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Environmental effects of human pharmaceuticals

The presence and risks

AquaSense

Ir. J.G.M. Derksen
Ir. G.M. van Eijnatten
Dr. ir. J. Lahr
P. van der Linde
Drs. ing. A.G.M. Kroon

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Authors

Ir. J. G. M. Derksen (AquaSense)
Ir. G.M. van Eijnatten (AquaSense)
Dr. ir. J. Lahr (AquaSense)
P. van der Linde (AquaSense)
Drs. ing. A.G.M. Kroon (AquaSense)

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Preface

Care for a good quality of drinking water and surface water, as well as recent information received from surrounding countries which indicates that pharmaceuticals are detectable in the environment, let the Association of River Waterworks (RIWA) and the Institute for Inland Water Management and Waste Water Treatment (RIZA) decide to have a literature study carried out on the presence and risks of pharmaceuticals in the environment. Because the emission routes of human pharmaceuticals for one thing, differ from those of veterinary drugs and animal feed additives for another thing, it was decided to publish two separate reports on these subjects.

This report describes the results of a literature study, in which information is gathered about the presence of human pharmaceuticals in surface water, groundwater and drinking water as well as the risks for humans and the aquatic environment that might result from this presence.

The study was carried out by AquaSense research and consultancy agency. Mrs. J.G.M. Derksen was project manager, in which she was guided by Mr. W.F.B. Jülich and Mr. P.G.M. Stoks of RIWA and Mr. G.B.J. Rijs of RIZA.

The draft report was sent to a great number of persons and institutes who gave their comments. These include Mr. J.W. Leenen (Farminform, also on behalf of the branch organizations Bogin and Neprofarm), Mr. M. van der Graaff (Nefarma), Mr. P. Leeuwangh (Ecotox), Mr. M.H.M.M. Montforts (RIVM), Mr. A. Dam (Pharma-chemie) as well as the project group 'Chemical substance studies' from RIWA and the 'Ecotoxicology' group from RIZA.

We express our thanks to the above-mentioned persons for their comments on the draft report, coming from their different points of view. Thanks are also expressed to Farminform and their associated manufacturers of human pharmaceuticals for providing data on consumption of pharmaceuticals in the Netherlands. We would also

like to thank Mr. A. Dam, coordinator 'Environment and Occupational Health & Safety' of Pharmachemie, for his efforts in gathering information on the pharmaceutical industry, cytostatics and ecotoxicology data.

Furthermore our acknowledgement is expressed to Mr. J. Römbke (ECT Oekotoxikologie), Mr. T.A. Ternes (ESWE-Institut für Wasserforschung und Wassertechnologie) and Mr. T. Heberer (Institut für Lebensmittelchemie, TU Berlin) in Germany and Mr. B. Halling-Sørensen (Royal Danish School of Pharmacy, Section of Environmental Chemistry) in Denmark for their inspiration and helpfulness in providing articles and reports.

Summary

Reason

Care for a good quality of drinking water and surface water, as well as recent information received from surrounding countries, which indicates that pharmaceuticals are detectable in the environment, were the reasons the Association of River Waterworks (RIWA) and the Institute for Inland Water Management and Waste Water Treatment (RIZA) decided to have a literature study carried out. This literature study focused solely on the presence of human pharmaceuticals in surface water, groundwater and drinking water and the possible resulting risks for people and the aquatic environment. The reason for limiting this study exclusively to human pharmaceuticals is the expectation that the emission route for human pharmaceuticals to surface water is, from a quantity point of view, much more important than the emission routes for veterinary drugs and animal feed additives to surface water.

Objective and research questions

The most important objective of the literature study was to gain additional insight into the potential problem areas and possible problem substances from the 'human pharmaceuticals' substance group in regard of the drinking water, surface water and groundwater quality in the Netherlands. In the process, the following questions were posed:

1. What is the emission route of human pharmaceuticals to the environment?
2. What concentrations of human pharmaceuticals have been detected in sewage water, surface water, groundwater and drinking water?
3. What are the potential risks of low concentrations of pharmaceuticals in the aquatic environment for human and water

organisms? What is known about the ecotoxicity of human pharmaceuticals?

4. What are the possible problem substances which require priority attention and which selection criteria form the basis for this analysis?
5. What is laid down in the law and regulations with regard to ecotoxicological aspects within the context of human pharmaceuticals being permitted in the European Union and the United States and how is this situation dealt with in the Netherlands?

Emission routes

Human pharmaceuticals can end up in the environment via three sources and emission routes, namely the post-production industrial route, the post-usage domestic route and in the form of unconsumed pharmaceuticals.

As far as the domestic route is concerned, the pharmaceuticals and their metabolites are after use excreted via urine and faeces and are then discharged by households, hospitals and nursing homes in their waste water into the sewer system and treated in a sewage treatment plant. Seen from a quantitative point of view, this diffuse emission route is much more important than the industrial route. In the case of the industrial route, only a small percentage of the pharmaceutical that is produced ends up in the waste water. This percentage is depending on the extent to which the active ingredient is harmful to the environment (and therefore disposed of seperately as chemical waste) and depending on the waste water treatment process that is used. If this waste water is discharged into the sewer system, biological breakdown and adsorption onto the sludge in a sewage treatment plant will take place as in the domestic route. The remaining amount will be discharged into surface water together with the effluent from the sewage treatment plant.

In the Netherlands, 8.3% of the prescribed pharmaceuticals are not consumed. Only 3% of the unconsumed pharmaceuticals ends up in the sewer through disposal by the consumers. The majority of the unused pharmaceuticals are, however, collected separately after they are handed in to pharmacies. One third of the liquid pharmaceuticals handed in to pharmacies still ends up in the sewer.

Diversity of substance groups and their presence in the aquatic environment

Human pharmaceuticals cover a very diverse group of substances. The most important groups of substances that have been analysed and that are described in the literature are:

- Blood lipid regulators and β-blockers (pharmaceuticals used to treat cardiovascular diseases and to treat high blood pressure);
- Antiepileptics (pharmaceuticals for the treatment of epilepsy);

- Analgesics (pain relievers);
- Cytostatics (pharmaceuticals for the treatment of cancer);
- Antibiotics;
- Antidepressants and other psychiatric pharmaceuticals;
- Bronchospasmolytics (pharmaceuticals used to treat asthma and similar ailments);
- Iodinated X-ray contrasting agents.

The group of 'hormonal disrupting substances' is also frequently referred to in the literature. Because this group of pharmaceuticals is dealt with in other contexts it is not included in this study.

Measurement data in public literature mostly concerns measurements in surface water and sewage treatment plant effluent. Almost all the pharmaceuticals investigated are included in these two matrices. In total, measurement data on 85 different active ingredients and 10 different metabolites are reported on in the reviewed literature. This is only an extremely small percentage of the thousands of active ingredients used in human pharmaceuticals.

As expected, the concentrations decrease along the wastewater emission route from households, companies and hospitals as well as the routes travelled by sewage water, sewage treatment plant effluents, surface water, groundwater and drinking water. In surface water, the concentrations of most human pharmaceuticals are between the detection limit and several hundred ng/l, with several substances peaking above the µg/l. These concentrations in the surface water are from the same magnitude as the concentrations of pesticides described in the literature. However, because pharmaceuticals are used all year round, the annual amounts of pharmaceuticals will be higher than those of pesticides. The concentrations of pharmaceuticals detected in rivers are closely related to the amount of sewage treatment plant effluent and the amount of non-purified municipal wastewater that is discharged into those rivers. In influents and effluents from sewage treatment plants, the concentrations of human pharmaceuticals are higher. Human pharmaceuticals are not, or only scarcely, present in drinking water (a few ng/l). In the Netherlands, no pharmaceuticals have been demonstrated as being present in drinking water to date.

Table 0.1 summarises the measurement data. This table shows for each matrix in which concentration class the maximum measured concentration of a pharmaceutical is found. Metabolites are shown in italics.

Table 0.1 Classification of the maximum measured concentrations into concentration classes, per matrix and type of pharmaceutical. Metabolites are shown in italics. STP = sewage treatment plant.

matrix & type of pharmaceutical	maximum >10000 ng/l	maximum >1000 ng/l	maximum >100 ng/l	maximum >10 ng/l	maximum >detection limit	maximum <detection limit
influent STP						
cardiovascular pharmaceuticals		Bezafibrate *Clofibric acid* *Fenofibric acid* Gemfibrozil	Pentoxifylline			
antiepileptics		Carbamazepine	Primidon			
analgesics	Ibuprofen Paracetamol *Salicylic acid*	Acetylsalicylic acid Diclofenac *Gentisic acid*	Indometacine Ketoprofen Naproxen Propyphenazone			
cytostatics		Methotrexate	Cyclophosphamide	Ifosfamide		
other substances		Dihydrocodeine Hydrocodone	Crotamiton Fenoprofen			
effluent STP						
cardiovascular pharmaceuticals		Bezafibrate *Clofibric acid* *Fenofibric acid* Gemfibrozil Metoprolol	Betaxolol Bisoprolol Carazolol Propranolol	Nadolol Timolol		Clofibrate Etofibrate Fenofibrate
antiepileptics		Carbamazepine				
analgesics	*Salicylic acid (1977)*	Acetylsalicylic acid Diclofenac Dihydrocodeine Ibuprofen *Ibuprofen-OH*	*Gentisic acid* *Ibuprofen-COOH* Indometacine Ketoprofen Naproxen Phenazone *Salicylic acid (1998)*			Meclofenamic acid
cytostatics				Bleomycin Cyclophosphamide Ifosfamide		
antibiotics		Erythromycin Roxithromycin Sulfamethoxazole	Chloramphenol Clarithomycin Erythromycin Trimethoprim			Cloxacillin Dicloxacillin Doxycycline Methicillin Nafcillin Oxacillin Oxytetracycline Penicillin G Penicillin V Sulfamethazine Tertracycline
antidepressants						Diazepam
iodinated X-ray contrasting agents	Iopromide	Diatrizoate Iopamidol		Iothalamic acid	Ioxithalamic acid	
other substances		Acetominophen Hydrocodone	Clenbuterol Sulbatamol Terbutalin	Fenoterol		Fenoprofen Tolfenamic acid

Table 0.1 continued.

matrix & type of pharmaceutical	maximum >10000 ng/l	maximum >1000 ng/l	maximum >100 ng/l	maximum >10 ng/l	maximum >detection limit	maximum <detection limit
surface water						
cardiovascular pharmaceuticals		Bezafibrate Bisoprolol *Clofibric acid* Metoprolol	Carazolol Fenofibrate *Fenofibric acid* Gemfibrozil Pentoxifylline Propanolol	Betaxolol Timolol	Clofibrate Nadolol	Etofibrate
antiepileptics		Carbamazepine				
analgesics		Detroproxyphene Diclofenac *Gentisic acid* *Ibuprofen-OH* *Propyphenazone* *Salicylic acid*	Acetylsalicylic acid Ibuprofen Indometacine Naproxen Phenazone	*Ibuprofen-COOH* Ketoprofen		Paracetamol *o-hydroxyhippuric acid*
cytostatics				Bleomycin		Cyclophosphamide Ifosfamide Methotrexate
antibiotics		Erythromycin Tetracycline (1983)	Clarithrymycin Roxithromycin Sulfamethoxazole Trimethoprim	Chloramphenicol		Cloxacillin Dicloxacillin Doxycycline Methicillin Nafcillin Oxacillin Oxytetracycline Penicillin G Penicillin V Tetracycline (1999)
antidepressants					Medazepam	Diazepam
iodinated X-ray constrasting agents	Iopamidol		Diatrizoate Iopromide	Iomeprol Iothalamic acid Ioxithalamic acid		
other substances		Theophylline (1983)		Clenbuterol Fenoterol Salbutamol	Terbutalin	Tolfenamic acid
groundwater						
cardiovascular pharmaceuticals		*Clofibric acid* *Clof. acid derivate*		Fenofibrate		Clofibrate
analgesics		Phenazone	Diclofenac Ibuprofen Propyphenazone			
iodinated X-ray contrasting agents		miscellaneous				

