferable drug-resistance. *Water Research* **10**,717-723.

Halling-Sørensen, B., Nielsen, S.N., Lanzky, P.F., Ingerslev, F., Lützhøft, H.C.H. and Jørgensen, S.E. (1998) Occurrence, fate and effects of pharmaceutical substances in the environment - a review. *Chemosphere*, **36** (2) 357-393

Harries, J.E., Jobling, S., Matthiessen, P., Sheahan, D.A. and Sumpter, J.P. (1995) *Effects of trace organics on fish - Phase 2. Report to the Department of the Environment*. Foundation for Water Research, Marlow, Report np. FR/D 0022, 90 pp.

Harries, J.E., Sheahan, D.A., Jobling, S., Matthiessen, P., Neall, P., Sumpter, J.P., Taylor, T. and Zaman, N. (1997) Estrogenic activity in five United Kingdom rivers detected by measurement of vitellogenesis in caged male trout. *Environmental Toxicology and Chemistry* **16**, 534-542.

Harris, J.E., Sheahan, D.A., Jobling, S., Matthieseen, P., Neall, P., Routledge, E., Rycroft, R., Sumpter, J.P. and Tylor, T. (1996) A survey of estrogenic activity in United Kingdom inland waters. *Environmental Toxicology and Chemistry* **15**, 1993-2002.

Hartig, C. and Jekel, M. (1998) Detection and identification of sulfonamide drugs in municipal waste water by LC-MS/MS. Poster of work conducted by the Technical University of Berlin.

Hartmann, A., Alder, A.C., Koller, T. and Widmer, R.M. (1998) Identification of fluoroquinone antibiotics as the main source of umuC genotoxicity in native hospital wastewater. *Environmental Toxicology and Chemistry* **17**(3), 377-382.

Heberer, T. (1995) Identifizierung and Quantifizerung von Pesticidruckstanden und Umweltkontaminanten in Grund- und Oberflachenwassern mittels Kapillargas-chromatographie-Massenspektroskopie. Wissenschaft und Tecknik Verlag, Berlin. 376S [In German].

Heberer T., Butz, S. and Stan, H.J. (1995) Analysis of phenoxycarboxylic acids and other acidic compounds in tap, ground, surface and sewage water at the low ng/l-level. *International Journal of Environmental and Analytical Chemistry*. **58**, 43-53.

Heberer, T and Stan, H.J (1996) Occurrence of polar organic contaminants in Berlin drinking water. *Vom Wasser* **86**, 19-31. [In German]

Heberer, T. and Stan, H.J. (1997) Determination of clofibric acid and N-(phenylsulfonyl)-sarcosine in sewage, river and drinking water. *International Journal of Environmental Analytical Chemistry* **67**, 113-124.

Heberer, T., Dünnbier, U, Reilich, C.H. and Stan, H.J. (1997) Detection of drugs and drug metabolites in ground water samples of a drinking water treatment plant. *Fresenius Environmental Bulletin* **6**, 438-443.

Heberer, T., Schmidt-Baumler, K. and Stan, H.J. (1998) Occurrence and distribution of organic contaminants in the aquatic system in Berlin. Part I: Drug residues and other polar contaminants in Berlin surface and groundwater. *Acta Hydroch Hydrob*. **26**, 272-278.

Hellmér, L. and Bolcsfoldi, G. (1992) An evaluation of the E.coli K-12 uvrB/recA DNA repair host-mediated assay. I. *In vitro* sensitivity of the bacteria to 61 compounds. *Mutation Research* **272**, 145-160.

Henschel, K.-P., Wenzel, A., Diedrich, M., and Fliedner, A. (1997) Environmental hazard assessment of pharmaceuticals *Regulatory Toxicology and Pharmacology*, **25**, 220-225.

Hignite, C. and Azarnoff, D.L. (1977) Drugs and drug metabolites as environmental contaminants: chlorophenoxyisobutyrate and salicylic acid in sewage water effluent. *Life Sciences* **20**(2), 337-341.

Hirsch R., Ternes, T.A., Mehlig, A., Ballwanz, F., Kratz, K.L. and Haberer, K. (1998) Determination of antibiotics in different water compartments via LC-electrospray-/MS/MS. *Journal of Chromatography* **815**, 213-223.

Hirsch, R., Ternes, T., Haberer, K. and Kratz, K.L. (1999) Occurrence of antibiotics in the aquatic environment. *The Science of the Total Environment* **225**, 109-118.

Hirsch, R., Ternes, T.A., Haberer, K., Kratz, K.L. (1996) Determination of beta-blockers and B2-sympatomimetics in the aquatic environment. *Vom Wasser* **87**, 263-274. [In German]

Holm, J.V., Rügge, K., Bjerg, P.L. and Christensen, T.H. (1995) Occurrence and distribution of pharmaceutical organic compounds in the groundwater downgradient of a landfill (Grinsted, Denmark). *Environmental Science and Technology* **29**(5), 1415-1420.

Hun, T. (1998) Studies indicate drugs in water may come from effluent discharges, *Water Environment and Technology*, July 1998, 17-22.

International Agency for Research on Cancer (IARC) (1996) IARC Monograph on the Evaluation of Carcinogenic Risks to Humans. Volume 66. Some pharmaceutical drugs. IARC, Lyon, France.

Ingerselev, F. and Halling-Sørensen, B. (1999) Pharmaceuticals in the environment - a source of endocrine disruption. In: IBC Conference Proceedings on Endocrine Disrupters in the Environment, London, UK, 12-13 May 1999.

Irwin, V. (1994a) European Regulatory Controls Addressing the Ecological Effects of Drug Use. Part I: Introduction and Requirements Affecting All Medical Products. *Pharmaceutical Technology Europe* **6**(10), 25-27.

James, H.A., Fielding, M., Franklin, O., Williams, D. and Lunt., D. (1997) Steroid concentrations in treated sewage effluents and water courses - implications for water supplies. Final Report to the Department of the Environment and UK Water Industry Research Limited. Report No. DWI 4323.

Jazrawi, S.F., Al-Doori, Z.A. and Haddad, T.A. (1988) Antibiotic resistant coliform and faecal coliform bacteria in drinking water. *Water, Air and Soil Pollution*, **39** 377-382.

Jobling, S., Reynolds, T., White, R., Parke, M.G. and Sumpter, J.P. (1995) A variety of environmentally persistent chemicals including some phthalate plasticizers, are weakly estrogenic. *Environmental Health Perspectives* **103**, 582-587.

Jobling, S., Sheahan, D., Osborne, J.A., Mathiessen, P. and Sumpter, J.P. (1996) Inhibition of testicular growth in rainbow trout (*Oncorhynchus mykiss*) exposed to estrogenic alkylphenolic chemicals. *Environmental Toxicology and Chemistry* **15**, 194-202.

Jobling, S., Tyler, C.R., Nolan, M. and Sumpter, J.P. (1998) The identification of oestrogenic effects in wild fish. R & D Technical Report W119, Environment Agency, Bristol, UK.

Johnson, A.C, Williams, R.J. and Ulahannan, T (1999) Comment on 'Identification of estrogenic chemicals in STW effluent. 1. Chemical fractionation and in vitro biological screening. Environmental Science and Technology 33(2), 369-370.

Jurgens, M.D., Williams, R.J. and Johnson, A.C. (1999) Fate and behavior of steroid oestrogens in rivers: a scoping study. EA R&D Technical Report P161.

Kalbus, W. (1995) Belastung bayerischer gewässer durch synthetische östrogene. Paper presented at 50 Factagung Bayerisches Landesamt for Wasserwirtschaft, Institut für Wasserforschung, Munchen 7/8, November 1995.

Kerry, J., Hiney, M., Coyne, R, NicGabhainn, S., Gilroy, D., Cazabon, D. and Smith, P. (1995) Fish feed as a source of oxytetracycline-resistant bacteria in the sediment under fish farms. *Aquaculture* **131**, 101-113.

Knoll, BASF (1995) Safety data sheet Ibuprofen. Issue/revision date 6/4/95. Knoll Pharmaceuticals, Nottingham, NG2 3AA England.

Kopf, W. (1995) Wirkung endokriner Stoffe in Biotests mit Wasserorganismen. Vortrag bei der 50. Fachtagung des Bay, LA für Wasserwirtschaft: Stoffe mit endokriner *Wirkung im Wasser* (Abstract) [in German].

Kümmerer, L., Sterger-Hartmann, T and Meyer, M. (1997) Biodegradability of the anti-tumour agent ifosfamide and its occurrence in hospital effluents and communal sewage. *Water Research* **31**, 2705-2710.

Kümmerer, K., Al-Ahmed, A. and Mersch-Sundermann, V. (2000) Biodegradation of some antibiotics, elimination of the genotoxity and affection of wastewater bacteria in a simple test. *Chemosphere* **40**, 701-710.

Lanzky, P.F. and Halling-Sorensen, B. (in press) The toxic effect of the antibiotic metronidazol on aquatic organisms. *Chemosphere*.

Lee, W.Y. and Arnold, C.R. (1983) Chronic Toxicity of Ocean-dumped Pharmaceutical Wastes to the Marine Amphipod Amphithoe valida. *Marine Pollution Bulletin* **14**, 150-153.

Leff, L.G., Dana, J.R., McArthur, J.V. and Shimkets, L.J. (1993) Detection of Tn5-like sequences in Kanamycin-resistant stream Bacteria and Environmental DNA. *Applied and Environmental Microbiology* **59**(2), 417-421.

Länge, R., Schweinfurth H., Croudace, C. and Panther, G. (1997) Growth and reproduction of fathead minnow (*Pimephales promelas*) exposed to the synthetic steroid hormrone ethinyloestradiol in a life-cycl test [Abstract]. 7th Annual Meeting of SETAC – Europe (April 6 –10, 1997), Amsterdam, The Netherland.

Lilius, H., Hastbacka, T. and Isonaa, B. (1995) A comparison of the toxicity of 30 reference chemicals to *Daphnia magna* and *Daphnia pulex*. *Environmental Toxicology and Chemistry*. **14**, 2085-2088.

Lunestad, B.T. (1992b) Fate and effects of antibacterial agents in aquatic environments. In: Chemotherapy in Aquaculture: From theory to reality. Michel, C and Aldermand, D.J. (eds.) Office Internatl. des Epizooties, Paris p.152-161.

Lye, C.M., Frid, C.J.J., Gill, M.E. and McCormick D. (1997) Abnormalities in the reproductive health of the flounder *Platichthys flesus* exposed to effluent from a sewage treatment works. *Marine Pollution Bulletin* **34**, 34-41.

Malik, A. and Ahmad, M. (1994) Incidence of drug and metal resistance in *E. coli* strains from sewage water and soil. *Chem Environ Res* **3**, 3-11.

Martindale (1993) The Extra Pharmacopoeia. Thirtieth edition. The Pharmaceutical Press.

Matthiessen, P., Allen, Y.T., Allchin, C.R., Feist, S.W., Kirby, M.F., Law, R.J., Scott, A.P., Thain, J.E. and Thomas, K.V. (1998) Oestrogenic endocrine disruption in flounder (*Platichthys flesus* L.) from United Kingdom estuarine and marine waters. Science Series Technical Report No 107. Centre for Environment, Fisheries and Aquaculture Science (CEFAS), UK.

Misra, D.S., Kumar, A. and Singh, I.P. (1979). Antibiotic resistance and transfer factor (R +) in *E. coli* isolated from raw sewage. *Indian Journal of Medical Research* **70**, 559-562.

Mohn, G.R. and De Raat, W.K. (1993) Ecological significance of mutagens. *Science of the Total Environment*. Supplement, 1771-1778.

Monteith, D.K., Conner, T.H., Venvenuto, J.A., Fairchild, E.J. and Theiss, J.C. (1987) Stability and inactivation of mutagenic drugs and their metabolites in the urine of patients administered antineoplastic therapy. *Environmental and Molecular Mutagenesis* **10**, 341-356.

Orme, M.L.E., Back, D.J. and Breckenbridge, A.M. (1983) Clinical pharmacokinetics of oral contraceptives. *Clinical Pharmacokinetics* **8**, 95-136.

Norpoth, K. *et al* (1973) Investigations on the problem of solubility and stability of steroid ovulation inhibitors in water, waste water and activated sludge. *Abl. Bakt. Hyg. I. Abt. Orig. B.* **156,** 500-511.

Pandey, S. and Musarrat, J. (1993) Antibiotic resistant coliform bacteria in drinking water. *Journal of Environmental Biology* **14**, 267-274.

Panter, G.H., Thompson, R.S., Beresord, N. and Sumpter, J.P. (1999) Transformation of a non-oestrogenic steroid metabolite to an oestrogenically active substance by minimal bacterial activity. *Chemosphere* **38,** 3579-3596.

Pathak, S.P., Gautam, A.R., Gaur, A., Gopal, K. and Ray, P.K. (1993) Incidence of transferable antibiotic resistance among enterotoxigenic *Escherichia coli* in urban drinking water. *Journal of Environmental Science and Health* Part A **28**, 1445-1455.

Pearce, F. (1999) Something in the water. *New Scientist* 6 March, 19-20.

Prösch J. *et al* (1998) *Vom Wasser* **91**, 207-214. [In German]

Purdom, C.E., Hardiman, P.A., Bye, V.A., Eno, N.C., Tyler, C.R. and Sumpter, J. P. (1994) Oestrogenic effects of effluents from sewage treatment works. *Chemistry and Ecology* **8**, 275-285.

Radtke, T.M. and Gist, G.L. (1989) Wastewater sludge disposal - antibiotic resistant bacteria may pose health hazard. *Journal of Environmental Health* **52**, 102-105.

Rathner, M. and Sonneborn, M. (1979) Biologically active oestrogens in potable water and effluents. *Forum Stadte-Hygiene* **30**, 45-49.

Richardson, M.L. and Bowron, J.M. (1985) The fate of pharmaceutical chemicals in the environment, *Journal of Pharmacy and Pharmacology*, **37**, 1-12.

Rogers, H.R. (1996) Sources, behaviour and fate of organic contaminants during sewage treatment and in sewage sludges. *The Science of the Total Environment* **185**, 3-26.

Rogers, I.H., Birtwell, I.K. and Kruzynski, G.M. (1986) Organic extractables in municipal wastewater Vancouver, British Columbia. *Water Pollution Research Journal Canada* **21**, 187-204.

Römbke, J., Knacker, T. and Stahlschmidt- Allner, P. (1996) Umweltprobleme durch Arzneimittel-Literaturstudie. ECT Oekotoxikologie GmbH. UBA Texte. Berichtsnummer. UBA-FB 96-060. Umweltbundesamt, Berlin.[In German]

Routledge, E.J., Sheahan, D., Desbrow, C., Brighty, G.C., Waldock, M. and Sumpter, J.P. (1998) Identification of estrogenic chemicals in STW effluent. 2. *In vivo* responses in trout and roach. *Environmental Science and Technology* **32**, 1559-1565.

Saamer, F.J., Zainab, A.A.D. and Tahreer, A.H (1988). Antibiotic resistant coliform and faecal coliform bacteria in drinking water. *Water Air and Soil Pollution* **39**,377-382.

Sanyal, A.K., Royd, D., Chowdhury, B. and Banerjee, A.B. (1993) Ibuprofen, a unique anti-inflammatory compound with antifungal activity against dermatophytes. *Letters in Applied Microbiology*. **17**, 109-111.

Schwabe, U. and Paffrath, D. (1995) *Arzneiverord-nungsreport '95 Aktuelle Daten. Kosten, Trends und Kommentare*. Drug prescribing report '95. Current data, costs, trends and comments. Gustav Fischer Verlag, Stuttgart, Jena.

Schweinfurth, H, Lange, R. and Gunzel, P. (1996) *Environmental fate and ecological effects of steroidal estrogens*. IBC Conference Proceedings of "Oestrogenic chemicals in the Environment", London, 9-10 May 1996.

Shelby, M.D., Newbold, R.R., Tully, D.B., Chae, K., Davis, V.L. (1996) Assessing environmental chemicals for estrogenicity using a combination of *in vitro* and *in vivo* assays. *Environmental Health Perspectives* **104**, 1296-1300.

Shore, LS, Gurevitz, M and Shemesh, M. (1993) Estrogen as an environmental pollutants. *Bulletin of Environmental Contamination and Toxicology* **51**, 361-366.

Stan, H.J. and Heberer, T. (1997) Pharmaceuticals in the aquatic environment. *Analusis Magazine*, **25** (7) M20-M23.

Stan, H.J. and Linkerhägner, M. (1992) Identification of 2-(4-chlorophenoxy)-2-methyl-propionic acid in groundwater with GC-AED and GC-MS. *Vom Wasser* **79**, 75-88. [In German]

Stan, H.J., Heberer, T. and Linkerhägner, M. (1994) Occurrence of clofibric acid in the aquatic system - does the medical application cause contamination of surface, ground and drinking water? *Vom Wasser* **83**, 57-68 [In German]

Steger-Hartmann, T., Kümmerer, K. and Hartmann, A. (1997) Biological determination of cyclosphosphamide and its occurrence in sewage water. *Ecotoxicology and Environmental Safety* **36**, 174-179.

Steger-Hartmann, T., Kümmerer, K. and Schecker, J. (1996) Trace analysis of the antineoplastics ifosfamide and cyclophosphamide in sewage water by two-step solid phase extraction and gas chromatography-mass spectroscopy. *Journal of Chromatography* A. **726**, 179-184.

Stelzer, W., Ziegert, E., Schneider, E. (1985) The occurrence of antibiotic-resistant Klebsiellae in wastewater. *Zentralbl Mikrobiol* **140**, 283-291.

Stuer-Lauridsen F., Birkved, M., Hansen, L.P., Holten Lutzhøft and Halling-Sørensen, B. (2000) Environmental risk assessment of human pharmaceuticals in Denmark after normal therapeutic use. *Chemosphere* **40**, 783-793.

Stumpf, M . *et a.l* (1998) *Vom Wasser* **91**, 291-303.

Stumpf, M., Ternes, T.A., Haberer, K., Seel, P. Baumann, W. (1996) Determination of drugs in sewage treatment plants and river water. *Vom Wasser* **86**, 291-303. [In German].

Stumpf, M. Ternes, T.A., Haberer, K and Baumann, W. (1996b) Determination of natural and synthetic estrogens in sewage plants and river water. *Vom Wasser* **87**, 251-261 [In German].

Stumpf, M., Ternes, T.A., Wilken, R.D., Rodrigues, S.V. and Baumann, W. (1999) Polar drug residues in sewage and natural waters in the state of Rio de Janeiro, Brazil. *The Science of the Total Environment* **225**, 135-141.

Suzaki, K (1979). Resistance of mycoplasma pneumoniae to macrolid and analogous antibiotics. *Sci Rep Res Inst Tohoku Univ* [Med] **26**, 71-91.

Tabak, H.H. and Bunch, R.L. (1970) Steroid hormones as water pollutants. I. Metabolism of natural and synthetic ovulation-inhibiting hormones by micro-organisms of activated sludge and primary settled sewage. *Devs. Ind. Microbiology* **11,** 367-376.

Tabak, H.H. *et al* (1981) *Steroid hormones as water pollutants. II. Studies on the persistence and stability of natural urinary and synthetic ovulation-inhibiting hormones in untreated and treated wastewaters*. In: Developments in Industrial Microbiology (22), Proc. 37, General Meeting of the Society Industrial Microbiology, August 1980, Flagstaff, Garamond/Pridemark Press Baltimore 1981: 497-519.

Technological Institute (2000) *International Seminar on Pharmaceuticals in the Environment*. March 9th 2000, Brussels.

Ternes, T.A. (1998) Occurrence of drugs in German sewage treatment plants and rivers. *Water Research* **32**, 3245-3260.

Ternes, T.A. (2000) Pharmaceuticals in rivers, groundwater and drinking water. In: Proceedings of *International Seminar on Pharmaceuticals in the Environment*. March 9th 2000, Brussels, Tecnological Institute.

Ternes, T.A., Hirsch, R., Muller, J. and Haberer, K. (1998) Methods for the determination of neutral drugs as well as betablockers and β-sympathomimetics in aqueous matrices using GC/MS and LC/MS/MS. *Fresenius Journal of. Analytical Chemistry* **362**, 329-340.

Ternes, T.A., Stumpf, M., Schuppert, B. and Haberer, K. (1998a) Methods for the dertermination of acidic drugs and antiseptics in water. *Vom Wasser* **90**, 295-309. [In German]

Ternes, T.A., Stumpf, M., Mueller, J., Haberer, K., Wilken, R.-D. and Servos, M. (1999a) Behaviour and occurrence of estrogens in municipal sewage treatment plants - I. Investigations in Germany, Canada and Brazil. *The Science of the Total Environment* **225**, 81-90.

Ternes, T.A., Kreckel, P. and Mueller, J. (1999b) Behaviour and occurrence of estrogens in municipal sewage treatment plants - II. Aerobic batch experiments with activated sludge. *The Science of the Total Environment* **225**, 91-99.

Thomulka, K.W., McGee, D.J. and Lange, J.H. (1993) Detection of Bioharzardous Materials in Water by Measuring Bioluminescence Reduction with the Marine Organism Vibrio harveyi, *Journal of Environmental. Science and Health* A **28**, 2153-2166.

Velagaleti, R.R. and Winberry, M.W. (1998) Risk assessment of human and animal health drugs in the environment: a chemical fate and environmental effects approach. *Environmental Toxicology and Risk Assessment: Seventh Volume, ASTM STP 1333*. Eds Little, E.E., DeLonay, A.J. and Greenberg, B.M., American Society for Testing and Materials, 1998.

Waggott, A. (1981) Trace organic substances in the River Lee (Great Britain). In: Chemistry in Water Reuse. ed. W.J. Cooper, Volume 2, 55-99. Ann Arbor Sci., Ann Arbor, MI.

Watts, C.D., Crathorne, B., Fielding, M and Steel, C.P. (1983) Identification of non-volatile organics in water using field desorption mass spectrometry and high performance liquid chromatography. Presented at the 3rd European Symposium on Organic Micropollutants in water, Oslo, Norway, September 19-21. *In: Analysis of Organic Micropollutants in Water*, ed. Angeletti, G. and Bjørseth, A., DD Reidel Publishing Co., Dordrecht. pp 120-131.

Webb, S. (1998) *An objective analysis of the environmental and indirect human health risks associated with pharmaceuticals*. Presented at the SETAC 19th Annual Meeting, North Carolina, USA. 15-19 November 1998.

Webb, S. (2000) Risk assessment for pharmaceuticals. In: Proceedings of *International Seminar on Pharmaceuticals in the Environment*. March 9th 2000, Brussels, Tecnological Institute.

Wilson, I. (1978) *Contraceptive steroids in water supplies*. M. Phil Thesis, WRc Medmenham.

Wood, L.B. and Richardson, M.L. (1980) Catchment quality control. *Progress in Water Technology* **12** (13), 1-12.

World Health Organisation (1999) Anatomical Therapeutic Chemical (ATC) Classification and Defined Daily Doses (DDD) for Pharmaceuticals and Vitamins. WHO Collaborating Centre for Drug Statistics Methodology.

Würgler, F.E. and Kramers, P.G.N. (1992) Environmental effects of genotoxins (eco-genotoxicology). *Mutagenesis* **7**, 321-327.

Yeager, R.L. and Halley, B.A. (1990) Sorption/desorption of ^{14}C[efromycin] with soils. *Journal of Agriculture and Food Chemistry*. **38**, 883-886.