Table 0.1 continued.

matrix & type of pharmaceutical	maximum >10000 ng/l	maximum >1000 ng/l	maximum >100 ng/l	maximum >10 ng/l	maximum >detection limit	maximum <detection limit
drinking water						
cardiovascular pharmaceuticals			*Clofibric acid* Fenofibrate			Betaxolol Bezafibrate Bisoprolol Carazolol Clofibrate Metoprolol Nadolol Propranolol Timolol
antiepileptics						Carbamazepine
analgesics			Acetylsalicylic acid			Diclofenac Ibuprofen Paracetamol *Salicylic acid*
cytostatics				Bleomycin		Ifosfamide Methotrexate
antibiotics						Erythromycin Sulfamethoxazole
antidepressants				Diazepam		
iodinated X-ray contrasting agents				Diatrizoate Iopamidol Iopromide Iothalamic acid		Ioxithalamic acid
other substances						Clenbuterol Fenoterol Salbutamol Terbutalin

Potential risks for people

Based on the knowledge of possible adverse side effects of the use of pharmaceuticals, the expectation is that human health will not be affected due to consumption of drinking water with pharmaceuticals in the concentrations that have been detected. There is an extremely large margin between the maximum therapeutic dosage and the sporadic concentrations shown in drinking water (a factor of 10^6).

Potential risks and ecotoxicity

Continual exposure to low concentrations of pharmaceuticals in surface water may in theory cause the following negative effects on organisms living in the water:

- ecotoxicological effects, which can be assessed by carrying out accepted biological tests such as acute and chronic toxicity tests, genotoxicity tests and carcinogenicity tests;
- effects which are a consequence of the pharmacological influence of the type of pharmaceutical on non-target organisms (for example, influences on the hormone and immune system);

- resistance-development in micro-organisms.

The reviewed literature refers to 456 ecotoxicity data on 76 substances and 6 metabolites. These data relate primarily to acute toxicity tests with a number of standard organisms (bacteria, algae and water fleas). Chronic ecotoxicity data was only found on a limited scale. In practice, however, one should expect water organisms to be exposed to a variety of pharmaceuticals over a lengthy, possibly even life-long, period. This combined influence by a variety of substances at the same time is extremely difficult to estimate. The effects may be additive, but some pharmaceuticals can also have an intensifying or weakening effect on each other.

As a result of the often specific ways in which they function it is also plausible that - as is the case with hormonal disrupting substances - pharmaceuticals can affect non-target (aquatic) organisms pharmacologically according to the therapeutic effect on people. Biological testing methods, which have been specifically developed to demonstrate such effects, with the exception of endocrine disruption effects, are as yet unavailable.

There is very little (publicly accessable) information on the negative effects of pharmaceuticals on, for example, aquatic organisms, and this information relates primarily to acute ecotoxicity data. The conclusion could be that, on the basis of this data, it is not possible to make a well-founded ecotoxicological risk assessment with regard to pharmaceuticals in the (aquatic) environment.

The possible risks posed by the formation of resistant micro-organisms and in particular the transfer of resistance genes from resistant to non-resistant micro-organisms, has been an element of discussion ever since antibiotics have been used. It is not clear what the possible negative consequences on, for example, aquatic organisms might be.

Risk assessment of the substances studied

Unfortunately, it turned out to be impossible to acquire a list of the most consumed pharmaceuticals in the Netherlands. For this reason, on the basis of expected high consumption, degradability, ecotoxicological data, the selection of substances in foreign studies and the availability of data, the following substance groups were selected for further study:

I. Cardiovascular pharmaceuticals
(Blood lipid regulators and β-blockers)

II. Antiepileptics

III. Analgesics

IV. Cytostatics

V. Antibiotics

VI. Antidepressants

VII. Iodinated X-ray contrasting agents

VIII. Pharmaceuticals that have recently been introduced onto the market, such as those used to treat impotence.

From the first five substance groups, twenty-one human pharmaceuticals were selected for particular attention. For these substances worst case calculations of the expected concentrations in brooks, canals and large rivers in the Netherlands have been made on the basis of consumption data. These estimates do not take any account of metabolic degradation in people or adsorption, degradation and evaporation at sewage treatment plants and in the environment. With the exception of the concentrations of Bezafibrate, Clofibrate, Cefalexine and cytostatics in the large rivers, all the calculated environmental concentrations are above the limit value of 0.01 µg/l stated in the most recent draft European directive. A comparison with the actually measured concentrations shows that, in most cases, the measured concentrations are clearly below the worst-case estimate. This applies to both influent of sewage treatment plants and surface waters. Due to lack of information it still remains unclear which metabolites in what concentrations are or might be present in the aquatic environment.

A closer examination of the various substances analysed reveals that too little details are known about most pharmaceuticals to enable a well-founded riks assessment to be made. In particular, there is a lack of chronic and specific toxicity data.

Two substances, namely Clofibric acid (a metabolite of the cardiovascular pharmaceuticals Clofibrate, Etofibrate & Etophyllin clofibrate) and the antiepileptic Carbamazepine are remarkable because high concentrations are shown in almost all matrices. The presence of Clofibric acid, but not Carbamazepine, was also demonstrated in drinking water. Neither substance breaks down easily. There is no or only very limited information about the ecotoxicity of these pharmaceuticals.

Analgesics are widely consumed and therefore high concentrations are found extensively in sewage water, sewage treatment plant effluents and in surface water. However, most analgesics appear to break down easily.

Despite the very low concentrations revealed in surface water, cytostatics certainly need to be looked at due to their specific pharmacological effect mechanisms and due to the fact that some cytostatics are very persistent.

Antibiotics are also present in relatively low concentrations in the aquatic environment. For antibiotics quite a lot of ecotoxicity data is available in public literature. As expected, bacteria and algae are extremely sensitive. The effects can be detected in quantities of just a few µg/l. Some antibiotics from the group of fluoroquinolones appear to be genotoxic.

Practically nothing is known about the presence of antidepressants in the environment. However, ecotoxicological research has been carried out on antidepressants. It appears that the 'Selective Serotonin

Reuptake Inhibitors' (SSRIs) have an effect on the reproduction of mussels at concentrations of just 0.3 µg/l or more.

X-ray contrasting agents that contain iodine are also present in relatively low concentrations in the aquatic environment. These substances have a very low level of biodegradability. Acute toxicological effects were not observed in quantities of up to 10 g/l in tests involving bacteria, algae, water fleas and fish. On the basis of this data, the expectation is that iodinated X-ray contrasting agents will not generate any unacceptable risk for water organisms in the short term. Given that insufficient chronic toxicity data is available (substances have been tested on just one trophic level), no conclusions can be drawn with respect to the possible environmental risks in the longer term.

The introduction of new pharmaceuticals, for example those to treat impotency, has increased the level of attention paid to this type of pharmaceuticals. While usage is expected to increase, practically nothing is known about the possible ecotoxicological effects. However, the fact that such pharmaceuticals affect very general enzymes justifies further research into their possible unintentional effects on non-target organisms.

Legislation

Several European guidelines state that, in principle, only registered pharmaceuticals may be used. In order to obtain (an extension of) registration, a whole series of investigations is required, in which particular attention has to be paid to the substance's effectiveness and any adverse side effects on people. Registrations can be regulated centrally for the EU or on a decentralised basis by one or more countries. Any consideration of environmental aspects would, in the case of central authorisation, have to take place via the European Agency for the Evaluation of Medicinal Products (EMEA) as commissioned by the Committee of Proprietary Medicinal Products (CPMP). In the Netherlands, substances are evaluated and approved by the College ter Beoordeling van Geneesmiddelen (Medicines Evaluation Board).

To date there are no official guidelines within the EU on the possible environmental risks of human pharmaceuticals. In 1994, a provisional draft directive (EU directive III/5504/94) was drawn up which detailed how the first phase of the environmental risk assessment should be elaborated. The EU withdraw this directive, however, before it took effect due to information received from the US - which later turned out to be true - that the US directives were to become less strict. Since 1999, the EU has been working together with the European Federation of Pharmaceutical Industries Associations (EFPIA) on a directive on the assessment of the environmental risks. This directive requires a calculation of the predicted environmental concentration (PEC; in surface water) on base of data on the expected use and the physical / chemical characteristics of the pharmaceutical. If available, data on the biodegradation may also be included. Ecotoxicological data are not

required for this environmental exposure assessment. If the calculated concentration in surface water exceeds a certain limit value (0.01 µg/l) a crude environmental effect analysis will be necessary. If the calculated concentration is lower than this limit value no additional ecotoxicological information is necessary. The crude environmental effect analysis involves a Predicted No Effect Concentration (PNEC) being calculated on base of acute toxicity divided by an uncertainty factor of 1000. If the PEC/PNEC ratio is greater than 1, an additional environmental effect analysis will be required. During this follow-up phase, a more detailed estimate of the expected concentration in various environmental compartments must be made and extra ecotoxicological data about the active substance and the most important metabolites must be submitted. The calculation in Phase I must be carried out for both the emitted substance and important metabolites (formed for >20 % in humans).

As already mentioned, the limit value for further investigation is stated in the most recent EU draft directive as being a 'Predicted Environmental Concentration' (PEC) of 0.01 µg/l in surface water. In the previous version (Draft 4) of this draft directive dated 1994, this limit value was a factor 10 lower (0.001 µg/l). The draft directives assume that in the case of concentrations under the proposed limit values no negative effects are to be expected for water organisms. The question is whether this assumption is justifiable for pharmaceuticals with their specific effect mechanisms. Similarly to substances with an hormonal disrupting effect, such as Ethinyloestradiol, it is plausible that due to specific pharmaceutical effects, water organisms could be harmed even at very low concentrations. The question is also whether the proposed limit value is meaningful when using on only acute toxicity data for determining the potential risks for water organisms which are exposed to (very) low concentrations of a cocktail of pharmaceuticals over a long period of time (perhaps even throughout their lives).

In the United States, there is an official directive issued by the Food and Drug Administration (FDA) on environment aspects at registration of pharmaceuticals. This directive also stipulates that a calculation has to be made of the expected environmental concentration. The procedure to be followed for the calculation and additional research in the event that the limit value is exceeded, is elaborated in much more detail than in European legislation. The American directives are, however, much less strict than the provisional European directives. For example, the estimated concentration in the water to which is discharged (estimated environmental concentration at point of entry) may not exceed 1 µg/l. Assuming a dilution factor of 10 to surface water, for example, this is equivalent to 0.1 µg/l. This is ten times higher than the limit value proposed in the most recent EU draft directive.

Conclusions

- The use of human pharmaceuticals results in contamination of the surface water and groundwater and incidental of drinking water. In surface water, the maximum measured concentrations of human

pharmaceuticals are between the detection limit and several hundreds ng/l, with several substances peaking above the µg/l. In influents and effluents from sewage treatment plants, the concentrations are higher. Human pharmaceuticals are not or sporadic present in drinking water (a few ng/l).

- High concentrations of the antiepileptic Carbamazepine and Clofibric acid, i.e. a metabolite of several fibrates, are present in almost all matrices. The presence of Clofibric acid, but not Carbamazepine, was also demonstrated in drinking water.

- On the basis of the usually very low concentrations of human pharmaceuticals in drinking water and the known adverse side effects of the use of pharmaceuticals, the expectation is that consumption of drinking water will not affect human health. There is an extremely large margin between the maximum therapeutic dosage and the sporadic concentrations shown in drinking water (factor of 10^6).

- Aquatic organisms in the surface water will be exposed to (very) low concentrations of several human pharmaceuticals as well as metabolites over a long period of time, possibly throughout their lives.

- There is still too little (public) information available on the presence and the possible effects of low concentrations of human pharmaceuticals and their resulting metabolites in the water environment to enable a well-founded estimate of the risks for the water environment.

- This lack of knowledge concerning the presence in the aquatic environment and chronic and specific toxicity of the initial substances and their metabolites, but above all the possible specific pharmacological effect of pharmaceuticals on non-target organisms, justifies further investigation of the possible negative effects on water organisms caused by human pharmaceuticals.

- The usual acute toxicity tests are expected to be unsuitable for the detection of potential chronic and specific effects on water organisms as a result of the release of human pharmaceuticals into the (aquatic) environment. A more realistic estimate of the possible environmental risks can perhaps be given by means of chronic (toxicity) tests although these tests as yet are also insufficiently specific to provide definitive answers about working mechanisms. In addition to tests, which have been specially developed for endocrine disruption, biological tests for other specific working mechanisms are not yet available.

- The registration policy with regard to human pharmaceuticals in the Netherlands and the EU only regulates the possible side effects and negative effects on humans. No legal basis yet exists and there are no official guidelines for determining the possible risks for the (aquatic) environment resulting from the use of human pharmaceuticals. Within the EU, work is currently being carried out on a draft directive. However, the expected effectiveness of this

draft directive is questionable as far as the protection of the (aquatic) environment is concerned. In the initial phase, an estimate of the concentration of human pharmaceuticals in the (aquatic) environment would be sufficient. If the expected environmental concentration is below a certain limiting value, no ecotoxicological information will have to be submitted by law. It is not inconceivable that even low concentrations of pharmaceuticals may have a negative effect on non-target (water) organisms exactly due to their specific working mechanisms.

- The knowledge related to the environmental risks of the various human pharmaceutical substance groups can be summarised as follows:

type of pharmaceutical	consumption	concentration in surface water	biodegradability	availability ecotoxicological data
blood lipid regulators/β-blockers	+[1]	+	-	a, b[2]
antiepileptics	+	+	-	a, b
analgesics	++	-	+	a, b
cytostatics	--	--	--	a, c
antibiotics	+	-	-	a, b, c
antidepressants	?	?	?	D
iodinated X-ray contrast media	?	++	--	a, b

1 ++ = very high, + = high, - = low and -- = very low
2 a = acute toxicity, b = chronic toxicity, c = genotoxicity, d = specific pharmacological effect

- This literature study provides a good insight into the potential problem areas and possible problematic substances for the water environment within the substance group 'human pharmaceuticals', but does not provide any answer to the question of which substances actually constitute a problem and which ones require priority attention.

Recommendations for follow-up

With regard to the future, the following ecotoxicological, policy and research-technical recommendations would help to gain a better overview of the potential side effects of the use of human pharmaceuticals on the aquatic environment, or at least help to focus attention on potential side effects.

- Prioritisation of problem substances

  Considering a lack of ecotoxicological data, potential problem substances will, in the first instance, have to be selected on the basis of the consumption of pharmaceuticals in the Netherlands. This should not only involve the substances themselves but also their

most important metabolites. Possible points of departure may be the substances reported on in the international literature and the information regarding possible side effects for people in the event of long-term use that is issued when the pharmaceuticals are authorised. Efforts to establish links with internationally selected substances may have the negative consequence of the focus remaining on the same substances all the time without any insight being created into the (environmental) relevance of these substances with regard to other human pharmaceuticals used but not yet researched in the Netherlands. The side effects for people referred to may, in some cases, only provide an indication of the possible relevance for the (aquatic) environment. A worst-case exposure assessment may serve as a first step for a general assessment of the risks. This would provide a basis for a more detailed elaboration of the risk assessment on the basis of metabolic degradation in people, biological degradation and adsorption and evaporation in a sewage treatment plant or from surface water.

- Chemical monitoring.

  When in a worst-case estimate for a pharmaceutical an exposure concentration is calculated which is greater than the detection limit of the analysis method, a chemical measurement campaign can provide additional insight into the actual concentrations which occur in the various matrices of sewage water, sewage treatment plant effluent, surface water, groundwater and drinking water.

- Generic risk analysis for the aquatic environment.

  The measured concentrations of pharmaceuticals will be combined with ecotoxicological measurement data to provide an indication of the environmental risk. The ecotoxicological research should, however, link up with the period of exposure in the environment and the time required for the effect to become noticeable. Because water organisms in surface water will be continuously exposed to (very) low concentrations of various pharmaceuticals, chronic (toxicity) tests would appear to be the most suitable. A combination of a number of chronic toxicity tests will allow a wide-spectrum risk analysis to be carried out that is independent of the specific effect mechanisms of the various pharmaceuticals.

- Specific risk analysis for the aquatic environment.

  Due to the often very specific pharmacological effect mechanisms of pharmaceuticals, it is conceivable that possible specific effects will occur even at very low concentrations. A possible risk analysis should be explicitly linked to the type of effect mechanism of a group of pharmaceuticals, as for example the effect on the hormone or immune system. Such biological testing methods are currently not, or only partially, available. It is recommended that an assessment is made of which specific pharmacological effect mechanisms can affect aquatic organisms and that specific biological test methods are developed which can be used in the future when screening the active substances and their metabolites. These newly developed testing methods can also be used in

the future for the biological monitoring of aquatic systems in addition to the collection of chemical data.

- Resistance development.

  It is also desirable that attention is paid to the consequences of low concentrations of antibiotics on water organisms, such as resistance development.

- International co-operation.

  Considering the complexity of a suitable method for assessing the risk pharmaceuticals pose to water organisms, as well as the comparable character of investigations and research requests in the countries around us, international co-operation and fine-tuning within the EU would obviously be a good idea. The international results could be used in the future in the further elaboration of a definitive European directive for the environmental risk assessment in relation to human pharmaceutical authorisation.

1 Introduction

The task of water companies and water quality managers is to safeguard a good quality of the drinking water and/or surface water. Attention is also given here to substance groups which, due to usage in high quantities, might be present in the form of micropollutants. In general, very little is known about the actual occurrence AND possible risks of micropollutants. One of the possible groups of micropollutants is pharmaceuticals. Pharmaceuticals are excreted by humans and animals in their urine or faeces and in this way may end up in the environment via various routes.

Only very recently any attention has been focused on the presence of pharmaceuticals in the environment. In the past, studies on pharmaceuticals were nearly exclusively focused on the effectiveness of the substance, on human metabolism and possible side-effects and on interactions with other pharmaceuticals. The environmental consequences of the use of pharmaceuticals and their fate in the environment were ignored for a long time. The result of this is that there is no, or only very limited information on the occurrence, breakdown and possible effect on the environment for many substances. In Germany, the country that is most active in the area of measuring concentrations of pharmaceuticals in the environment, about 2900 pharmaceuticals have been authorised according to the 'Red List' (Rote Liste, 1996). Of these, no more than 2% have been investigated for their presence in the environment (Ternes, 1998a). According to Kümmerer (Kümmerer, 2000), 50,000 pharmaceuticals were authorised up to 1990, of which 90% of the consumption volume can be attributed to 2700 pharmaceuticals. These 2700 pharmaceuticals contain 900 active substances. Among others from the point of view of care for a good water quality, the possible effects of pharmaceuticals on the environment are given increasingly more attention by researchers.

In 1997, sponsored by RIWA[1], an inventory study on the presence and risks of pharmaceuticals in drinking water, groundwater and surface water and the possible consequences for the treatment of drinking water was carried out (Derksen & de Poorter, 1997). In this study, pharmaceuticals referred to human pharmaceuticals, veterinary drugs and medicinal animal feed additives. The study focused principally on the Rhine and Meuse basins in the Netherlands and Belgium. This study demonstrated that so far very little was actually known about the presence of pharmaceuticals in the environment AND about the possible risks of low concentrations (ng/l up to a few µg/l) of pharmaceuticals to humans and the environment.

After the completion of this project, the interest in the subject increased significantly, among others as a consequence of additional measurement results in Germany. These measurements demonstrated that most of the pharmaceuticals studied could be detected in sewage treatment plant effluent in concentrations ranging from ng/l up to a few µg/l. A number of pharmaceuticals could also be detected in low concentrations (ng/l level) in surface water and a single pharmaceutical could even be detected in drinking water, although in very low concentrations (a few ng/l). Partly based on these results, the effort to measure pharmaceuticals in surface water, groundwater and drinking water has increased considerably in the past two years. Reason enough for RIWA to have a follow-up study carried out on the presence and the possible risks of human pharmaceuticals (for motivation of the restriction to human pharmaceuticals, see section 2.1).

Meanwhile, RIZA has also demonstrated interest in studying the presence and risks of pharmaceuticals in surface water. The angle of approach of RIZA is care for the quality of surface water, including possible negative effects on nature in the surface water on the short and on the long term.

Both projects have been combined into one joint project. The most important objective for both institutes is to obtain more insight into possible problem substances for the Netherlands. On the basis of measurement data and/or concentration estimates, it can be determined which substances a future (measurement) effort could best be focused on. This principal objective and a number of sub objectives can be described with the following research questions:

1. What is the legislation with regard to ecotoxicological aspects for authorisation of human pharmaceuticals? This question will be restricted to the legislation in the Netherlands, the European Union and the United States.
2. What is the fate of human pharmaceuticals in the aquatic environment?
3. What concentrations of human pharmaceuticals have been detected in sewage water, surface water and groundwater?

[1] The RIWA Substance studies project group is having studies done on substance groups which could be of interest or important from the perspective of drinking water.

4. What methods of analysis can be used to measure low concentrations of human pharmaceuticals in sewage water, surface water and groundwater?
5. What are the possible problem substances on which an eventual measurement effort should be focused? The determination of possible problem substances will be supported by estimates of concentrations in the Netherlands on the basis of consumption data.
6. What is known about the ecotoxicity of human pharmaceuticals?
7. What are the risks of low concentrations of pharmaceuticals in surface water and groundwater for humans and the environment?

The data have been collected by consulting staff members of relevant institutions, by reviewing literature and by searching the Internet.

Chapter 2 first of all will discuss a number of general aspects of human pharmaceuticals, such as the type of substances, their use, the fate in the environment and the legislation with regard to environmental aspects of human pharmaceuticals. Chapter 3 presents a summary of concentrations measured in different studies and the analysis methods used. Chapter 4 indicates the selection of the substances for which consumption data were requested. Based on the consumption data, an estimate was made of the concentrations to be expected in sewage treatment plant influent and in the surface water in the Netherlands. Possible effects of human pharmaceuticals (and especially of the selected substances) in surface water, groundwater and drinking water on humans and the environment are discussed in chapter 5. Chapter 6 presents the conclusions and recommendations.