APPENDIX A CONSUMPTION OF PRESCRIBED DRUGS IN THE UK

Table A1 Consumption of prescribed drugs in the UK for 1997

Active ingredient	Number prescription items (thousands)	Detected in sewage effluent or in the aquatic environment?
Amoxycillin	16585.4	No
Salbutamol	16167.8	Yes
Aspirin	11634.6	Yes
Beclomethasone dipropionate	10407.7	No
Co-Proxamol (Dextroprop HCl/paracetamol)	10159.0	-
Paracetamol	9569.5	Yes
Atenolol	8133.0	No
Bendrofluazide	7591.5	No
Co-Codamol (codeine phosphate/paracetamol)	7345.4	-
Hydrocortisone	7147.8	No
Diclofenac sodium	7129.2	Yes
Thyroxine	6739.6	No
Ibuprofen	6639.2	Yes
Frusemide	6238.6	No
Influenza vaccine	5887.9	No
Alginic acid compound preparations	5855.8	No
Nifedipine	5450.0	No
Temazepam	5252.5	No
Omeprazole	4911.3	No
Isosorbide mononitrate	4582.2	No
Ranitidine hydrochloride	4278.3	No
Lactulose	4098.1	No
Prednisolone	4075.4	No
Co-amilofruse (amiloride hydrocarbon/frusemide)	3860.5	No
Digoxin	3840.4	No
Diazepam	3798.5	Yes
Combined ethinyloestradiol (30 ug)	3794.3	Yes
Enalapril maleate	3783.7	No
Co-Dydramol	3670.8	No
Phenoxymethylpenicillin (penicillin V)	3578.5	No
Amlodipine desylate	3450.4	No
Dothiepin hydrochloride	3389.2	No
Erythromycin	3342.5	Yes
Lisinopril	3341.2	No
Glyceryl trinitrate	3194.8	No
Amitriptyline hydrochloride	3062.0	No
Fluoxetine hydrochloride	3036.2	No
Bethamethasone valerate	2961.9	No
Warfarin sodium	2902.9	-
Co-Amoxiclav (Amoxycillin/Calvul acid)	2795.0	-

Active ingredient	Number prescription items (thousands)	Detected in sewage effluent or in the aquatic environment?
Trimethoprim	2782.3	Yes
Diltriazem hydrochloride	2583.6	No
Propanolol hydrochloride	2525.7	Yes
Chloramphenicol	2450.0	No
Ispaghula husk	2448.4	-
Nitrazepam	2425.9	No
Simvastatin	2412.2	No
Paroxetine hydrochloride	2287.3	No
Flucloxacillin sodium	2178.5	No
Ferrous sulphate	2177.3	-
Clotrimazole	2171.4	No
Budesonide	2163.4	No
Metformin hydrochloride	2138.9	No
Cimetidine	2052.1	No
Carbamazepine	2031.7	Yes
Cephalexin	2019.7	No
Dihydrocodeine tartrate	2014.4	No
Prochlorperazine maleate	1980.9	No
Glucose blood testing reagents	1971.5	-
Erythromycin ethylsuccinate	1961.6	Yes
Gliclazide	1888.8	No
Senna	1852.6	-
Captopril	1829.7	No
Liquid paraffin	1809.8	-
Terbutaline sulphate	1808.2	No
Allopurinol	1763.6	No
Lansoprazole	1723.9	No
Fusidic acid	1716.0	No
Naproxen	1698.4	Yes
Emulsifying wax	1697.7	-
Zopiclone	1679.2	No
Thoridazine	1662.7	No
Loratadine	1652.6	No
Heparinoid	1651.2	No
Pseudoephedrine hydrochlorine	1646.2	No
Metronidazole	1633.3	No
Hepatitis A	1625.0	-
Ipratropium bromide	1604.8	No
Cefaclor	1522.1	No
Quinine sulphate	1521.7	-
Pholcodine	1516.6	No
Salmeterol	1487.4	No
Hypromellose	1472.6	No
Oxytetracycline	1469.6	Yes
Codeine phosphate	1425.9	No
Oestrogen conjugated with progestogen	1409.2	Yes
Tetanus	1382.4	-

Active ingredient	Number prescription items (thousands)	Detected in sewage effluent or in the aquatic environment?
Simple	1380.1	-
Fluticasone propionate	1374.6	No
Sodium cromoglycate	1369.4	No
Timolol maleate	1343.9	Yes
Typhoid	1322.7	-
Co-amilozide (Amiloride HCl/hydchloroth)	1270.1	No
Malathion	1262.7	No
Phenytoin sodium	1252.5	No
Sodium valproate	1237.0	No
Urine testing reagents	1232.1	-
Oestradiol with progestogen	1228.8	Yes
Oestradiol	1214.9	Yes
Hydrocortisone acetate	1207.6	No
Sodium chloride	1186.2	-
Cetirizine hydrochloride	1176.0	No
Glibenclamide	1173.0	No
Oestrogens conjugated	1165.3	Yes
Combined ethinyloestradiol 35meg	1165.2	Yes
Methadone hydrochloride	1163.2	No
Mebeverine hydrochloride	1160.7	No
Co-tenidone (Atenolol/chlorthalidone)	1129.7	No
Clobetasol butyrate	1109.1	No
Clarithromycin	1062.0	Yes
Ciprofloxacin	1054.1	Yes
Tamoxifen citrate	1036.1	No
Coal tar	1018.1	-
Betahistine hydrochloride	1017.6	No
Piroxicam	1015.0	No
Fluticasone	1003.7	No

Source: DoH (PPRS)

APPENDIX B ENVIRONMENTAL MONITORING DATA

Table B1 Concentration of human pharmaceuticals detected in sewage effluent

Compound	Therapeutic use	Typical oral therapeutic dose (ng/day)[d]	Concentration detected (ng l^{-1})	LOD (ng l^{-1})	Country	Reference
UK						
Bleomycin	Anti-neoplastic	-	11-19	5	UK	Aherne *et al.* (1990)
17α-Ethinyloestradiol	Hormone	10,000 - 50,000	nd - 7	1	UK	Aherne and Briggs (1989)
			nd - 7	0.2	UK	Desbrow *et al.* (1998)
Norethisterone	Hormone	5,000,000	8 - 20	2	UK	Aherne and Briggs (1989)
17β-Oestradiol	Hormone	2,000,000	2.7-48	0.2	UK	Desbrow *et al.* (1998)
Oestrone	Hormone	1,000,000	1.4-76	0.2	UK	Desbrow *et al.* (1998)
Other countries						
Acetaminophen (paracetamol)	Analgesic	2000,000,000	nd[a], nd[b], 6000[c]	500	Germany	Ternes (1998)
Acetylsalicylic acid (aspirin)	Analgesic	1200,000,000	nd-95, 620	±40	US	Hignite and Azarnoff (1977)
			290	-	Germany	Stan and Heberer (1997)
			nd - 1510	50	Germany	Stumpf *et al.* (1996)
			220[a], 320[b], 1500[c]	100	Germany	Ternes (1998)
			50[a], 3100[c]	50	Brazil	Stumpf *et al.* (1999)
Betaxolol	β-Blocker	20, 000,000	nd - 190	25	Germany	Hirsch *et al.* (1996)
			57[a], 100[b], 190[c]	25	Germany	Ternes (1998)
Bezafibrate	Lipid regulator	600,000,000	3320	-	Germany	Stan and Heberer (1997)
			nd - 4560	250	Germany	Stumpf *et al.* (1996)
			2200[a], 3400[b], 4600[c]	25	Germany	Ternes (1998)
			1010[a], 1020[c]	50	Brazil	Stumpf *et al.* (1999)
Bisoprolol	β-Blocker	10,000,000	nd - 370	25	Germany	Hirsch *et al.* (1996)
			57[a], 130[b], 370[c]	25	Germany	Ternes (1998)
Carazolol	β-Blocker	10,000,000[e]	nd - 120	25	Germany	Hirsch *et al.* (1996)
			nd[a], 70[b], 120[c]	25	Germany	Ternes (1998)
Carbamazepine	Anti-epileptic	1000,000,000	2100[a], 3700[b], 6300[c]	50	Germany	Ternes (1998)
Chloramiphenol	Antibiotic	3000,000,000	nd[a], nd[b], 560[c]	20	Germany	Hirsch *et al.* (1999)
Chlorotetracycline	Antibiotic	1000,000,000	nd	50	Germany	Hirsch *et al.* (1999)

Compound	Therapeutic use	Typical oral therapeutic dose (ng/day)[d]	Concentration detected (ng l^{-1})	LOD (ng l^{-1})	Country	Reference
Clarithromycin	Antibiotic	500,000,000	nd[a], nd[b], 240[c]	20	Germany	Hirsch *et al.* (1999)
Clenbuterol	β_2-Sympathomimetic	60,000[e]	nd - 180	25	Germany	Hirsch *et al.* (1996)
			nd - 80	25	Germany	Ternes (1998)
Clofibrate	Lipid regulator	2000,000,000[f]	nd	100	Germany	Ternes (1998)
Clofibric acid	Lipid regulator metabolite	-	2540 - 9740	±140	US	Hignite and Azarnoff (1977)
			up to 4550	-	Germany	Stan and Heberer (1997)
			nd - 2050	250	Germany	Stan and Heberer (1997)
			nd – 1030	-	Germany	Stan and Heberer (1997)
			nd – 1560	50	Germany	Stumpf *et al.* (1996)
			450, 680	-	Germany	Heberer *et al.* (1998)
			360[a], 720[b], 1600[c]	50	Germany	Ternes (1998)
			102[a], 1030[c]	50	Brazil	Stumpf *et al.* (1999)
Cloxacillin	Antibiotic	2000,000,000	Nd	20	Germany	Hirsch *et al.* (1999)
Cyclophosphamide	Anti-neoplastic	-	nd[a], 18[b], 20[c]	100	Germany	Ternes (1998)
			nd-17	6	-	Steger-Hartmann *et al.* (1997)
			8-143	-	-	Kümmerer *et al.* (1997)
Diazepam	Psychiatric drug	10,000,000	nd[a], 30[b], 40[c]	30	Germany	Ternes (1998)
Diclofenac	Analgesic	100,000,000	1000	-	Germany	Stan and Heberer (1997)
			nd – 1590	50	Germany	Stumpf *et al.* (1996)
			135, 760	-	Germany	Heberer *et al.* (1998)
			810[a], 1600[b], 2100[c]	50	Germany	Ternes (1998)
			310 – 930	1	Switzerland	Buser *et al.* (1998a)
			130[a], 930[c]	50	Brazil	Stumpf *et al.* (1999)
Dicloxacillin	Antibiotic	2000,000,000	Nd	20	Germany	Hirsch *et al.* (1999)
Dimethylaminophenazone	Analgesic	-[f]	nd[a], 150[b], 1000[c]	100	Germany	Ternes (1998)
Doxycycline	Antibiotic	100,000,000	Nd	50	Germany	Hirsch *et al.* (1999)
Erhythromycin-H_2O	Antibiotic	1000,000,000	2500[a], 5100[b], 6000[c]	20	Germany	Hirsch *et al.* (1999)
17α-Ethinyloestradiol	Hormone	10,000 - 50,000	1[a], 4[b], 15[c]	1	Germany	Ternes *et al.* (1999a)
			17[a], 62[c]	1	Germany	Stumpf *et al.* (199b)
			9[a], 29[b], 42[c]	1	Canada	Ternes *et al.* (1999a)
			nd - 7.5	0.3-1.8	Netherlands	Belfroid *et al.* (1999)
Etofibrate	Lipid regulator	900,000,000[e]	Nd	100	Germany	Ternes (1998)
Fenofibrate	Lipid regulator	300,000,000[e]	nd[a], nd[b], 30[c]	50	Germany	Ternes (1998)