2 General aspects

In this chapter a number of aspects of the use of human pharmaceuticals which could be important regarding the presence and the possible risks of pharmaceuticals in surface water, groundwater and drinking water will be discussed. After giving a motivation for the limitation of the study, the type of substances and their use, possible sources and fate in the environment and the legislation with respect to environmental aspects of human pharmaceuticals will be discussed consecutively.

2.1 Motivation for limiting the study to human pharmaceuticals

From the earlier mentioned preliminary study (Derksen & de Poorter, 1997), which focused on the presence and risks of human pharmaceuticals, veterinary drugs and medicinal animal feed additives in surface water, groundwater and drinking water, it appeared that human pharmaceuticals were the quantitatively most important source of pharmaceuticals towards the surface water. After excretion in urine and faeces, human pharmaceuticals are discharged into the surface water via the sewer water and treatment in a sewage treatment plant. The most important emission route of veterinary drugs and animal feed additives is via manure that is spread over the soil, either after having been temporarily stored or not. Emission to the surface water occurs via surface runoff, flushing and/or seepage of contaminated groundwater. These concentrations of veterinary medicines in the surface water are expected to be generally lower than those of human pharmaceuticals. Therefore, this study is limited to human pharmaceuticals.

One substance group on which many studies have been carried out consists of substances with an hormonal effect (estrogens), including

17α-ethinyloestradiol, a component of the contraceptive pill. Since this substance group was discussed extensively in the publications of the Health Council (1999), Belfroid *et al.* (2000) and Vethaak *et al.* (2000), it will not be taken into consideration in this study.

2.2 Types of pharmaceuticals and their use

Human pharmaceuticals comprise a very diverse group of substances. The largest portion consists of organic substances, from simple ones to complex ones. In addition, there are many substances based on salts. An impression of the diversity of substances can be obtained by examining the structural formulas in supplement 1.

In a general sense, a pharmaceutical consists of an active substance (usually in a low concentration, but sometimes in concentrations up to 50%), mixed with a number of auxiliary substances to make it possible to handle and dose the pharmaceutical. These auxiliary substances are, for example, lactose, cellulose, vaseline, syrup, sugars, sorbitol, taste additives, etc. (van der Meer *et al.*, 1992). When this report refers to a pharmaceutical it means the active substance.

Active substances can be processed into a large number of formulations, meaning a combination of administration form (tablet, capsule, syrup, injection fluid, salve, etc.) and concentration of the active substance.

In the Medicines Act it is laid down that only registered pharmaceuticals may be used. A separate registration is necessary for each formulation. A whole series of tests precede the registration of a medication, in which the activity and toxicity to humans and animals are given special attention.

Every quarter, the Medicines Evaluation Board (College ter Beoordeling van Geneesmiddelen: CBG) provides a list of all pharmaceutical products which are authorised to be traded in the Netherlands. At the moment, about 12,000 formulations have been authorised (CBG, 1999). On the basis of an estimate from the Repertorium 98/99 (Nefarma, 1999) about 850 active substances are involved (not including vitamins, vaccines, herbs and homeopathic substances).

The use of pharmaceuticals can be divided into three categories: a) pharmaceuticals which can only be obtained by prescription, b) pharmaceuticals which can obtained exclusively from a pharmacy and c) pharmaceuticals for home treatment (over the counter substances).

The most important users of human pharmaceuticals are hospitals, health care and infirmaries and private households.

Data on production, sales and use of pharmaceuticals are kept updated by:

- IMS Health
  This is a worldwide organisation which collects, processes and

analyses very detailed data on the pharmaceutical industry. The pharmaceutical industry provides data on sales and production to IMS Health and receives them in return in a processed and analysed form. These data are used by the pharmaceutical industry for developping market strategies, among other things. In principle the IMS Health data are not available to third parties.

- Foundation for Pharmaceutical Statistics (Stichting Farmaceutische Kengetallen: SFK)
  SFK collects detailed data on the use of pharmaceuticals in the Netherlands. It receives its information directly from a pharmacy panel, in which 850 of the total 1,547 public pharmacies are associated.
- Statistics Netherlands (Centraal Bureau voor de Statistiek: CBS)
  CBS regularly carries out studies on the Dutch population, including studies on the use of pharmaceuticals.

The above-mentioned organisations primarily express their data in guilders and/or number of prescriptions. For the concentration of a pharmaceutical in surface water, groundwater and drinking water and its possible risks, the important factor is not so much the number of prescriptions but rather the quantity of *active substance* being used annually. These data are calculated by the IMS Health company, but are in principle not available to third parties. However, in this study, in co-operation with Farminform (the company that provides IMS Health in the Netherlands with its data) and the involved manufacturers, insight was obtained into the use of active substances of a number of pharmaceuticals (see chapter 4).

A number of characterisations of the use of pharmaceuticals in the Netherlands will be discussed below. The top 10 of the most frequently prescribed substances are listed in table 2.1. In table 2.2. the number of prescriptions is subdivided according to anatomy, while in table 2.3 the results of an interview carried out by CBS on the use of pharmaceuticals by the Dutch population are summarised. It involves a regularly taken Health survey. In this survey, a representative random sample of the population[2] is asked whether they used any pharmaceuticals in the 14 days previous to the interview and if so, which ones. In this case, a differentiation was made between prescribed and non-prescribed pharmaceuticals.

It appears from tables 2.2 and 2.3 that most prescribed pharmaceuticals affect the central nervous system (pain relievers, sleeping pills, antidepressants and so on), the heart and vascular system (mainly antihypertensives) and the gastrointestinal system (to treat a bloated feeling, nausea, excessive gastric acid, diarrhoea, constipation and diabetes).

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[2] With exception of the population in institutions and residential treatment centres (nursing homes, infirmaries, institutions for the handicapped, boarding schools, jails, etc.).

Table 2.3 also demonstrates that one third of the Dutch population uses pharmaceuticals prescribed by the doctor. A little less than a third of the population uses non-prescribed pharmaceuticals.

Table 2.1 Top ten of the pharmaceuticals most prescribed in the Netherlands in 1997 (SFK, 1998).

	Medication	**type**	**form**	**prescriptions (millions)**
1	Paracetamol[1]	analgesic	tablet 500 mg	2.3
2	Oxazepam	tranquilizer	tablet 10 mg	2.2
3	Diclofenac-sodium	analgesic, antirheumatic	tablet 50 mg	1.2
4	Acetylsalicylic acid[1]	analgesic, blood diluent	tablet 80 mg	1.2
5	Ethinyloestradiol/ levonorgestrel	contraconceptive	coated tablet	1.2
6	Temazepam	sleeping pill	capsule 10 mg	1.2
7	Furosemide	diuretic	tablet 40 mg	1.1
8	Doxycyline	antibiotic	tablet 100 mg	1.0
9	Omeprazol	gastric antacid	capsule 20 mg	1.0
10	Temazepam	sleeping pill	capsule 20 mg	0.8

1 The majority of these pharmaceuticals are sold without prescription.

Table 2.2 Summary of the use of pharmaceuticals in 1997, subdivided according to anatomy, as a percentage of the number of prescriptions (SFK, 1998).

	anatomy	**%**	**pharmaceuticals are used as or to treat**
1	central nervous system	21.1	pain relievers, sleeping pills, antidepressants, etc.
2	heart and vascular system	15.8	blood pressure regulating pharmaceuticals, among others
3	gastrointestinal system	11.1	excessive gastric acid, among others
4	respiration system	9.7	asthma, chronic pulmonary diseases, among others
5	dermatological	7.3	skin diseases
6	urogenital system and sexual hormones	6.8	diseases of the bladder, kidneys, sexual organs and contraconception
7	skeletal muscle system	6.6	rheumatism, muscle relaxation, among others
8	systematic antimicrobial substances	6.4	infections
9	blood and blood producing organs	4.9	blood diluents, anaemia, among others
10	sensory organs	3.9	eye salve, ear infection, among others
11	others	6.4	

Table 2.3 Use of pharmaceuticals in the Netherlands in 1995/1996. Data based on the Health survey, taken by CBS, in which a random sample of the population was asked about their use of medication in the two weeks prior to the interview. The use of parmaceuticals is expressed in % of the users in two weeks, unless mentioned otherwise (CBS, 1997).

type	prescribed	non-prescribed
total number of users of pharmaceuticals in the two weeks prior to the interview	5.1 million	4.5 million
(converted to the total population of the Netherlands)		
use of medication in the two weeks prior to the interview, classified by type of medication		
pain relievers and fever reducers such as aspirin	6.7	70.0
pharmaceuticals to treat coughing, colds, flu, sore throat, etc.	5.5	11.8
preventative pharmaceuticals such as vitamins, minerals, tonics	3.8	10.2
pharmaceuticals to treat the heart, blood vessels or hypertension	30.1	0.1
diuratics (pills to stimulate urination)	6.6	-
Laxatives	1.1	0.4
pharmaceuticals for gastrointestinal disorders, digestives	9.7	1.9
sleeping pills and sedatives, psychiatric drugs	11.7	1.4
antibiotics	6.2	-
pharmaceuticals to treat the skin (for acne, eczema, itching, dandruff, wounds)	9.7	1.3
pharmaceuticals to treat rheumatism and pain in the joints	7.9	1.0
pharmaceuticals to treat allergy	6.5	-
pharmaceuticals to treat asthma	8.5	-
hormones	3.3	-
pharmaceuticals to treat diabetes	5.4	-
pharmaceuticals to treat eye diseases	3.6	-
homeopathic substances	-	7.9
other pharmaceuticals	20.7	3.7
type of pharmaceutical unknown	2.1	0.6

2.3 Sources and emission routes

Three sources and emission routes can be indicated for contamination of the environment by human pharmaceuticals:

1. The industrial route
   Waste water and solid waste emitted in the production of pharmaceuticals;
2. The domestic route
   Pharmaceuticals and their metabolites are secreted in urine and faeces during use and thus end up in the environment via waste water from households, hospitals, health care centres and nursing homes;
3. The route of unconsumed pharmaceuticals.

These emission routes and their associated sources will be discussed separately in sections 2.3.1 through 2.3.3. The most important route, namely discharge via a sewage treatment plant, is presented in figure 2.1.

2.3.1 The industrial route

The total chemical waste flow in the Netherlands was 950,000 tonnes in 1990. The production of cosmetics and pharmaceuticals contributed 1,500 tonnes to this annually (1.5% including package). The waste arising from production of pharmaceuticals (active substance, solid and liquid) is collected carefully. If possible, active substances are recovered as much as possible, due to the damage they may cause to the environment and/or because they are worth a lot of money. The residue is disposed of to waste incinerators as hazardous waste.

The quantity of pharmaceuticals that is discharged in the sewer by a manufacturer is low in comparison to other industries (Richardson & Bowron, 1985). The experience is that in batch productions about 0.2% of the active substance is discharged per batch with the flushing water (Oranjewoud, 1999). Depending on the hazard category of the active substance, the first flushing water will not be discharged, but collected and disposed of in a different manner. The waste water from the consecutive flushings is usually discharged into the sewer, either after pre-treatment or not. Some of the contamination is degradated in the sewage treatment plant, some of it will end up in the sewage sludge and some is discharged to the surface water. The fate depends a great deal on the adsorption properties of the substance and the extent to which it degradates in water.

Next, the treated sewage water is discharged to the surface water. Surface water can be used for drinking water production, either after staying some time in a retention basin or not. Again, some of the substances will be removed during the treatment process for drinking water production.

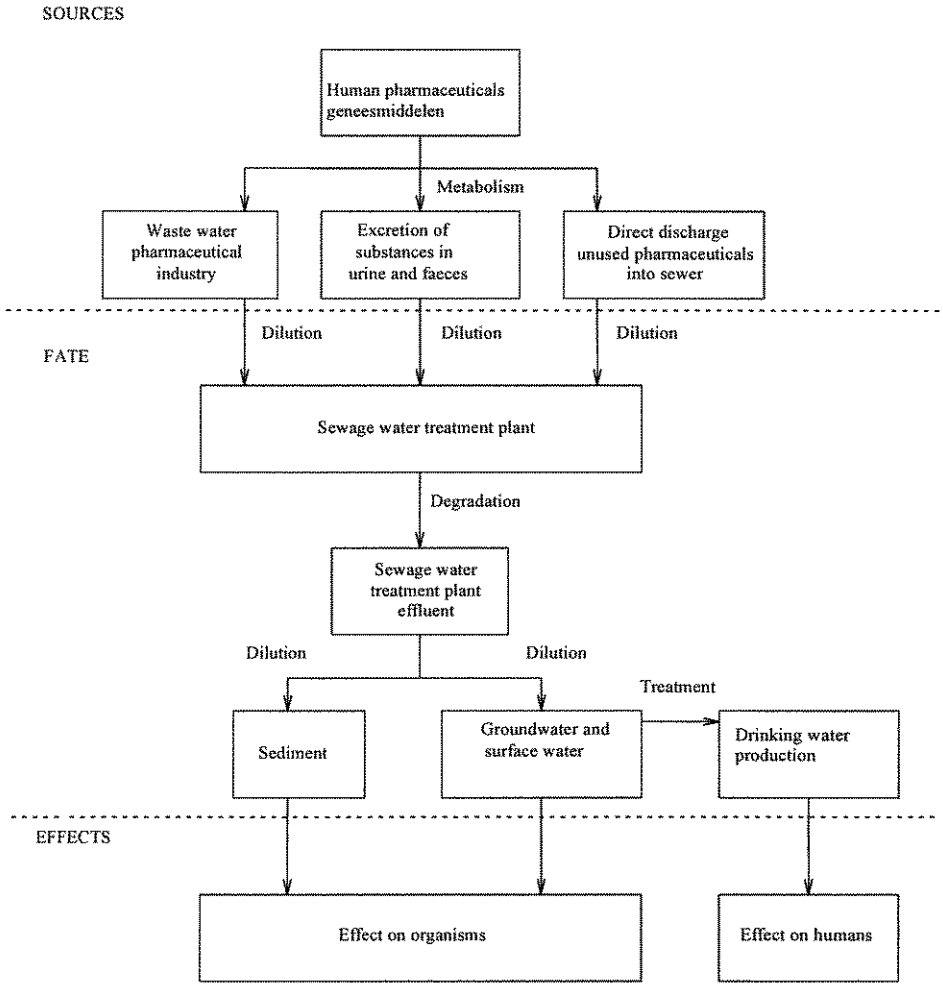


Figure 2.1 The most important sources and emission routes of human pharmaceuticals in the environment.

For many pharmaceuticals it is improbable that they will survive the sewage treatment plant, the period in the surface water and the retention basin as well as the treatment process to produce drinking water as the original substance (Richardson & Bowron, 1985). However, in targeted measurements, a number of pharmaceuticals (Acetylsalicylic acid, Bleomycin, Clofibric acid, Diazepam and Fenofibrate, see supplement 4) could be detected in drinking water. Moreover, it must be realised that until now only a very limited number of pharmaceuticals have been studied as to their presence in surface water and drinking water.

2.3.2 The domestic route

From a quantitative perspective the diffuse emission via the domestic route is much more important than the industrial route (Richardson &

Bowron, 1985; Stumph *et al.*, 1996; Halling-Sørensen *et al.*, 1998; Seel, 1998). However, reduction of the diffuse contamination by domestic use is much more difficult than reducing the emission in the production of pharmaceuticals.

After having been administered, pharmaceuticals can either be directly excreted via urine or faeces (mainly hydrophilic substances) or are metabolised (mainly polar and lipophilic substances). Metabolism of a pharmaceutical in the body usually consists of two phases: one phase in which the substance is oxidised, reduced or hydrolysed and a second phase in which the metabolites formed in the first phase are linked to a several low-molecular substances available in the body itself. The latter process is called conjugation. The conjugated substances are often biologically re-activated in the sewage system and/or sewage treatment plant. Examples of conjugation are sulfidation, glucuronidation, methylation or acetylation. Conjugation usually makes the substance more water-soluble and causes easier excretion. Most pharmaceuticals are inactivated by metabolism, but there are also pharmaceuticals that are not active unless they are metabolised. Some metabolites are more toxic than the original substance.

The manner in which the pharmaceutical is administered has a great deal of effect on the absorption in the body and the metabolism of the pharmaceutical. Differentiation can be made, among other things, in oral administration in the form of pills or potions, intravenous administration (injected in the vein), intramuscular administration (injected in the muscle) and subcutaneous administration (injected under the skin) (Grahame-Smith & Aronson, 1992). In oral administration, a (sometimes considerable) portion of the pharmaceutical is not absorbed and is excreted into the faeces unchanged. The portion that is absorbed will disperse in the body, where the pharmaceutical can be metabolised.

Eventually, the pharmaceutical and its metabolites are excreted via faeces and/or urine and thus end up in the sewage water, where its fate is comparable with the pharmaceuticals which are discharged via the industrial route.

2.3.3 Unconsumed pharmaceuticals

Pharmaceuticals do not contain substances from the so-called 'black list' exceeding the concentrations which are listed in the Decision on Indication of Hazardous Waste Substances (Besluit Aanwijzing Gevaarlijke Afvalstoffen: BAGA). Residues of pharmaceuticals are therefore, on base of the hazard they pose to the environment, not considered to be domestic chemical waste. From the perspective of public health however, they are collected through the circuit of domestic chemical waste, in order to promote safe disposal (van der Meer *et al.*, 1992).

In a study by Blom *et al.* (1995), commissioned by, among others, the pharmaceutical industry it was demonstrated that 83% of the prescribed

pharmaceuticals in the Netherlands is not used. No data have been published about the over the counter pharmaceuticals. Table 2.4 indicates what happens to unused prescribed pharmaceuticals.

Pharmaceutical waste that is collected via the municipal disposal channels such as Domestic Chemical Waste (Klein Chemisch Afval: KCA) and waste from pharmaceutical wholesaler's is incinerated in waste incinerator installations. It is estimated that 260 tonnes per year of solid pharmaceuticals (including packaging material) is returned via the pharmacies to the wholesaler and then incinerated. This is 3% of the total amount of pharmaceuticals produced.

Table 2.4 shows that a major portion of the unused prescribed pharmaceuticals are returned to the pharmacy or collected through KCA channels and disposed of through an incinerator installation. Some of it is used for landfill and some ends up in the sewer. It does not become clear from Blom *et al.* (1995) how large portion of the liquid pharmaceuticals is returned.

Table 2.4 What happens to unused prescribed pharmaceuticals in the Netherlands (Blom *et al.*, 1995). Percentages refer to weight percentages, in which the package is included.

route of unused pharmaceuticals	**% of total sold**	**% of unused pharma-ceuticals**		**% of total returns to pharmacy**	**% of total returns to pharmacy**
returned to pharmacies	4.8	58	of which removed via:		
				solid	liquid
			municipal collection	39	33
			sewer	-	31
			wholesale	62	9
			unknown	-	27
municipal domestic chemical waste	1.3	16			
garbage bag	0.7	9			
sewer	0.3	3			
unknown	1.2	14			
total	*8.3*	*100*		*100*	*100*

2.4 Legislation with regard to environmental aspects of pharmaceuticals

A summary and introduction to European legislation and regulations with regard to pharmaceuticals is provided by Blasius & Cranz (1998). Ecotoxicological aspects of pharmaceuticals come up for discussion

when authorising new substances, extending authorisation of existing substances or authorising new formulations of substances already authorised. The legislation with regard to ecotoxicological aspects for the European Union and the United States will be explained below. For a more detailed explanation of the legal framework concerning ecotoxicological aspects for authorisation of human pharmaceuticals we refer to Römbke *et al.* (1996) and Gärtner (1998).

For further legislation with regard protection of the environment, it can be stated in general that no specific standards exist for the presence of human pharmaceuticals in surface water, groundwater and/or drinking water. Because such a complex group of substances is involved and because the emission into the environment is of a diffuse nature, these types of standards are not to be expected in the near future either.

Because of this, no specific discharge requirements for the pharmaceutical category were set by the Coordinating Committee for the Implementation of the Pollution of Surface Waters Act (Coördinatiecommissie Uitvoering Wet Verontreiniging Oppervlaktewateren: CUWVO). However, procedures were imposed in order to limit emissions as much as possible by 'good housekeeping' (for example separate collection of cytostatics). Emission standards for the pharmaceutical industry exist in the form of discharge requirements for the industry laid down in WVO discharge permits.

Formally (according to the law), pharmaceutical residues are not considered as Domestic Chemical Waste (KCA), but from an environmental protection perspective the goal is to collect them as KCA anyway and/or have them handed back to pharmacies (see section 2.3.3).

2.4.1 Environmental aspects of authorising pharmaceuticals in the European Union and the Netherlands

The basis for the European regulations in the area of pharmaceuticals is directive 65/65/EWG, supplemented by directive 93/39/EG (art. 4.6) and directive 75/318/EWG. It is laid down in these directives that in principle only registered pharmaceuticals may be authorised. For (extension of) registration a whole serie of studies is necessary, in which the effectivity of the substance and the toxicity to humans receives the most attention. For which types of pharmaceuticals and under what conditions registration is necessary is indicated in Blasius & Cranz (1998).

Consideration of the environmental aspects of the centralised authorisation of pharmaceuticals in Europe is in the hands of the European Medications Evaluation Agency (EMEA). EMEA is an umbrella organisation that is engaged in all aspects of the authorisation of human and veterinary pharmaceuticals and constitutes the secretariat for the Committee of Proprietary Medicinal Products (CPMP), among other things. For further information, see Blasius & Cranz (1998).

In addition to centralised authorisation, pharmaceuticals can also be authorised in only one or more countries, in which case a request for authorisation must be handed in for every country separately (decentralised authorisation). Consideration of the environmental aspects for the decentralised method in the Netherlands is in hands of the Medicines Evaluation Board (CBG).

To date, there are *no official* directives in the EU with respect to the possible environmental risks of human pharmaceuticals. The limited physical and chemical data which must be provided in the dossier for authorisation of a pharmaceutical, such as water solubility, vapour pressure, distribution coefficient, pH value, octanol/water coefficient and degradability provide some insight into the possible fate of a substance in the environment and with that the possible environmental compartments where effects could take place.

In addition, the European Committee of Proprietary Medicinal Products (CPMP) has in the past worked on draft directives, in which a procedure for determining the possible environmental risks of human pharmaceuticals has been elaborated. The procedure for the risk assessment in the draft directive comes down to an estimate of ecotoxicological risks in two phases. Phase 1 is described in EU directive III/5504/94 (European Commission, 1994). This draft directive (Draft 4) is included in supplement 2. Until recently Draft 4 was the latest draft version of the directive which was distributed to the public. This directive was intended to go into effect on January 1th, 1995, but was withdrawn before that time because reports were received from the United States that the directives there were going to be less strict, which did indeed happen. The directive for Phase II, EU directive III/5505/94, which was intended for both human and veterinary pharmaceuticals, was also withdrawn in expectation of more clarity about the requirements that had to be met by the environmental risk assessment for authorisation of human pharmaceuticals.