Compound	Therapeutic use	Typical oral therapeutic dose (ng/day)[d]	Concentration detected (ng l^{-1})	LOD (ng l^{-1})	Country	Reference
Fenofibric acid	Lipid regulator metabolite	-	380[a], 680[b], 1200[c]	50	Germany	Ternes (1998)
			680	-	Germany	Stan and Heberer (1997)
			nd – 1190	50	Germany	Stumpf *et al.* (1996)
			50[a], 750[c]	50	Brazil	Stumpf *et al.* (1999)
Fenoprofen	Analgesic	1200,000,000	nd	50	Germany	Stan and Heberer (1997)
			nd	-	Germany	Stumpf *et al.* (1996)
			nd	50	Germany	Ternes (1998)
Fenoterol	β_2-Sympathomimetic	10,000,000	nd - 70	25	Germany	Hirsch *et al.* (1996)
			nd[a], nd[b], 60[c]	50	Germany	Ternes (1998)
Gemfibrozil	Lipid regulator	1200,000,000	1320	-	Germany	Stan and Heberer (1997)
			nd – 1460	50	Germany	Stumpf *et al.* (1996)
			400[a], 840[b], 1500[c]	50	Germany	Ternes(1998)
			130[a], 950[c]	50	Brazil	Stumpf *et al.* (1999)
Gentisic acid	Aspirin metabolite	-	nd[a], 200[b], 590[c]	200	Germany	Ternes (1998)
16α-Hydroxyoestrone	Hormone	-	1[a], 4[b], 5[c]	1	Germany	Ternes *et al.* (1999a)
Ibuprofen	Analgesic	1200,000,000	3350	-	Germany	Stan and Heberer (1997)
			nd – 3350	50	Germany	Stumpf *et al.* (1996)
			10	-	Germany	Heberer *et al.* (1998)
			370[a], 1200[b], 3400[c]	50	Germany	Ternes (1998)
			600[a], 3000[c]	50	Brazil	Stumpf *et al.* (1999)
			+	-	Canada	Rogers *et al.* (1986)
Ifosfamide	Anti-neoplastic	-	nd[a], 40[b], 2900[c]	10	Germany	Ternes (1998)
			nd-43, 6.5[a], 9.5[a]	6	Germany	Kümmerer *et al.* (1997)
Indomethacine	Anti-inflammatory	100,000,000	0.29	-	Germany	Stan and Heberer (1997)
			nd – 520	50	Germany	Stumpf *et al.* (1996)
			270[a], 400[b], 600[c]	50	Germany	Ternes (1998)
			50[a], 1000[c]	50	Brazil	Stumpf *et al.* (1999)
Ketoprofen	Anti-inflammatory	150,000,000	nd	50	Germany	Stan and Heberer (1997)
			nd – 380	50	Germany	Stumpf *et al.* (1996)
			200[a], 250[b], 380[c]	50	Germany	Ternes (1998)
			170[a], 650[c]	50	Brazil	Stumpf *et al.* (1999)
Meclofenamic acid	Anti-inflammatory	400,000,000[e]	Nd	50	Germany	Ternes (1998)
Menstranol	Hormone	10,000 – 50,000[e]	nd[a], 1[b], 4[c]	1	Germany	Ternes *et al.* (1999a)
			nd	1	Canada	Ternes *et al.* (1999a)
Methicillin	Antibiotic	4000,000,000	nd	20	Germany	Hirsch *et al.* (1999)

Compound	Therapeutic use	Typical oral therapeutic dose (ng/day)[d]	Concentration detected (ng l^{-1})	LOD (ng l^{-1})	Country	Reference
Metoprolol	β-Blocker	200,000,000	nd – 2200	25	Germany	Hirsch *et al.* (1996)
			730[a], 1300[b], 2200[c]	25	Germany	Ternes (1998)
Nadolol	β-Blocker	160,000,000	nd – 290	25	Germany	Hirsch *et al.* (1996)
			25[a], 42[b], 60[c]	25	Germany	Ternes (1998)
Nafcillin	Antibiotic	4000,000,000[e]	Nd	20	Germany	Hirsch *et al.* (1999)
Naproxen	Analgesic	500,000,000	300[a], 420[b], 520[c]	50	Germany	Ternes (1998)
			600[a], 3000[c]	50	Brazil	Stumpf *et al.* (1999)
			+	-	Canada	Rogers *et al.* (1986)
o-Hydroxyhippuric acid	Aspirin metabolite	-	nd	200	Germany	Ternes (1998)
17α-Oestradiol	Hormone	2,000,000	nd - 5	0.1-1.2	Netherlands	Belfroid *et al.* (1999)
17β-Oestradiol	Hormone	2,000,000	nd - 12	0.5-2.4	Netherlands	Belfroid *et al.* (1999)
			nd[a], 2[b], 3[c]	1	German	Ternes *et al.* (1999a)
			6[a], 14[b], 64[c]	1	Canada	Ternes *et al.* (1999a)
Oestrone	Hormone	1,000,000	4.5[a], 47[c]	0.3-1	Netherlands	Belfroid *et al.* (1999)
			9[a], 22[b], 70[c]	1	Germany	Ternes *et al.* (1999a)
			3[a], 10[b], 48[c]	1	Canada	Ternes *et al.* (1999a)
Oxacillin	Antibiotic	2000,000,000	nd	20	Germany	Hirsch *et al.* (1999)
Oxytetracycline	Antibiotic	1000,000,000	nd	50	Germany	Hirsch *et al.* (1999)
Penicillin G	Antibiotic	3600,000,000	nd	20	Germany	Hirsch *et al.* (1999)
Penicillin V	Antibiotic	2000,000,000	nd	20	Germany	Hirsch *et al.* (1999)
Phenazone	Analgesic	3000,000,000	160[a], 300[b], 410[c]	100	Germany	Ternes (1988)
Propanolol	β-Blocker	160,000,000	nd - 290	25	Germany	Hirsch *et al.* (1996)
			730[a], 1300[b], 290[c]	25	Germany	Ternes (1998)
Propylphenazone	Analgesic	3000,000,000	360, 1900	-	Germany	Herberer *et al.* (1998)
Roxithromycin	Antibiotic	300,000,000	680[a], 800[b], 1000[c]	20	Germany	Hirsch *et al.* (1999)
Salbutamol	β_2-Sympathomimetic	12,000,000	nd - 170	25	Germany	Hirsch *et al.* (1996)
			nd[a], 72[b], 170[c]	50	Germany	Ternes (1998)
Salicylic acid	Aspirin metabolite	-	nd[a], 63[b], 140[c]	50	Germany	Ternes (1998)
			39,190-95,620	-	USA	Hignite and Azarnoff (1977)
Sulfamethazine	Antibiotic	4000,000,000	nd	20	Germany	Hirsch *et al.* (1999)
Sulphamethoxazole	Antibiotic	2000,000,000	400[a], 900[b], 2000[c]	20	Germany	Hirsch *et al.* (1999)
Terbutalin	β_2-Sympathomimetic	15,000,000	nd - 120	25	Germany	Hirsch *et al.* (1996)
Tetracycline	Antibiotic	1000,000,000	nd	50	Germany	Hirsch *et al.* (1999)
Timolol	β-Blocker	20,000,000	nd - 70	25	Germany	Hirsch *et al.* (1996)
			nd[a], nd[b], 70[c]	25	Germany	Ternes (1998)

Compound	Therapeutic use	Typical oral therapeutic dose (ng/day)[d]	Concentration detected (ng l^{-1})	LOD (ng l^{-1})	Country	Reference
Tolfenamic acid	Anti-inflammatory	300,000,000	nd	50	Germany	Ternes (1998)
Trimethoprim	Antibiotic	400,000,000	320[a], 620[b], 660[c]	20	Germany	Hirsch *et al.* (1999)

Notes:
nd = not detected
[a] = median
[b] = 90 percentile
[c] = maximum
d = Defined daily doses taken from WHO (1999) unless otherwise stated
e = Typical oral therapuetic dose taken from Martindale (1993)
f = Drug rarely used due to side effects in patients
+ = positive identification

Table B2 Concentrations of human pharmaceuticals detected in surface water

Compound	Therapeutic use	Typical oral therapeutic dose (ng/day)[d]	Concentration detected (ng l^{-1})	LOD (ng/l)	Country	Reference
UK						
Bleomycin	Anti-neoplastic	-	nd-17	5	UK	Aherne *et al.* (1990)
17α-Ethinyloestradiol	Hormone	10,000 – 50, 000	nd	5	UK	Aherne *et al.* (1985)
			2-15	1	UK	Aherne and Briggs (1989)
Methotrexate	Anti-neoplastic	-	nd	6.25	UK	Aherne *et al.* (1990)
Norethisterone	Hormone	5,000,000	nd - 17	10	UK	Aherne *et al.* (1985)
			nd - 10	2	UK	Aherne and Briggs (1989)
Progesterone	Hormone	300,000,000	nd - 6	5	UK	Aherne *et al.* (1995)
Sulphamethoxazole	Antibiotic	2000,000,000	~ 1000	-	UK	Watts *et al.* (1983)
Tetracycline	Antibiotic	1000,000,000	~ 1000	-	UK	Watts *et al.* (1983)
Theophylline	Antiasthma	240,000,000	~ 1000	-	UK	Watts *et al.* (1983)
Other countries						
Acetaminophen (paracetamol)	Analgesic	2000,000,000	nd	150	Germany	Ternes (1998)
Acetylsalicylic acid (aspirin)	Analgesic	1200,000,000	nd	500	Germany	Stan and Heberer (1997)
			nd	-	Germany	Stumpf *et al.* (1996)
			nd[a] 160[b], 340[c]	20	Germany	Ternes (1998)
Betaxolol	β-Blocker	20, 000,000	nd - 28	3	Germany	Hirsch *et al.* (1996)
			nd[a], nd[b], 28[c]	10	Germany	Ternes (1998)
Bezafibrate	Lipid regulator	600,000,000	380	-	Germany	Stan and Heberer (1997)
			nd - 380	25	Germany	Stumpf *et al.* (1996)
			350[a], 1200[b], 3100[c]	25	Germany	Ternes (1998)
			100[a], 250[c]	-	Germany	Stumpf *et al.* (1998)
			190[c]	10	Brazil	Stumpf *et al.* (1999)
Bisoprolol	β-Blocker	10,000,000	nd - 124	3	Germany	Hirsch *et al.* (1996)
			nd[a], 190[b], 2900[c]	10	Germany	Ternes (1998)
Carazolol	β-Blocker	10,000,000[e]	nd - 124	3	Germany	Hirsch *et al.* (1996)
			nd[a], 100[b], 110[c]	10	Germany	Ternes (1998)
Carbamazepine	Anti-epileptic	1000,000,000	250[a], 820[b], 1100[c]	30	Germany	Ternes (1998)
			+	-	Germany	Franke *et al.* (1995)
Chloramiphenol	Antibiotic	3000,000,000	nd[a], nd[b], 60[c]	20	Germany	Hirsch *et al.* (1999)

Compound	Therapeutic use	Typical oral therapeutic dose (ng/day)[d]	Concentration detected (ng l^{-1})	LOD (ng/l)	Country	Reference
Chlorotetracycline	Antibiotic	1000,000,000	nd	50	Germany	Hirsch *et al.* (1999)
Clarithromycin	Antibiotic	500,000,000	nd[a] 150[b] 260[c]	20	Germany	Hirsch *et al.* (1999)
Clenbuterol	β_2-Sympathomimetic	60,000[e]	nd	-	Germany	Hirsch *et al.* (1996)
			nd[a], nd[b], 50[c]	10	Germany	Ternes (1998)
Clofibrate	Lipid regulator	2000,000,000[f]	nd	30	Germany	Ternes (1998)
Clofibric acid	Lipid regulator metabolite	-	nd - 1750	1	Germany	Stan and Heberer (1997)
			140 - 180	-	Germany	Stan and Heberer (1997)
			nd - -300	1	Germany	Stan and Heberer (1997)
			nd - 90	5	Germany	Stumpf *et al.* (1996)
			nd - 875	-	Germany	Heberer *et al.* (1998)
			66[a], 210[b], 550[c]	10	Germany	Ternes (1998)
			19 - 222	-	Germany	Stan *et al.* (1994)
			nd - 9	-	Switzerland	Buser *et al.* (1998b)
			90[c]	10	Brazil	Stumpf *et al.* (1999)
Cloxacillin	Antibiotic	2000,000,000	nd	20	Germany	Hirsch *et al.* (1999)
Cyclophosphamide	Anti-neoplastic	-	nd	10	Germany	Ternes (1998)
Diazepam	Psychiatric drug	10,000,000	nd	30	Germany	Ternes (1998)
Diclofenac	Analgesic	100,000,000	90	-	Germany	Stan and Heberer (1997)
			nd - 489	5	Germany	Stumpf *et al.* (1996)
			nd - 960	1	Germany	Heberer *et al.* (1998)
			150[a], 800[b], 1200[c]	10	Germany	Ternes (1998)
			200[a], 500[c]	-	Germany	Stumpf *et al.* (1998)
			20[a], 450[c]	10	Brazil	Stumpf *et al.* (1999)
			nd-370	1	Switzerland	Buser *et al.* (1998a)
Dicloxacillin	Antibiotic	2000,000,000	nd	20	Germany	Hirsch *et al.* (1999)
Dimethylaminophenazone	Anti-inflammatory	-[f]	nd[a], nd[b], 340[c]	10	Germany	Ternes (1998)
Doxycycline	Antibiotic	100,000,000	nd	50	Germany	Hirsch *et al.* (1999)
Erythromycin-H_2O	Antibiotic	1000,000,000	150[a], 630[b], 1700[c]	20	Germany	Hirsch *et al.* (1999)
Ethinyloestradiol	Hormone	10,000 - 50,000	nd[a], 4.3[c]	0.1-0.3	Netherlands	Belfroid *et al.* (1999)
			nd	0.5	Germany	Ternes *et al.* (1999a)
Etofibrate	Lipid regulator	900,000,000[e]	nd	30	Germany	Ternes (1998)
Fenofibrate	Lipid regulator	300,000,000[e]	nd - 100	1	Germany	Stan and Heberer (1997)
			nd	10	Germany	Ternes (1998)