A request from the European Federation of Pharmaceutical Industries' Associations (EFPIA) is on the table to put an end to this unclear situation and to adopt the FDA directive from the United States (see section 2.4.2). Since 1999, partially as a result of this request, work has started again on a directive for determining risks to the environment. This has recently led to discussion paper CPMP/SWP/4447/00 from EMEA that was circulated for comments (EMEA, 2001). This draft directive, ('Risk assessment of non-genetically modified organism containing medicinal products for human use') has also been included in supplement 2.

The procedure for the risk assessment in the above-mentioned draft directives is limited in the first instance to calculating the concentration to be expected in the surface water. This calculation must be made for the original substance as well as for the important metabolites (> 20% formed in humans). The calculation is based on data on the expected use and physical/chemical properties of the active components. In addition, data on the degradation under environmental conditions are also included if they are known. In this exposure calculation ('environmental exposure assessment') ecotoxicological data are not necessary. If the calculated concentration exceeds a certain limit value,

a crude ecotoxicological risk assessment is necessary. The limit value for no hazard is, for the most recent draft directive, at a PEC of 0.01 µg/l[3] in surface water. If the calculated concentration exceeds this limit value, a crude ecotoxicological risk assessment ('crude environmental effect analysis') must be carried out. A PNEC is calculated in this case based on acute toxicity divided by an uncertainty factor of 1000. If the PEC/PNEC ratio is larger than 1, an additional, detailed ecotoxicological risk assessment is required. In this follow-up phase, a more detailed estimate of the expected concentration in various environmental compartments must be made and additional ecotoxicological data of the active substance and the most important metabolites must be submitted. The ecotoxicological requested information may differ significantly for each active substance.

The basic assumption of the draft directive is that concentrations lower than the proposed limit values are no longer expected to present any negative effects for water and soil organisms. The question is whether this assumption is correct for the pharmaceutical substance group with its specific effect mechanisms. Just as for substances with an hormonal disrupting effect, such as Ethinyloestradiol, it can be assumed that pharmaceuticals could cause harmful effects in water organisms even at very low concentrations due to their specific pharmacological mechanisms. The question is also whether the proposed limit value, based on only acute toxicity tests, is meaningful for determining potential risks to water organisms that are exposed to (very) low concentrations of several pharmaceuticals for a long time (possibly lifelong).

For calculating of the concentrations of human pharmaceuticals in surface water and for a crude risk assessment in other compartments, contact is sought with the EU directive for veterinary pharmaceuticals EMEA/CVMP/055/95 ('Environmental Risk Assessment for Veterinary Medicinal Products other than GMO-containing and Immunological Products').

Pharmaceuticals containing substances which have been synthesised by genetically modified organisms pose a special risk. A special directive exists for these substances: Environmental risk assessment for human medicinal products containing or consisting of GMOs (III/5507/94).

2.4.2 Environmental aspects for authorisation of pharmaceuticals in the United States

The legal basis for the protection of the environment in the United States is laid down in the National Environmental Policy Act (NEPA) of 1969. This Act stipulates that weighing the environmental aspects for authorisation of pharmaceuticals is in the hands of the Food and Drug Administration (FDA). FDA regulations stipulate that:

[3] In Draft 4 of the draft directive this limit value was still 0.001 µg/l.

"Environmental Assessments (EAs) must be submitted as part of certain new drug applications (NDAs), abbreviated applications, applications for marketing approval of a biologic product, supplements to such applications, investigational new drug applications (INDs) and for various other actions, unless the action qualifies for categorical exclusion."

A handbook for implementing EAs is provided in the 'Guidance for industry. Environmental assessment of human drug and biologics applications' (FDA, 1998). This handbook is included in supplement 3. Among other topics, the following subjects are covered in the handbook:

- What categories of pharmaceuticals are subject to categorical exclusion from the EA obligation;
- When an EA is required;
- What an EA consists of;
- Information about the environmental problems which human pharmaceuticals and biological products may cause;
- What test methods must be used.

Categories of pharmaceuticals excluded form the obligation of an EA are:

- New submission of already registered pharmaceuticals for which approval of the submission does not lead to an increase of the use of the active substance, and for which an EA has been submitted in the past;
- A new submission of already registered pharmaceuticals for which approval of the submission will lead to an increase in use of the active substance, but the estimated concentration of effluent of a sewage treatment plant ('estimated environmental concentration at point of entry') does not exceed 1 µg/l. Assuming a dilution factor of 10, for example, for the transition from effluent to surface water, this corresponds with 0.1 µg/l. Thus, this limit value is 10 times the value in the draft EU directive;
- Substances which occur naturally, provided approval of the submission does not significantly change the concentration or distribution of the substance and its metabolites or degradation products in the environment;
- 'Investigational new drug applications' (INDs);
- Submission for approval for trading biological products of for transfusion appropriate human blood, blood components or plasma.

An EA is necessary unless the intended action is included in the categorical exclusions listed above. However, if special conditions indicate that the intended action could affect the quality of the human environment, an EA is necessary anyway. This is the case, for example, when there is an increase in the use of the active substance (for instance at a higher dose or longer period of administration), if the estimated concentration of a pharmaceutical at its point of entry to the surface

water is higher than 1 µg/l, or for substances that are suspected of being capable of affecting the environment directly or indirectly in the expected concentrations.

In addition to a number of general matters, such as a description of the pharmaceutical and its formulation, an EA must provide insight into the (expected) fate of the pharmaceutical in the environment, the possible effects, measures to prevent any negative effects the pharmaceutical may have on the environment and possible alternatives to the pharmaceutical. A step-wise approach is recommended for testing the fate and effects (see figure 2.2).

It may be concluded that the American legislation with regard to including environmental risks in authorisation of human pharmaceuticals is more advanced in comparison with the European legislation. However, the American directives are much less strict than the provisional European directives. In practise, only very few pharmaceuticals will exceed the limit value for additional ecotoxicological studies, according to FDA's Kearns in an interview with Science News. Therefore, the FDA decided in 1999 that the manufacturers may supply less extensive information. This situation is experienced by the US Environmental Protection Agency as undesirable.

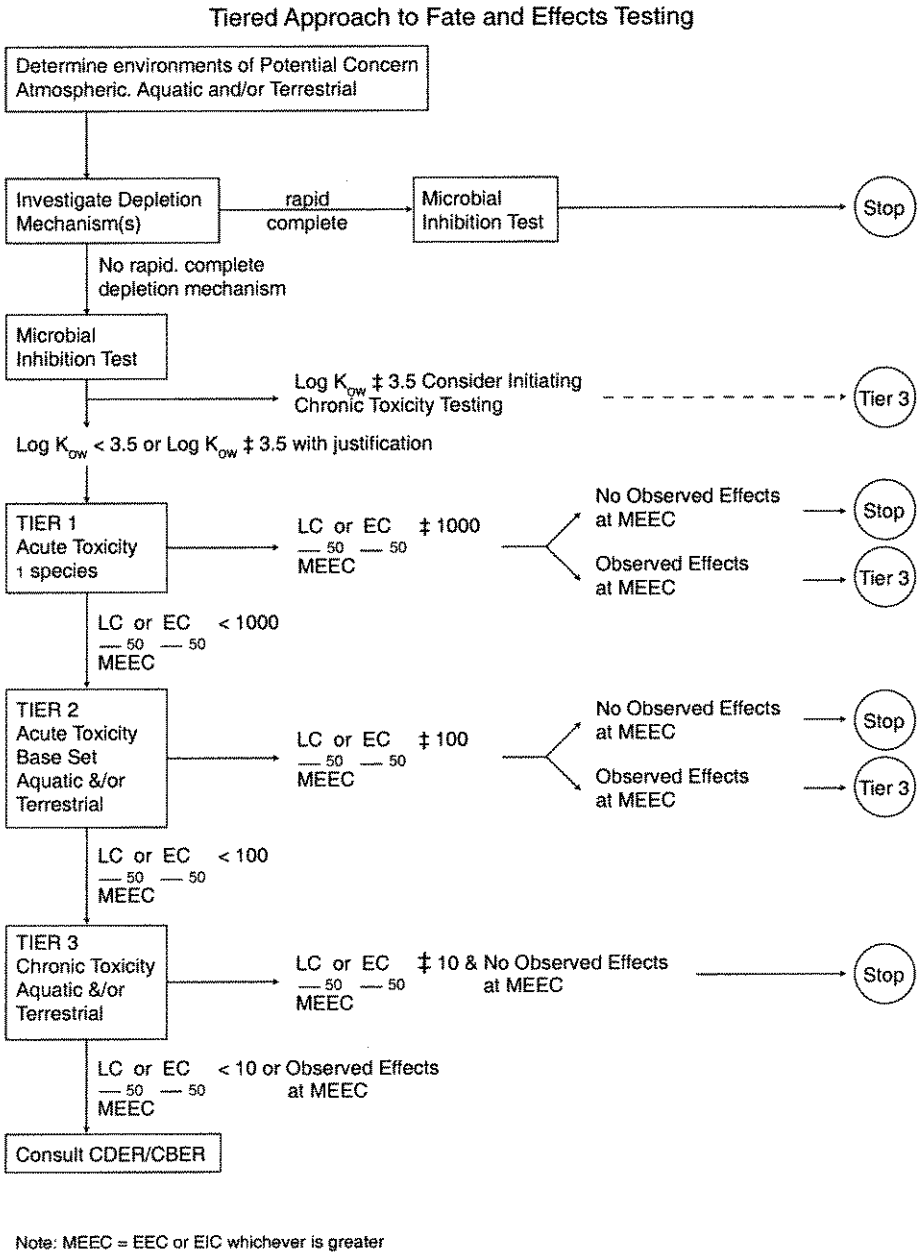


Figure 2.2 Step-wise approach for determining the fate and effects of human pharmaceuticals on the environment (FDA, 1998). The results of such studies must be supplied by the manufacturer with a request for authorisation in the United States. Explanation of the abbreviations used: EIC = Expected Introduction Concentration (introduction into the environment via a sewage treatment plant); EEC = Expected Environmental Concentration (sometimes also called the Predicted Environmental Concentration (PEC); MEEC = Maximum Expected Environmental Concentration; CDER = Centre for Drug Evaluation and Research; CBER = Centre for Biologics Evaluation and Research.

3 Measurement data and analysis methods

This chapter provides a summary of concentrations measured from various studies and the analysis methods used. Section 3.3 discusses the removal of pharmaceuticals from sewer water and during drinking water production.

3.1 Measuring pharmaceuticals

There are a number of research groups in Europe which have been very active in the past few years in the area of measuring human pharmaceuticals in the aquatic environment and drinking water. The most important research groups are (more or less in chronological order of when they started studying pharmaceuticals):

- ESWE-Institut für Wasserforschung und Wassertechnologie GmbH, Wiesbaden, Germany.
  Studies on many different pharmaceuticals, including blood lipid regulators, β-blockers, bronchospasmolytics, antirheumatics, analgesics (pain relievers), antibiotics and iodinated X-ray contrasting agents in different matrices including influents and effluents of sewage treatment plants, surface water, bank filtrates and drinking water.
- Technologiezentrum wasser (TZW), Internationale Arbeitsgemeinschaft der Wasserwerke im Rheineinzugsgebiet (IAWR) and Arbeitsgemeinschaft Rhein-Wasserwerke (AWR).
  Measurements of various pharmaceuticals, including blood lipid regulators, analgesics, Clofibric acid and Carbamazepine in the river Rhine.

- Institut für Lebensmittelchemie, Technische Universität Berlin, Germany.
  Studies on various pharmaceuticals, especially polar substances, in various matrices.
- Institute of Environmental Medicine and Hospital Epidemiology, Freiburg, Germany.
  Mainly studies on the occurrence of cytostatics, antibiotics and iodinated X-ray contrasting agents and their capacity to break down.
- Research Laboratories, Schering AG, Berlin, Germany.
  Studies on iodinated X-ray contrasting agents.
- Swiss Federal Research Station, Wädenswil, Switzerland.
  Studies on Clofibric acid in Swiss lakes and the North Sea and on Diclofenac in rivers and lakes.
- Swiss Federal Institute for Environmental Science and Technology (EAWAG), Dübendorf, Switzerland.
  Studies on antibiotics (macrolids and sulfonamides), among others, in sewer water and surface water.
- Royal School of Pharmacy, Copenhagen, Denmark.
  Studies on concentrations, action and ecotoxicity of mainly veterinary pharmaceuticals, but also of human pharmaceuticals.
- RIWA, VEWIN and KIWA, the Netherlands.
  Studies on the occurrence of a few human pharmaceuticals in the Netherlands and Belgium.

In addition to the measurement efforts made, six extensive literature reviews about environmental aspects of human (and veterinary) pharmaceuticals were conducted, in which, among others, summaries of measurement data are presented. These are (in chronological order):

- Richardson & Bowron (1985)
  First demonstration that pharmaceuticals occurred in sewage treatment plant effluent.
- Römbke *et al.* (1996)
  Very extensive study of the literature on effects on the environment of human and veterinary pharmaceuticals in the environment.
- Derksen & de Poorter (1996)
  Inventory literature study on the presence and the risk of human and veterinary pharmaceuticals in the aquatic environment.
- Halling-Sørensen *et al.* (1998)
  Extensive review article on human and veterinary pharmaceuticals in the environment.
- Daughton & Ternes (1999)
  Extensive summarising review article on pharmaceuticals and 'Personal Care Products' in the environment.
- Ayscough *et al.* (2000)
  English review on human pharmaceuticals in the environment.

The studies by Römbke *et al.* (1996) and Derksen & de Poorter (1996) were also, as a result of a question from the Dutch Consumer Union and by commission of the Inspection Environmental Hygiene (Inspectie milieuhygiëne), summarised and provided with commentary in a RIVM report by Vlaardingen & Montforts (1999).

In addition, there were three symposiums on human (and veterinary) pharmaceuticals in the environment:

- Arzneimittel in Gewässern. Risiko für Mensch, Tier und Umwelt 4. June 1998, Landesmuseum Wiesbaden. Organised by: Hessische Ministerium für Umwelt, Energie, Jugend, Familie und Gesundheit; Wirtschaftsförderung Hessen Investitionsbank AG; Wasser Agentur Hessen & Hessische Landesanstalt für Umwelt. (Toussaint, 1998).
- Pharmaceuticals in the Environment. March 9, 2000, Hotel Sofitel, Brussels. Organised by the Technological Institute, Section on Environmental Technology (TI KVIV), Belgium.
- DIA Workshop on Environmental Risk Assessment of Non-GMO Pharmaceuticals. February 12-13, 2001, Copthorne Tara Hotel, London. Organised by the Drug Information Association, Switzerland.

Two Special Issues, devoted to pharmaceuticals in the environment, have also been published in the following magazines:

- The Science of the Total Environment Special Issue: Drugs and hormones as pollutants of the aquatic environment: determination and ecotoxicological impacts. January 1999, Vol. 225, no. 1&2.
- Chemosphere Special Issue: Drugs in the environment. April 2000, Vol. 40, no. 7.

It becomes clear from the information that measurements were principally made in Germany, including in influent and effluent of sewage treatment plants, in the rivers Rhine, Elbe, Main and Ruhr, and also in the North Sea and lakes in Switzerland. In the Netherlands, measurements were also made recently on a limited scale (Mons *et al.*, 2000).

Supplement 4 presents a summary of the measurement data from different sources in the literature. The data have been classified according to the matrices in which the pharmaceuticals were measured. The following classes have been distinguished:

- effluent from hospitals or industry;
- influent from sewage treatment plants;
- effluent from sewage treatment plants;
- waste water (not indicated in more detail);
- surface water;
- sediment;
- groundwater;

- surface water during the treatment process for drinking water production;
- drinking water.

Data on measurements in urine or faeces immediately after excretion and in domestic waste water were not included in this summary.

The in the literature described and studied pharmaceuticals were selected on the basis of their extensive use, detection at low concentrations and/or the possibility of chemical identification of the active ingredients. The most important groups of the substances studied are (in alphabetic order):

- analgesics (pain relievers);
- antibiotics;
- antiepileptics;
- β-blockers (pharmaceuticals for preventing high blood pressure and heart problems);
- bronchospasmolytics (pharmaceuticals for treating asthma and similar diseases);
- fibrates i.e. blood lipid regulators (cholesterol and triglycerid reducing pharmaceuticals for treatment of heart and vascular diseases);
- iodinated X-ray contrasting agents;
- cytostatics (pharmaceuticals for treatment of cancer).

In table 3.1, the frequency distribution of the measurement data from supplement 4 is classified by matrix.

Table 3.1 Frequency distribution of all measurement data from supplement 4 classified by matrix. The number of data refers to the number of separate reported measurements (meaning one datum is one line in supplement 4).

matrix	number of data	number of pharmaceuticals	number of metabolites
total	533	85	10
hospital or industry effluent	22	18	0
of which estimated	*16*	*15*	
of which measured	*6*	*5*	
sewage water treatment plant influent	43	24	5
of which estimated	*5*	*5*	*0*
of which measured	*38*	*20*	*5*
sewage treatment plant effluent	156	58	8
waste water (miscellaneous)	21	15	3
surface water	223	64	9
sediment	3	2	1
groundwater	12	>9	2
surface water during the treatment process for drinking water production	11	10	1
drinking water	43	31	2

This table demonstrates that most measurement data are related to measurements in surface water and to a lesser extent in sewage water treatment plant effluents. The highest number of pharmaceuticals was also studied in these matrices. Measurements in sediment were only described in one literature reference, measurements in groundwater in two. In total, measurement data of 85 different pharmaceuticals and 10 different metabolites were reported in the reviewed literature. The largest portion of the pharmaceuticals was measured in more than one matrix.

The data from supplement 4 have been summarised in table 3.2. This table indicates in which concentration class the maximum measured concentration of a pharmaceutical is listed. Metabolites are represented in italics. The classification is based on the maximum measured concentration because the median measured value of most measurements is not provided.

The concentrations measured in the (waste) sewage water and sewage treatment plant effluents, surface water, groundwater and drinking water vary from ng/l to a few µg/l. The highest peak is a concentration of Carbamazepine, a pharmaceutical for treatment of epilepsy, of 2.5

mg/l in pharmaceutical industry effluent. The general trend is that the concentrations decrease as they follow the route of effluent from hospitals and industry, influent and effluent of sewage treatment plants, surface water and drinking water. The concentrations of most pharmaceuticals in surface water are between the detection limit and a few hundred ng/l, with peaks for some pharmaceuticals above the µg/l order. These concentrations in the surface water are on the same order of magnitude as concentrations of pesticides described in the literature (Ternes, 1998a). However, because pharmaceuticals are used year-round, the annual burden of pharmaceuticals will exceed that of pesticides.

The concentrations of pharmaceuticals detected in rivers correspond to a large extent with the share of sewage treatment plant effluent being discharged into the river (Ternes, 1998b; Seel, 1998). In Germany, this share is usually a few tenths percent, but especially in larger brooks and small rivers it can be as high as 100% under extreme conditions at low water levels (Seel, 1998). The share of the sewage treatment plant effluent in the river is generally lower in the lower course of rivers. In the Netherlands, standard dilution factors are are used for discharge of sewage treatment plant effluents into the surface water: 3 for a brook (33% share), 10 for a canal (10% share) and 100 for a large river (1% share) (Westphal, 1990).

Relatively high concentrations were measured in groundwater, especially of Clofibric acid, with peaks as high as 7,300 ng/l.

Generally, no pharmaceuticals or hardly any (a few ng/l) were detected in drinking water. In addition to supplement 4, no antibiotics, psychiatric drugs, β-blockers and bronchospasmolytics could be detected either, despite their low detection limits below 1 ng/l (Ternes, 1998a). Pharmaceuticals that were detected in drinking water are Acetylsalicylic acid, Bleomycin, Clofibric acid (a metabolite of Clofibrate, Etofibrate & Etophyllinclofibrate), Fenofibrate, Diazepam, iodinated X-ray contrasting agents, and, sporadically, Bezafibrate, Diclofenac and Ibuprofen.

Table 3.2 Classification of the maximum concentrations measured in concentration classes, per matrix and type of pharmaceutical. Metabolites are shown in italics.

	maximum >10000 ng/l	maximum >1000 ng/l	maximum >100 ng/l	maximum >10 ng/l	maximum >detection limit	maximum <detection limit
hospital or industrial effluent						
antiepileptics	Carbamazepine					
cytostatics		Cyclophosphamide		Ifosfamide		
antibiotics	Ciprofloxacin					
other pharmaceuticals		Methaqualone				
influent of sewage treatment plant						
cardiovascular pharmaceuticals		Bezafibrate	Pentoxifylline			
		Clofibric acid				
		Fenofibric acid				
		Gemfibrozil				
antiepileptics		Carbamazepine	Primidon			
analgesics	Ibuprofen	Acetylsalicylic acid	Fenoprofen			
	Paracetamol	Diclofenac	Indometacine			
	Salicylic acid	*Gentisic acid*	Ketoprofen			
		o-hydroxyhippuric acid	Naproxen			
			Propyphenazone			
cytostatics		Methotrexate	Cyclophosphamide	Ifosfamide		
other pharmaceuticals		Dihydrocodeine	Crotamiton			
		Hydrocodone				

Table 3.2 Continued.

	maximum >10000 ng/l	maximum >1000 ng/l	maximum >100 ng/l	maximum >10 ng/l	maximum >detection limit	maximum <detection limit
effluent of sewage treatment plant						
cardiovascular pharmaceuticals		Bezafibrate *Clofibric acid* *Fenofibric acid* Gemfibrozil Metoprolol	Betaxolol Bisoprolol Carazolol Propranolol	Nadolol Timolol		Clofibrate Etofibrate Fenofibrate
antiepileptics		Carbamazepine				
analgesics	*Salicylic acid* (1977)	Acetylsalicylic acid Diclofenac Ibuprofen *Ibuprofen-OH* Paracetamol	Phenazone *Gentisic acid* *Ibuprofen-COOH* Indometacine Ketoprofen Naproxen *Salicylic acid* (1998)			*o-hydroxyhippuric acid* Fenoprofen
cytostatics				Bleomycin Cyclophosphamide Ifosfamide		
antibiotics		Erythromycin-H2O Roxithromycin Sulfamethoxazole	Chloramphenicol Clarithromycin Erythromycin Trimethoprim			Cloxacillin Dicloxacillin Doxycycline Methicillin Nafcillin Oxacillin Oxytetracycline Penicillin G Penicillin V Sulfamethazine Tetracycline
antidepressants						Diazepam
iodinated X-ray contrasting agents	Iopromide	Diatrizoate Iopamidol		Iothalamic acid	Ioxithalamic acid	
other pharmaceuticals		Dihydrocodeine Hydrocodone	Clenbuterol Terbutalin Salbutamol	Fenoterol		Tolfenamic acid