Compound	Therapeutic use	Typical oral therapeutic dose (ng/day)[d]	Concentration detected (ng l^{-1})	LOD (ng/l)	Country	Reference
Fenofibric acid	Lipid regulator metabolite	-	50	50	Germany	Stan and Heberer (1997)
			nd - 172	5	Germany	Stumpf *et al.* (1996)
			45[a], 170[b], 280[c]	10	Germany	Ternes (1998)
			30[a], 350[c]	10	Brazil	Stumpf *et al.* (1999)
Fenoprofen	Anti-inflammatory	1200,000,000	nd	50	Germany	Stan and Heberer (1997)
			nd	-	Germany	Stumpf *et al.* (1996)
			nd	10	Germany	Ternes (1998)
Fenoterol	β_2-Sympathomimetic	10,000,000	nd - 8	3	Germany	Hirsch *et al.* (1996)
			nd[a], nd[b], 61[c]	10	Germany	Ternes (1998)
Gemfibrozil	Lipid regulator	1200,000,000	120	-	Germany	Stan and Heberer (1997)
			nd - 190	5	Germany	Stumpf *et al.* (1996)
			52[a], 190[b], 510[c]	10	Germany	Ternes (1998)
			5[a], 250[c]	-	Germany	Stumpf *et al.* (1998)
Gentisic acid	Aspirin metabolite	-	nd[a], 110[b], 1200[c]	75	Germany	Ternes (1998)
Ibuprofen	Analgesic	1200,000,000	140	-	Germany	Stan and Heberer (1997)
			nd - 139	5	Germany	Stumpf *et al.* (1996)
			nd - 280	5	Germany	Heberer *et al.* (1998)
			70[a], 280[b], 530[c]	10	Germany	Ternes (1998)
			190[c]	10	Brazil	Stumpf *et al.* (1999)
Ifosfamide	Anti-neoplastic	-	nd	10	Germany	Ternes (1998)
Indomethacine	Anti-inflammatory	100,000,000	50	-	Germany	Stan and Heberer (1997)
			nd - 121	5	Germany	Stumpf *et al.* (1996)
			40[a], 170[b], 200[c]	10	Germany	Ternes (1998)
Ketoprofen	Anti-inflammatory	150,000,000	nd	50	Germany	Stan and Heberer (1997)
			nd	-	Germany	Stumpf *et al.* (1996)
			nd[a], 120[b], 120[c]	10	Germany	Ternes (1998)
			210[c]	10	Brazil	Stumpf *et al.* (1999)
Medazepam	Sedative	20,000,000	+	-	Germany	Franke *et al.* (1995)
Menstranol	Hormone	10,000 – 50,000	nd	0.5	Germany	Ternes *et al.* (1999a)
Metaclofenamic acid	Anti-inflammatory	400,000,000[e]	nd	10	Germany	Ternes (1998)
Methicillin	Antibiotic	4000,000,000	nd	20	Germany	Hirsch *et al.* (1999)
Metoprolol	β-Blocker	200,000,000	nd - 1540	3	Germany	Hirsch *et al.* (1996)
			45[a], 1200[b], 2200[c]	10	Germany	Ternes (1988)

Compound	Therapeutic use	Typical oral therapeutic dose (ng/day)[d]	Concentration detected (ng l^{-1})	LOD (ng/l)	Country	Reference
Nadolol	β-Blocker	160,000,000	nd - 9	5	Germany	Hirsch *et al.* (1996)
			nd	10	Germany	Ternes (1998)
Nafcillin	Antibiotic	4000,000,000[e]	nd	20	Germany	Hirsch *et al.* (1999)
Naproxen	Analgesic	500,000,000	70[a],150[b], 390[c]	10	Germany	Ternes (1998)
			20[a], 210[c]	10	Brazil	Stumpf *et al.* (1999)
N-methylphenacetin	Phenacetin metabolite	-	+	Not quantified	Germany	Heberer *et al.* (1998)
o-Hydroxyhippuric acid	Aspirin metabolite	-	nd	75	Germany	Ternes (1998)
17α-Oestradiol	Hormone	2,000,000	nd[a], 3	0.1-0.3	Netherlands	Belfroid *et al.* (1999)
17β-Oestradiol	Hormone	2,000,000	nd[a], 5.5	0.3-0.6	Netherlands	Belfroid *et al.* (1999)
			nd	0.5	Germany	Ternes *et al.* (1999a)
Oestrone	Hormone	1,000,000	0.3[a], 3.4[c]	0.2-0.3	Netherlands	Belfroid *et al.* (1999)
			nd[a], 1[b], 1.6[c]	0.5	Germany	Ternes *et al.* (1999a)
Oxacillin	Antibiotic	2000,000,000	nd	20	Germany	Hirsch *et al.* (1999)
Oxytetracycline	Antibiotic	1000,000,000	nd	50	Germany	Hirsch *et al.* (1999)
Penicillin G	Antibiotic	3600,000,000	nd	20	Germany	Hirsch *et al.* (1999)
Penicillin V	Antibiotic	2000,000,000	nd	20	Germany	Hirsch *et al.* (1999)
Phenazone	β-Blocker	3000,000,000	+	Not quantified	Germany	Heberer *et al.* (1998)
			24[a], 150[b], 950[c]	20	Germany	Ternes (1998)
Propanolol	β-Blocker	160,000,000	nd – 98	3	Germany	Hirsch *et al.* (1996)
			12[a], 440[b], 590[c]	5	Germany	Ternes (1998)
Propylphenazone	Analgesic	3000,000,000	nd – 350	5	Germany	Herberer *et al.* (1998)
			+	-	Germany	Franke *et al.* (1995)
Roxithromycin	Antibiotic	300,000,000	nd[a], 200[b], 560[c]	20	Germany	Hirsch *et al.* (1999)
Salbutamol	β_2-Sympathomimetic	12,000,000	Nd	-	Germany	Hirsch *et al.* (1996)
			nd[a], nd[b], 35[c]	10	Germany	Ternes (1998)
Salicylic acid	Aspirin metabolite	-	25[a], 130[b], 4100[c]	10	Germany	Ternes (1998)
Sulfamethazine	Antibiotic	4000,000,000	Nd	20	Germany	Hirsch *et al.* (1999)
Sulphamethoxazole	Antibiotic	2000,000,000	30[a], 140[b], 480[c]	20	Germany	Hirsch *et al.* (1999)
Terbutalin	β_2-Sympathomimetic	15,000,000	nd – 9	3	Germany	Hirsch *et al.* (1996)
			nd	10	Germany	Ternes (1998)
Tetracycline	Antibiotic	1000,000,000	Nd	50	Germany	Hirsch *et al.* (1999)

Compound	Therapeutic use	Typical oral therapeutic dose (ng/day)[d]	Concentration detected (ng l^{-1})	LOD (ng/l)	Country	Reference
Timolol	β-Blocker	20,000,000	nd – 10	3	Germany	Hirsch *et al.* (1996)
			nd[a], nd[b], 10[c]	10	Germany	Ternes (1998)
Tolfenamic acid	Anti-inflammatory	300,000,000	Nd	10	Germany	Ternes (1998)
Trimethoprim	Antibiotic	400,000,000	nd[a], 90[b], 200[c]	20	Germany	Hirsch *et al.* (1999)

Notes:

~ = approximate value
nd = not detected
[a] = median value
[b] = 90 percentile
[c] = maximum value
d = Defined daily doses taken from WHO (1999) unless otherwise stated
e = Typical oral therapuetic dose taken from Martindale (1993)
f = Drug rarely used due to side effects in patients
+ = positive identification

Table B3 Concentrations of human pharmaceuticals in groundwater

Compound	Therapeutic use	Typical oral therapeutic dose (ng/day)[a]	Concentration detected (ng l^{-1})	LOD (ng l^{-1})	Country	Reference
Chloramiphenol	Antibiotic	3000,000,000	nd	20	Germany	Hirsch *et al.* (1999)
Chlorotetracycline	Antibiotic	1000,000,000[b]	nd	50	Germany	Hirsch *et al.* (1999)
Clarithromycin	Antibiotic	500,000,000	nd	20	Germany	Hirsch *et al.* (1999)
Clofibric acid	Lipid regulator metabolites	-	70 - 7300	-	Germany	Heberer *et al.* (1997)
			4000	-	Germany	Heberer and Stan (1997)
Clofibric acid derivative	Metabolite of clofibric acid	-	~ 50 - 2900	-	Germany	Heberer *et al.* (1997)
Cloxacillin	Antibiotic	2000,000,000	nd	20	Germany	Hirsch *et al.* (1999)
Diclofenac	Analgesic	100,000,000	nd - 380	-	Germany	Heberer *et al.* (1997)
Dicloxacillin	Antibiotic	2000,000,000	nd	20	Germany	Hirsch *et al.* (1999)
Doxycycline	Antibiotic	100,000,000	nd	50	Germany	Hirsch *et al.* (1999)
Erythromycin-H_2O	Antibiotic	1000,000,000	nd	20	Germany	Hirsch *et al.* (1999)
Fenofibrate	Lipid regulator	300,000,000b	nd - 45	-	Germany	Heberer *et al.* (1997)
Ibuprofen	Analgesic	12000,000,000	nd - 200	-	Germany	Heberer *et al.* (1997)
Meprobamate	Sedative	1200,000,000	+	-	USA	Eckel *et al.* (1993)
Methicillin	Antibiotic	4000,000,000	nd	50	Germany	Hirsch *et al.* (1999)
Nafcillin	Antibiotic	4000,000,000[b]	nd	20	Germany	Hirsch *et al.* (1999)
N-Methylphenacetin	Metabolite of phenacetin	-	~ nd - 470	5	Germany	Heberer *et al.* (1997)
Oxacillin	Antibiotic	2000,000,000	nd	20	Germany	Hirsch *et al.* (1999)
Oxytetracycline	Antibiotic	1000,000,000	nd	50	Germany	Hirsch *et al.* (1999)
Penicillin G	Antibiotic	3600,000,000	nd	20	Germany	Hirsch *et al.* (1999)
Penicillin V	Antibiotic	2000,000,000	nd	20	Germany	Hirsch *et al.* (1999)
Pentobarbitol	Sedative	60,000,000	+	-	USA	Eckel *et al.* (1993)
Phenazone	Analgesic	3000,000,000	nd - 1250	10	Germany	Heberer *et al.* (1997)
Phensuximide	Anti-convulsant	2000,000,000	+	-	USA	Eckel *et al.* (1993)
Propylphenazone	Analgesic	3000,000,000	nd - 1465	-	Germany	Heberer *et al.* (1997)
Roxithromycin	Antibiotic	300,000,000	nd	20	Germany	Hirsch *et al.* (1999)
Sulfamethazine	Antibiotic	4000,000,000	160	20	Germany	Hirsch *et al.* (1999)

Compound	Therapeutic use	Typical oral therapeutic dose (ng/day)[a]	Concentration detected (ng l^{-1})	LOD (ng l^{-1})	Country	Reference
Sulfamethoxazole	Antibiotic	4000,000,000	470	20	Germnay	Hirsch *et al.* (1999)
Tetracycline	Antibiotic	1000,000,000	nd	50	Germany	Hirsch *et al.* (1999)
Trimethoprim	Antibotic	4000,000,000	nd	20	Germany	Hirsch *et al.* (1999)

Notes:
~ = approximate value
nd = not detected
+ = positive identification
a = Defined daily doses taken from WHO (1999) unless otherwise stated
b = Typical oral therapuetic dose taken from Martindale (1993)
c = Drug rarely used due to side effects in patients

Table B4 Concentration of human pharmaceuticals detected in drinking water

Compound	Therapeutic use	Typical oral therapeutic dose (ng/day)[a]	Concentration detected (ng l^{-1})	LOD (ng l^{-1})	Country	Reference
UK						
Bleomycin	Anti-neoplastic	-	nd - 13	5	UK	Aherne *et al.* (1990)
Caffeine	Psychomotor stimulant		<1000*	1000	UK	Richardson and Bowron (1985)
Clofibric acid	Lipid regulator metabolite	2000,000,000	+	-	UK	Fielding *et al. (*1981)
Diazapam	Psychiatric drug	10,000,000	10	-	UK	Waggott (1981)
Ethinyloestradiol	Hormone	10,000 – 50,000	nd	5	UK	Aherne *et al.* (1985)
			nd - 4	1	UK	Aherne and Briggs (1989)
			nd	0.4	UK	James *et al.* (1997)
Methotrexate	Anti-neoplastic	-	nd	6.25	UK	Aherne *et al.* (1985)
Norethisterone	Hormone	5,000,000	nd	10	UK	Aherne *et al.* (1985)
			nd	2	UK	Aherne and Briggs (1989)
17β-Oestradiol	Hormone	2,000,000	nd	0.2	UK	James *et al.* (1997)
Oestrone	Hormone	1,000,000	nd	0.2	UK	James *et al.* (1997)
Progesterone	Hormone	300,000,000	nd - 6	5	UK	Aherne *et al.* (1985)
Other countries						
Bezafibrate	Lipid regulator	600,000,000	27	-	Germany	Stumpf *et al.* (1996)
Clofibric acid	Lipid regulator metabolite	200,000,000	1, 70 (max)	-	Germany	Stumpf *et al.* (1996)
			10 - 165	-	Germany	Stan *et al.* (1994)
			270	-	Germany	Heberer and Stan (1997)
			nd - 170	1	Germany	Heberer and Stan (1996)
Diclofenac	Analgesic	100,000,000	2, 6 (max)	-	Germany	Stumpf *et al.* (1996)
Ethinyloestradiol	Hormone	10,000 – 50,000	0.83 - 6.4	-	Germany	Rurainski *et al.* (1977)
			0.6	-	Netherlands	Rathner and Sonnenborn (1979)
Ibuprofen	Analgesic	1200,000,000	1, 3 (max)	-	Germany	Stumpf *et al.* (1996)

Notes:

nd = not detected
\+ = positive identification
* = Incorrectly reported in published paper as >1000 ng l^{-1}, likely to be present for reasons other than its use as a pharmaceutical.
a = Defined daily doses taken from WHO (1999) unless otherwise stated

APPENDIX C ENVIRONMENTAL FATE AND BEHAVIOUR

Table C1 Fate of Pharmaceuticals in the environment

Compound	Therapeutic use	Sphere/conditions	Fate	Reference
Acetylsalicylic acid	Analgesic	Activated sludge STW	81% removal	Ternes (1998)
		Sewage treatment	Readily biodegradable	Richardson and Bowron (1985)
Amitriptyline	Antidepressant	Sewage treatment	Non-biodegradable	Richardson and Bowron (1985)
Ampicillin	Antibiotic	Sewage treatment	48% biodegradable	Richardson and Bowron (1985)
Bezafibrate	Lipid regulator	Biological filter STW	27% removal	Stumpf *et al.* (1999)
		Activated sludge STW	50% removal	Stumpf *et al.* (1999)
		Activated sludge STW	83% removal	Ternes (1998)
Betaxolol	β-Blocker	Activated sludge STW	80% removal	Ternes (2000)
Bisoprolol	β-Blocker	Activated sludge STW	65% removal	Ternes (2000)
Caffeine	Psychomotor stimulant	Sewage treatment	Readily biodegradable	Richardson and Bowron (1985)
Carazolol	β-Blocker	Actibated sludge STW	66% removal	Ternes (2000)
Carbamazepine	Anti-epileptic	Activated sludge STW	7% removal	Ternes (1998)
Chlorhexidine	Disinfection	Sewage treatment	Non-degradable	Richardson and Bowron (1985)
Ciprofloxacin	Antibiotic	Closed bottle test	Non-degradable	Kummerer *et al.* (2000)
Clofibrate	Lipid lowering agent	Sewage treatment	Non-degradable	Richardson and Bowron (1985)
Clofibric acid	Lipid regulator metabolite	Biological filter STW	15% removal	Stumpf *et al.* (1999)
		Activated sludge STW	34% removal	Stumpf *et al.* (1999)
		Sewage treatment	<20% removal	Hignite and Azarnoff (1977)
		Activated sludge STW	51% removal	Ternes (1998)
		OECD Guideline 301F	Negative	Henschel *et al.* (1997)
		OECD Guideline 302B	Negative	Steger-Hartman *et al. (*1996)
Codeine phosphate	Narcotic analgesic	Sewage treatment	Non-degradable	Richardson and Bowron (1985)
Cyclophosphamide	Anti-neoplastic	Closed bottle test	Not degradable at 5 mg $^{-1}$ in 57 days	Kümmerer *et al.* (1996)
		Laboratory scale sewage treatment plant	Non-degradable	Steger-Hartmann *et al. (*1996)
		OECD 302B	Non-degradable	Steger-Hartmann *et al.* (1997)
		Laboratory scale sewage treatment plant	Non-degradable	Steger-Hartmann *et al.* (1997)

Compound	Therapeutic use	Sphere/conditions	Fate	Reference
Dextropropoxyphene	Analgesic	Sewage treatment	Non-degradable	Richardson and Bowron (1985)
Diclofenac	Anti-inflammatory	Biological filter STW	9% removal	Stumpf *et al.* (1999)
		Activated sludge STW	75% removal	Stumpf *et al.* (1999)
		Activated sludge STW	69% removal	Ternes (1998)
Dimethylaminophenazone	Anti-inflammatory	Activated sludge STW	38% removal	Ternes (1998)
Ephedrine	Asthma, nasal decongestion	Sewage treatment	Readily degradable after acclimatisation	Richardson and Bowron (1985)
Erythromycin	Antibiotic	Sewage treatment	Non-degradable	Richardson and Bowron (1985)
17α-Ethinylestradiol	Hormone	Activated sludge STW	78% removal	Ternes *et al.* (1999a)
		Biological filter STW	64% removal	Ternes *et al.* (1999a)
Fenofibric acid	Lipid regulator metabolite	Biological filter STW	6% removal	Stumpf *et al.* (1999)
		Activated sludge STW	45% removal	Stumpf *et al.* (1999)
		Activated sludge STW	69% removal	Ternes (1998)
Gemfibrozil	Lipid regulator	Biological filter STW	16% removal	Stumpf *et al.* (1999)
		Activated sludge STW	46% removal	Stumpf *et al.* (1999)
		Activated sludge STW	64% removal	Ternes (1998)
16α-Hydroxyestrone	Hormone	Activated sludge STW	68% removal	Ternes *et al.* (1999a)
Ibuprofen	Analgesic	Biological filter STW	22% removal	Stumpf *et al.* (1999)
		Activated sludge STW	75% removal	Stumpf *et al.* (1999)
		Activated sludge STW	90% removal	Ternes (1998)
		Sewage treatment	Inherently biodegradable	Richardson and Bowron (1985)
Ifosfamide	Anti-neoplastic agent	Laboratory scale sewage treatment plant	Non-degradable	Steger-Hartmann *et al.* (1996) Kümmerer *et al.* (1997)
		OECD Guideline 302B	Non-degradable	Kümmerer *et al.* (1997)
		Closed bottle test	Not degradable at 5 mg $^{-1}$ within 57 days	Kümmerer *et al.* (1996)
Indomethacine	Anti-inflammatory	Biological filter STW	71% removal	Stumpf *et al.* (1999)
		Activated sludge STW	83% removal	Stumpf *et al.* (1999)
		Activated sludge STW	75% removal	Ternes (1998)
Ketoprofen	Anti-inflammatory	Biological filter STW	48% removal	Stumpf *et al.* (1999)
		Activated sludge STW	69% removal	Stumpf *et al.* (1999)
Meprobamate	Hyponotics	Sewage treatment	Non-degradable	Richardson and Bowron (1985)
Methotrexate	Anti-neoplastic	OECD Guideline 301F	Negative	Henschel *et al.* (1997)
Methyldopa	Hypertension	Sewage treatment	Non-degradable	Richardson and Bowron (1985)
Metoprolol	β-Blocker	Activated sludge STW	83% removal	Ternes (1998)

Compound	Therapeutic use	Sphere/conditions	Fate	Reference
Metronidazole	Antiprotozoal, antibiotic	Sewage treatment	Non-degradable	Richardson and Bowron (1985)
		Closed Bottle Test	Non-degradable	Kummerer *et al.* (2000)
Naproxen	Analgesic	Biological filter STW	15% removal	Stumpf *et al.* (1999)
		Activated sludge STW	78% removal	Stumpf *et al.* (1999)
		Activated sludge STW	66% removal	Ternes (1998)
		Sewage treatment	Non-degradable	Richardson and Bowron (1985)
Nicotinamide	Treatment of pellagra	Sewage treatment	Readily degradable	Richardson and Bowron (1985)
17β-Oestradiol	Hormone	Activated sludge STW	99.9% removal	Ternes *et al.* (1999a)
		Biological filter STW	92% removal	Ternes *et al.* (1999a)
		Activated sludge STW	64% removal	Ternes *et al.* (1999a)
Oestrogen and diethylstilbestrol	Hormones	Soil and faeces	Persistent	Gregers and Hansen (1964)
Oestrogen	Hormone	Sewage and lake water	Persistent	Shore *et al.* (1993)
Oestrone	Hormone	Activated sludge STW	83% removal	Ternes *et al.* (1999a)
		Biological filter STW	67% removal	Ternes *et al.* (1999a)
Ofloxacin	Antibiotic	Closed Bottle Test	Non-degradable	Kummerer *et al.* (2000)
Paracetamol	Mild analgesic	OECD Guideline 301F	Positive (57%)	Henschel *et al.* (1997)
		Sewage treatment	Readily degradable after acclimatisation	Richardson and Bowron (1985)
		Activated sludge STW	>99%	Ternes (2000)
Phenazone	Analgesic	Activated sludge STW	33% removal	Ternes (1998)
Propranolol	β-Blocker	Activated sludge STW	96% removal	Ternes (1998)
Salbutamol	β_2-Sympathomimetic	Activated sludge STW	>90% removal	Ternes (20000
Salicylic acid	Aspirin metabolite	Sewage treatment	90% removal	Hignite and Azarnoff (1977)
		OECD Guideline 301F	Positive (94%)	Henschel *et al.* (1997)
Sulpasalazine	Antibiotic	Sewage treatment	Non-biodegradable	Richardson and Bowron (1985)
Sulphamethoxazole	Antibiotic	Sewage treatment	Non-biodegradable	Richardson and Bowron (1985)
Terbutalin	β_2-Sympathomimetic	Activated sludge STW	67% removal	Ternes (2000)
Tetracycline	Antibiotic	Sewage treatment	Non-biodegradable	Richardson and Bowron (1985)
Theobromine	Hypertension	Sewage treatment	Readily degradable after acclimatisation	Richardson and Bowron (1985)

Compound	Therapeutic use	Sphere/conditions	Fate	Reference
Theophlline	Psychomotor stimulant	Sewage treatment	Readily degradable	Richardson and Bowron (1985)
Tolbutamide	Hypoglycaemic agent	Sewage treatment	Non-biodegradable	Richardson and Bowron (1985)

STW = sewage treatment plant
OECD Guideline 301F = manometric respiration test (inherent biodegradability)
OECD Guideline 302 B = Zahn-Wellens/EMPA test (inherent biodegradability)
N.B. Nearly all of the data available refer to the parent drug rather than metabolites, the latter being more likely to occur in sewage

APPENDIX D AQUATIC TOXICITY

Table D1 Aquatic toxicity of pharmaceuticals

Compound	Therapeutic use	Test organisms	Toxic effect	Concentration (mg l^{-1})	Reference
Acetylsalicylic acid	Analgesic	*Daphnia magna*	21 day EC50 (reproduction)	61-68	Stuer-Lauridsen *et al.* (2000)
Ciprofloxacin	Antibotic	*Pseudomonas putida*	EC0 (growth inhibition)	0.01	Kummerer *et al.* (2000)
			EC50 (growth inhibition)	0.08	Kummerer *et al.* (2000)
			EC100 (growth inhibition)	0.320	Kummerer *et al.* (2000)
Clofibrate	Lipid regulator	Algae	EC10 (growth inhibition)	5.4	Kopf (1995)
			EC50 (growth inhibition)	12	Kopf (1995)
		Daphnia magna (water flea)	LC10 (acute test)	17.7	Kopf (1995)
			LC50 (acute test)	28.2	Kopf (1995)
			NOEC (reproduction test)	0.01	Kopf (1995)
			LC10 (reproduction test)	0.0084	Kopf (1995)
			LC50 (reproduction test)	0.106	Kopf (1995)
Clofibric acid	Lipid regulator metabolite	*Scenedesmus subspicatus* (algae)	72 hr EC50 (growth inhibition)	89	Henschel *et al.* (1997)
		Tetrahymena pyriformis (ciliate)	48 hr EC50 (growth inhibition)	175	Henschel *et al.* (1997)
		Daphnia magna (water flea)	EC50 (acute, immobilisation)	106	Henschel *et al.* (1997)
		Vibrio fischeri (bacteria)	30 minute EC50 (luminescence)	100	Henschel *et al.* (1997)
		Bluegill sunfish cells *in vitro*	EC50 (acute, cytotoxicity)	14	Henschel *et al.* (1997)
		Brachydanio rerio (zebra fish) embryos	Mortality	86	Henschel *et al.* (1997)
			Pulse rate	126	
Diazepam	Psychiatric drug	*Daphnia magna* (water flea)	LC50	13.9	Lilius *et al.* (1995)
			LC50	4.3	Calleja *et al.* (1993)
Diethylstilbestrol	Hormone	*Oeddogonium cardiacum* (algae)	LC50	>10	Coats *et al.* (1976)
		Daphnia magna (water flea)	LC50	4	Coats *et al.* (1976)

Compound	Therapeutic use	Test organisms	Toxic effect	Concentration (mg l^{-1})	Reference
		Culex pipiens (mosquito)	LC50	4	Coats *et al.* (1976)
		Physa sp.(snail)	LC50	>10	Coats *et al.* (1976)
		Gambusia affinis (mosquito fish)	LC50	>1	Coats *et al.* (1976)
Diethylstibestrol acetate	Hormone	*Oedogonium cardiacum* (algae)	LC50	>10	Coats *et al.* (1976)
		Daphnia magna (water flea)	LC50	10	Coats *et al.* (1976)
		*Culex pipiens (*mosquito)	LC50	10	Coats *et al.* (1976)
		*Physa sp. (*snail)	LC50	>10	Coats *et al.* (1976)
		Gambusia affinis (mosquito fish)	LC50	>10	Coats *et al.* (1976)
Digoxine		*Daphnia magna*	24 hr EC50	21.2	Stuer-Lauridsen *et al.* (2000)
Estrogen	Hormone	Alfalfa plants	Significantly decreased plant growth	200-2000 nmol	Shore *et al.* (1993)
	Hormone	*Medicago satida*	Increased growth	0.005-0.537	Shore *et al.* (1992)
	Hormone	*Daphnia magna*	48 hr LC50	1.09	Stuer-Lauridesen *et al.* (2000)
17α-Ethinylestradiol	Hormone	*Pseudomonas putida* (bacteria)	Microbial growth inhibition test	>20	Schweinfurth *et al.* (1996)
		Azotobacter beijerincki (bacteria)		>20	
		Aspergillus niger (bacteria)		>20	
		Chaetomium globosum (bacteria)		>20	
		Nostoc ellipsosporum (bacteria)		>20	
		Algae	EC10	0.054	Kopf (1995)
			EC50	0.84	Kopf (1995)
		Daphnia	NOEC (reproduction test)	0.01	Kopf (1995)
			EC10 (reproduction test)	0.0125	Kopf (1995)
			EC50 (reproduction test)	0.105	Kopf (1995)
		Daphnia	EC10 (acute test)	3.2	Kopf (1995)
			EC50 (acute test)	5.7	Kopf (1995)
		Daphnia	48 hr EC50	6.4	Schweinfurth *et al. (*1996)
			NOEC (immobilisation)	3	Schweinfurth *et al.* (1996)
			21 day NOEC (number of offspring)	>0.387	Schweinfurth *et al.* (1996)
			21 day NOEC (immobilisation)	>0.387	Schweinfurth *et al.* (1996)
		Fathead minnow	96 hr EC50	1.6l	Schweinfurth *et al.* (1996)

Compound	Therapeutic use	Test organisms	Toxic effect	Concentration (mg l^{-1})	Reference
		Fathead minnow (larvae)	28 day LOEC (histological changes to kidney/liver)	0.00001	Schweinfurth *et al.* (1996)
			28 day LOEC (decreased growth)	0.0001	Schweinfurth *et al.* (1996)
			28 day LOEC (mortality)	0.001	Schweinfurth *et al.* (1996)
		Fathead minnow (juvenile)	28 day LOEC (histological changes to kidney/liver)	0.00001	Schweinfurth *et al.* (1996)
			28 day LOEC (mortality)	0.001	Schweinfurth *et al.* (1996)
		Fathead minnow (adult)	28 day LOEC (inhibited egg production)	0.00001	Schweinfurth *et al.* (1996)
			28 day LOEC (mortality)	0.001	Schweinfurth *et al.* (1996)
Methotrexate	Anti-neoplastic	*Scenedesmus subspicatus* (algae)	72 hr EC50 (growth inhibition)	260	Henschel *et al.* (1997)
		Tetrahymena pyriformis (ciliate)	48 hr EC50 (growth inhibition)	45	Henschel *et al.* (1997)
		Daphnia magna (water flea)	EC50 (acute, immobilisation)	>1000	Henschel *et al.* (1997)
		Vibrio fischeri (bacteria)	30 minute EC50 (luminescence)	1220	Henschel *et al.* (1997)
		Bluegill sunfish cells *in vitro*	EC50 (acute, cytotoxicity)	3	Henschel *et al.* (1997)
		Brachydanio rerio (zebra fish) embryos	Mortality	85	Henschel *et al.* (1997)
			Pulse rate	142	
Metronidazole	Antibotic	*Pseudomonas putida*	EC0 (growth inhibition)	64	Kummerer *et al.* (2000)
			EC50 (growth inhibition)	>64	Kummerer *et al.* (2000)
			EC100 (growth inhibition)	>64	Kummerer *et al.* (2000)
Mitomycin C and/or Cisplatin in hospital wastewater	Anti-neoplastic	Umu C test (bacteria)	Genotoxic activity	-	Giuliana *et al.* (1996)
Ibuprofen	Analgesic	*Trichphyton rubrum* (dermatophytes)	MIC at pH 5	5-10	Sanyal *et al.* (1993)
		Trichophyton mentagrophytes (dermatophytes)	MIC at pH 5	5-20	Sanyal *et al.* (1993)
		Trichophyton tonsurans (dermatophytes)	MIC at pH 5	20-40	Sanyal *et al.* (1993)

Compound	Therapeutic use	Test organisms	Toxic effect	Concentration (mg l^{-1})	Reference
		Microsporum fulva (dermatophytes)	MIC at pH 5	10-40	Sanyal *et al.* (1993)
		Epidermophytes floccosum (dermatophytes)	MIC at pH 5	20-40	Sanyal *et al.* (1993)
		Candida albicans (pathogenic yeast)	MIC at pH 5	140-160	Sanyal *et al.* (1993)
		Staphylococus aureus (bacteria)	MIC at pH 5	40-80	Sanyal *et al.* (1993)
		Mucor sp	MIC at pH 5	120-140	Sanyal *et al.* (1993)
		Staphylococus aureus (bacteria)	MIC at pH 7 MIC at pH 6	150 50[1]	Elvers and Wright (1995) Elvers and Wright (1995)
		Selenastrum capricornutum (freshwater green algae)	96 hr NEL	> 30	Knoll, BASF (1995)
Ibuprofen		*Skeletonema costatum* (saltwater, diatom)	96 hr EC50	7.1	Knoll, BASF (1995)
		Microtox® (bacteria)	5 minute EC50	12.3	Knoll, BASF (1995)
		Daphnia magna (water flea)	48 hr EC50 NOEC	9.06 to 11.5 ≈ 3	Knoll, BASF (1995)
		Mysidopsis bahia (mysid shrimp)	96 hr NEL NOEC	>100 30	Knoll, BASF (1995)
		Lepomis machrochirus (bluegill sunfish)	96 hr LC50 NOEC	173 10	Knoll, BASF (1995)
		Cyprinodon variegatus (sheepshead minnow)	96 hr NEL	> 300	Knoll, BASF (1995)

Compound	Therapeutic use	Test organisms	Toxic effect	Concentration (mg l^{-1})	Reference
Kanamycin	Antibiotic	Bacteria	Antibiotic resistance developed in environmental samples		Leff *et al.* (1993)
Metronidazol	Antibiotic	*Chlorella sp.* (green algae)	72 hr EC10	2.03	Lanzky and Halling-Sorensen (in press)
		Selenastrum carpricronutum (freshwater green algae)	72 hr EC10	19	
Neomycin	Antibiotic	Bacteria	Antibiotic resistance developed in environmental samples		Leff *et al.* (1993)
Nicotin		*Daphnia magna* (water flea)	LC50	3.7	Lilius *et al.* (1995)
			LC50	5.7	Calleja *et al.* (1993)
Ofloxacin	Antibotic	*Pseudomonas putida*	EC0 (growth inhibition)	<0.01	Kummerer *et al.* (2000)
			EC50 (growth inhibition)	0.01	Kummerer *et al.* (2000)
			EC100 (growth inhibition)	0.04	Kummerer *et al.* (2000)
Paracetamol	Analgesic	*Scenedesmus subspicatus* (algae)	72 hr EC50 (growth inhibition)	134	Henschel *et al.* (1997)
		S. proboscideu	24 hr LC50 (acute toxicity)	29.6	Stuer-Lauridsen *et al.* (2000)
		Tetrahymena pyriformis (ciliate)	48 hr EC50 (growth inhibition)	112	Henschel *et al.* (1997)
		Daphnia magna (water flea)	EC50 (acute, immobilisation)	50	Henschel *et al.* (1997)
		Daphnia magna (water flea)	24 hr EC50	136	Stuer-Lauridsen *et al.* (2000)
		Daphnia magna (water flea)	48 hr EC50	9.2	Stuer-Lauridsen *et al.* (2000)
Paracetamol (cont)		*Vibrio fischeri* (bacteria)	30 minute EC50 (luminescence)	650	Henschel *et al.* (1997
		Bluegill sunfish cells *in vitro*	EC50 (acute, cytotoxicity)	19	Henschel *et al.* (1997)
		Brachydanio rerio (zebra fish) embryos	Mortality	378	Henschel *et al.* (1997)
			Pulse rate	920	
Propanolol HCI	β-Blocker	*Daphnia magna* (water flea)	LC50	17.7	Lilius *et al.* 1995)
			LC50	3.1	Calleja *et al.* (1993)
Salicylic acid	Aspirin metabolite	*Scenedesmus subspicatus* (algae)	72 hr EC50 (growth inhibition)	>100	Henschel *et al.* (1997)
		Tetrahymena pyriformis (ciliate)	48 hr EC50 (growth inhibition)	>100	Henschel *et al.* (1997)

Compound	Therapeutic use	Test organisms	Toxic effect	Concentration (mg l^{-1})	Reference
		Daphnia magna (water flea)	EC50 (acute, immobilisation)	118	Henschel *et al.* (1997))
		Vibrio fischeri (bacteria)	30 minute EC50 (luminescence)	90	Henschel *et al.* (1997)
		Bluegill sunfish cells *in vitro*	EC50 (acute, cytotoxicity)	>500	Henschel *et al.* (1997)
		Brachydanio rerio (zebra fish)	Mortality	37	Henschel *et al.* (1997)
		embryos	Pulse rate	50	

MIC = minimum inhibitory concentration
NOEC = no observed effect concentration

APPENDIX E STW MODELLING

The STW model selected used the fugacity approach to find the partitioning likely during treatment. Fugacity (f, Pa) is shown as:

$$f = \frac{C}{Z} \quad (1)$$

where Z if the fugacity capacity (mol m^{-3} Pa^{-1}) and C is the concentration (mol m^{-3}).

The fugacity capacity of a chemical can then be calculated in different media. For air:

$$Z_a = \frac{1}{RT} \quad (2)$$

where R is the gas constant (8.314 Pa m^3 mol^{-1} K^{-1}) and T is the absolute temperature (K). In water:

$$Z_w = \frac{1}{H} \quad (3)$$

where H is the Henrys law constant. In biomass, assumed to be equivalent to 20% octanol and 80% water:

$$Z_b = 0.2K_{OW}K_w + 0.8K_w \quad (4)$$

where K_{OW} is the octanol water partition coefficient.

The rates of transport are expressed in terms of D (mol h^{-1} Pa^{-1}) the fugacity rate parameter. The rate is therefore defined as Df (mol h^{-1}). Three types of D values are then used, movement of a chemical in the same phase, movement of a chemical between phases and degradation.

Movement in the same phase, due to the flow of water, air or biomass, can be shown as:

$$Df = GC \quad (5)$$

where G is the flow (m^3 h^{-1}). Combining (1) and (5) gives:

$$D = GZ \quad (6)$$

The rate of vaporisation can be expressed as:

$$D_v(f_w - f_a) = \frac{K_v}{A}\left(C_w - \frac{C_a}{K_{aw}}\right) \quad (7)$$

where K is the mass transfer coefficient and A the area (m^2).

Degradation may be defined as:

$$Df = VCk \quad (8)$$

where V is the phase volume (m^3) and k is a first-order rate constant (h^{-1}). Combining (1) and (8) gives:

$$D = VZk \tag{9}$$

The plant selected to run this model is shown in Figure 2.

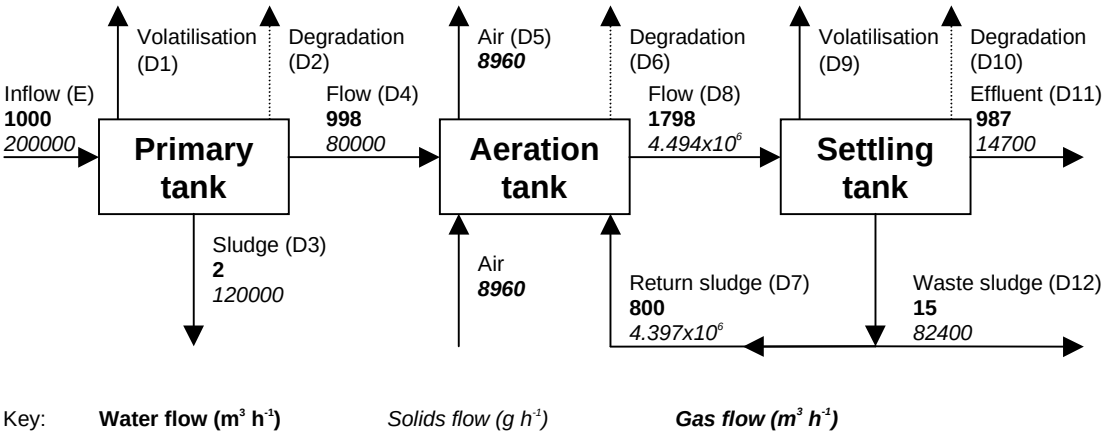

Figure E.2. STW used for fugacity modelling

Using STW can then be described using a number of steady-state mass balance equations. Using the fugacity rate parameters shown above a solution can be obtained for each tank.

For the primary tank, fugacity (f_p):

$$E = f_p(D1 + D2 + D3 + D4) \tag{10}$$

For the aeration tank, fugacity (f_a):

$$D2f_p + D7f_s = f_a(D5 + D6 + D8) \tag{11}$$

For the settling tank, fugacity (f_s):

$$D8f_a = f_s(D7 + D9 + D10 + D11 + D12) \tag{12}$$

These equations can be solved by:

$$f_p = \frac{E}{D1 + D2 + D3 + D4} \tag{13}$$

$$f_a = \frac{D4f_p(D7 + D9 + D10 + D1 + D12)}{D5 + D6 + D8 - (D8 \times D7)} \tag{14}$$

$$f_s = \frac{D8f_p}{D7 + D9 + D10 + D11 + D12} \tag{15}$$

The computer model (The STP or Toronto model) is used to solve this equation for each substance. The model uses QSARs to find the physical chemistry perimeters required. However the calculation of the biodegradability of the molecule by this method is very limited and can produce large errors in the result.

A number of pharmaceuticals, for which STW removal was known were run through the model and the results are shown below.

Compound	Calculated reduction (%)				Measured reduction %)	Reference
	Biodeg'n	Sludge absorption	Volatilization	Total		
Bezafibrate	0.4	42	0.0	42	50	Stumpf *et al.* (1999)
Clofibric acid	0.1	3.2	0.0	3.3	34	Stumpf *et al.* (1999)
					<20	Hignite and Azarnoff (1977)
Diclofenac	0.5	56	0.0	57	75	Stumpf *et al.* (1999)
Fenofibric acid	0.3	30	0.0	30	45	Stumpf *et al.* (1999)
Gemfibrozil	0.6	68	0.0	69	46	Stumpf *et al.* (1999)
Ibuprofen	0.3	28	0.0	29	75	Stumpf *et al.* (1999)
Ifosfamid	0.1	1.8	0.0	1.9	0	Steger-Hartmann *et al.* (1996)
Indomethacine	0.3	21	0.0	21	83	Stumpf *et al.* (1999)
Ketoprofen	0.1	6.7	0.0	6.9	69	Stumpf *et al.* (1999)
Naproxen	0.1	7.4	0.0	7.6	78	Stumpf *et al.* (1999)
Salicylic acid	0.1	2.5	0.0	2.6	90	Hignite and Azarnoff (1977)

No correlation between the model output and the experimental values could be found.

Large errors should be expected because of the difficulty in obtaining accurate analytical data form the experiments and the variations between the STW tested experimentally and the STW in the model.

The only conclusion that can be drawn is that in all cases except two (gemfibrozil and ifosfamid) the model under estimated the removal, possibly due to the low biodegradation figures calculated for each of the compounds being examined.

APPENDIX F AQUATIC RISK ASSESSMENT FOR SELECTED PHARMACEUTICALS IN THE UK

Drug	UK use (t/a)[1]	PEC (μg l^{-1})	PNEC (μg l^{-1})[2]	PEC/PNEC
Paracetamol	**2000**	**367.3**	**9.2**	**39.92**
Aspirin	770	141.4	141	1.00
Metformin	106.1	19.49	101*	0.19
Cimetidine	72	13.22	740	0.02
Ranitidine	69	12.67	582*	0.02
Erythromycin	67.7	12.43	>74	<0.17
Naproxen	60.6	11.13	128	0.09
Dextroproxyphene	**42.5**	**7.81**	**3.79***	**2.06**
Oxytetracycline	**33.7**	**6.19**	**0.23**	**26.8**
Quinine	29.7	5.45	10.1*	0.54
Theophylline	21	3.86	155	0.02
Lithium salts	20.5[3]	0.35 (Li)	4.18 (Li)	0.08
Metronidazole	15.5	2.85	12.5	0.23
Iopromide	11.9	2.19	>92	<0.01
Propanolol	**11.8**	**2.17**	**1.87**	**1.16**
Verapamil	9.9	1.82	5.78*	0.31
Amitiptyline	**5.5**	**1.01**	**0.78**	**1.29**
Tetracycline	4.7	0.86	16	0.05
Omeprazole	3.9	0.72	88	<0.01
Thioridazine	**3.8**	**0.70**	**0.27***	**2.59**
Chloroquine	2.9	0.53	2.72*	0.20
Gabapentin	2.6	0.48	>1100	<0.01
Etidronic acid	2.1	0.39	3	0.13
Fluoxetine	**2**	**0.37**	**0.026***	**14.19**
Phenobartitol	1.7	0.31	484	<0.01
Tramadol	1.7	0.31	64*	<0.01
Clofibrate	1.5	0.28	12	0.02
Paroxetine	1.3	0.24	1.8	0.13
Orphenadrine	1.1	0.20	3.82*	0.05
Diazepam	0.957	0.18	4.3	0.04
Acarbose	0.918	0.17	>1000	<0.01
Isoniazid	0.690	0.13	24.4	<0.01
Nefazodone	0.618	0.11	6.5*	0.02
Quinidine	0.601	0.11	7.2*	0.02
Sumatriptan	0.521	0.1	207*	<0.01
Aminosidin/Neomycin E	0.487	0.09	340*	<0.01
Warfarin	0.476	0.09	12	<0.01
Lansoprazole	0.434	0.08	18	<0.01
Cisapride	0.413	0.08	1000	<0.01

Drug	UK use (t/a)[1]	PEC (µg l^{-1})	PNEC (µg l^{-1})[2]	PEC/PNEC
Chloramphenicol	0.377	0.07	305	<0.01
Famciclovir	0.286	0.05	820	<0.01
Azithromycin	0.276	0.05	120	<0.01
Cetirizine	0.273	0.05	278*	<0.01
Famotidine	0.246	0.05	398	<0.01
Ceftibuten	0.095	0.017	>520	<0.01
Lorsatan	0.087	0.016	331	<0.01
Budesonide	0.081	0.015	>19	<0.01
Finasteride	0.067	0.012	20	<0.01
Perindopril	0.047	0.009	>990*	<0.01
Didanosine	0.039	0.007	>1021	<0.01
Midazolam	0.037	0.007	0.2	0.04
Fluticasone	0.034	0.006	0.48*	0.01
Digoxin	0.031	0.006	24	<0.01
Ethinyl oestradiol	0.029	0.005	0.84	<0.01
Risperidone	0.021	0.004	6	<0.01
Atropine	0.016	0.003	221*	<0.01
Carvedilol	0.008	0.001	1	<0.01
Salmeterol	0.007	0.001	20	<0.01
Bicalutamide	0.007	0.001	>1	<0.01
Alendronic acid	0.007	0.001	0.46*	<0.01
Darzolamide	0.004	0.001	604*	<0.01
Diethylstilbestrol	0.002	<0.001	1.09	<0.01
Paclitaxel	0.001	<0.001	0.74	<0.01
Zalcitabine	<0.001	<0.001	>1790	<0.01
Thiotepa	<0.001	<0.001	>546	<0.01
Flumazenil	<0.001	<0.001	>500	<0.01
Milrinone	<0.001	<0.001	223*	<0.01

Webb (2000)

1. Quoted figures are all assumed to refer to the organic parent molecule (although in some cases, the active will actually be the salt and the values will therefore be overestimates).
2. Asterisk denotes adjustment for molar equivalent of organic parent molecule
3. Includes 16.89 tonnes/annum lithium citrate and 3.54 tonnes/annum lithium carbonate. PEC and PNEC values are adjusted to the lithium ion

The assumption of no human metabolism, passage of all material to drain, no removal during wastewater treatment (via biodegradation, sorption or volatilisation) and no surface water dilution of effluent were used to calculate the PEC. These assumptions are all conservative and considered worst case. The PNEC values were derived using an assessment factor of 1000 with relevant acute data.

For PEC:PNEC ratios >1, further refinements of the PECs which take into account dilution and biodegradation result in PEC:PNEC ratios less than 1 (see Section 7.1)