Table 3.2 Continued.

	maximum >10000 ng/l	maximum >1000 ng/l	maximum >100 ng/l	maximum >10 ng/l	maximum >detection limit	maximum <detection limit
surface water						
cardiovascular pharmaceuticals		Bezafibrate Bisoprolol *Clofibric acid* Metoprolol	Carazolol Fenofibrate *Fenofibric acid* Gemfibrozil Pentoxyfilline Propranolol	Betaxolol Timolol	Clofibrate Nadolol	Etofibrate
antiepileptics		Carbamazepine				
analgesics		Detropropoxyphene Diclofenac *Gentisic acid* *Ibuprofen-OH* Propyphenazone *Salicylic acid*	Acetylsalicylic acid Phenazone Ibuprofen Indometacine Naproxen	Fenoprofen *Ibuprofen-COOH* Ketoprofen		Paracetamol *o-hydroxyhippuric acid*
cytostatics				Bleomycin		Cyclophosphamide Ifosfamide Methotrexate
antibiotics		Erythromycin Erythromycin-H2O Tetracycline (1983)	Clarithromycin Roxithromycin Sulfamethoxazole Trimethoprim	Chloramphenicol		Cloxacillin Dicloxacillin Doxycycline Methicillin Nafcillin Oxacillin Oxytetracycline Penicillin G Penicillin V Tetracycline (1999)
antidepressants					Medazepam	Diazepam
iodinated X-ray contrasting agents	Iopamidol		Diatrizoate Iopromide	Iomeprol Iothalamic acid Ioxithalamic acid		
other pharmaceuticals		Theophylline (1983)		Clenbuterol Fenoterol Salbutamol	Terbutalin	Tolfenamic acid

Table 3.2 Continued.

	maximum >10000 ng/l	maximum >1000 ng/l	maximum >100 ng/l	maximum >10 ng/l	maximum >detection limit	maximum <detection limit
groundwater						
cardiovascular pharmaceuticals		*Clofibric acid* *Clofibric acid derivative*		Fenofibrate		Clofibrate
analgesics		Phenazone	Diclofenac Ibuprofen Propyphenazone			
iodinated X-ray contrasting agents		miscellaneous				

Table 3.2 Continued.

	maximum >10000 ng/l	maximum >1000 ng/l	maximum >100 ng/l	maximum >10 ng/l	maximum >detection limit	maximum <detection limit
surface water during the treatment proces for drinking water production						
cardiovascular pharmaceuticals				Clofibric acid		Bezafibrate Fenofibrate Metoprolol
antiepileptics			Carbamazepine			
analgesics						Diclofenac Ibuprofen
cytostatics						Paracetamol Ifosfamide
antibiotics			Sulfamethoxazole			Erythromycin

Table 3.2 Continued.

	maximum >10000 ng/l	maximum >1000 ng/l	maximum >100 ng/l	maximum >10 ng/l	maximum >detection limit	maximum <detection limit
drinking water						
cardiovascular pharmaceuticals			*Clofibric acid*			Betaxolol
			Fenofibrate			Bezafibrate
						Bisoprolol
						Carazolol
						Clofibrate
						Metoprolol
						Nadolol
						Propranolol
						Timolol
antiepileptics						Carbamazepine
analgesics			Acetylsalicylic acid			Diclofenac
						Ibuprofen
						Paracetamol
						Salicylic acid
cytostatics				Bleomycin		Ifosfamide
						Methotrexate
antibiotics						Erythromycin
						Sulfamethoxazole
antidepressants				Diazepam		
iodinated X-ray contrasting agents				Diatrizoate		Ioxithalamic acid
				Iopamidol		
				Iopromide		
				Iothalamic acid		
other pharmaceuticals						Clenbuterol
						Fenoterol
						Salbutamol
						Terbutalin

When comparing the concentrations in surface water and the drinking water prepared from it, a clear reduction in concentration is generally observed (Hirsch *et al.*, 1996; Stumph *et al.*, 1996). Haberer & Ternes (1996) and Mons *et al.* (2000) also concluded that pharmaceuticals or their metabolites were not detected in drinking water, or only in very low concentrations.

It must be emphasised that the major part of the measurement data is related to measurements abroad, mostly in Germany, but also in Switzerland, Brazil and the United States. When interpreting these measurement data for the situation in the Netherlands, a few critical observations can be made. First of all, it is impossible to retrieve the location, conditions and measurement methods that were used in the studies cited. Therefore, it is difficult to establish the relevance of the data for the situation in the Netherlands. For example, sewage treatment plant effluents in Germany are often discharged into relatively minor water bodies. The quantity of purified waste water can run up to a very high level in these minor water bodies, especially in dry seasons, causing the measured concentrations to become relatively high. The surface water flow in the Netherlands is more constant and effluent is also discharged into larger flows of water, so that it may be expected that the concentration will be lower in general. Furthermore, it is known that the efficiency and degree of coverage of the water purification processing in the Netherlands is generally very effective, which also could result in lower concentrations.

As far as is known, targeted measurements of the presence of pharmaceuticals were only carried out once in the Netherlands. This study is described in Mons *et al.* (2000) and is presented here. The study was carried out by a consortium of RIWA, VEWIN and KIWA. The results are summarised in table 3.3. This table shows that 7 of the 11 pharmaceuticals studied in the effluent of the two selected sewage treatment plants could be detected. Metoprolol, Erythromycin, Carbamazepine and Diclofenac were detected in all effluent samples.

The concentrations in surface water were generally lower. Carbamazepine was detected in almost all surface water samples and was also the highest concentration detected in surface water with a peak concentration of 310 ng/l. Paracetamol, Ifosfamide and Fenofibrate were not detected in surface water.

In the samples of surface water during the treatment process of drinking water production, only three of the eleven pharmaceuticals could be detected, namely: Sulfamethoxazole, Clofibric acid and Ibuprofen. No pharmaceuticals were detected in drinking water. It must be observed with these results that methods of analysis have not been optimised yet and that for some pharmaceuticals (Paracetamol, Sulfamethoxazole and Ifosfamide) the percentage recovery is very low (0-20%). The real concentrations could therefore be much higher (up to a factor of 2-10) than the concentration listed. For a number of pharmaceuticals (Bezafibrate, Ibuprofen, Diclofenac and Fenofibrate), however, the percentage recovery is already fairly high (>75%).

Table 3.3 Summary of the measurements of a number of human pharmaceuticals in the Netherlands and Belgium (in ng/l; from: Mons *et al.*, 2000); n = number of measurements. The number of measurements of Paracetamol and Sulfamethoxazol is twice as high as for the other pharmaceuticals because they were measured in the same samples by two different analysis methods.

pharmaceutical	sewage treatment plant effluent	n	surface water	n	during/after treatment for drinking water	n	drinking water	n
Paracetamol	<100	4	<100	22	<100	8	<100	12
Sulfamethoxazole	<10 – 70	4	<10 – 70	22	<10 – 100	8	<10	12
Metoprolol	220 – 530	2	<10 – 30	11	<10	4	<10	6
Ifosfamide	<10	2	<10	11	<10	4	<10	6
Erythromycin	120 – 900	2	<10 – 30	11	<10	4	<10	6
Clofibric acid	<10 – 70	2	<10 – 30	11	<10 – 10	4	<10	6
Bezafibrate	<10 – 20	2	<10 – 40	11	<10	4	<10	6
Carbamazepine	580 – 870	2	<10 – 310	11	<10	4	<10	6
Ibuprofen	<10	2	<10 – 40	11	<10 – 190	4	<10	6
Diclofenac	100 – 280	2	<10 – 20	11	<10	4	<10	6
Fenofibrate	<10	2	<100	11	<100	4	<100	6

3.2 Available analysis techniques

The summary of analysis techniques is limited to the list of selected substances for which consumption data will be requested (this list is presented in chapter 4). The techniques that were used are listed in supplement 5. Analysis techniques for other pharmaceuticals are described in Kalsch (1999) and Falter & Wilken (1999), among other publications.

From a more general point of view it can be stated that a number of analysis techniques are available for measuring very low concentrations of pharmaceuticals (µg tot ng/l):

- GC/MS or GC/MS/MS
  Used for, among others, betablockers, bronchospasmolytics, blood lipid regulators, antirheumatics and pain relievers (Hirsch *et al.*, 1996; Stumpf *et al.*, 1996; Sachter *et al.*, 1998; Ternes *et al.*, 1998a, Heberer *et al.*, 1997, 1998; Buser *et al.*, 1998b and Steger-Hartmann *et al.*, 1996).
  With GC/MS, only substances that are volatile or can easily be derivatized to volatile substances can be measured. This means that only 20 to 25% of the substances that are expected to be present in water can be measured with GC/MS (Richardson & Bowron, 1985).

- LC/MS/MS
  Suitable for measuring samples for a broad spectrum of micro-contaminations (personal information from Mr. Ruijten, Xenobiosis). Used by Ternes *et al.* (1998a) for measuring Carbamazepine and Cyclophophamide, among other pharmaceuticals. Also used for measuring iodinated X-ray contrasting agents (Hirsch *et al.*, 2000).
- HPLC
  Used for, among others, measuring the antibiotics Sulphamethoxazole, Tetracycline, Erythromycin and Theophylline (Watts *et al.*, 1983), Doxycycline and Erythromycin (Hirsch *et al.*, 1998) and Ciprofloxacin (Hartmann *et al.*, 1998).
- Immunoassays (ELISA)
  Very sensitive and specific, especially suitable for larger molecules (Richardson & Bowron, 1985; Aherne *et al.*, 1990).

Prior to the analysis, some type of extraction is usually necessary. Examples of techniques which can be used for this are XAD extraction, solid phase extraction (SPE), gas strips and PE extraction (Van Genderen *et al.*, 1994; Hirsch *et al.*, 1996; Stumpf *et al.*, 1996; Sachter *et al.*, 1998; Ternes *et al.*, 1998a, Heberer *et al.*, 1997, 1998; Buser *et al.*, 1998b and Steger-Hartmann *et al.*, 1996; unpublished information from Mr. Ruijten, Xenobiosis).

For most metabolites there are no suitable reference substances, which are necessary for a meaningful development of a method and for quantification (Ternes, 1998a).

Hirsch (1998) states that analysis methods for demonstrating antibiotics are mainly developed to determine concentrations of active substances or metabolites in plasma or urine, on the one hand, and on the other hand in food items such as milk, meat or fish. This involves mostly liquid chromatography methods with UV detection. LC/MS and LC/MS/MS techniques are also used. Using gas-chromatography techniques for analysis of antibiotics is limited by insufficient thermal stability (e.g. penicillins), high molecular weight (e.g. macrolids) and/or high polarity (e.g. tetracycline) (Hirsch, 1998). Therefore, only a limited number of antibiotics can be detected by means of GC/MS, such as Chloramphenicol (Kijak, 1994) or Sulfamethazine (Cannavan *et al.*, 1996). For analysis of antibiotic residues in surface water and drinking water hardly any methods have been described. Watts *et al.* (1983) used reprocessing with XAD-2 resin and freeze-drying, followed by fractioning by means of HPLC and detection with mass spectrometry. This technique was used successfully for the analysis of Erythromycin, Tetracycline, Methylxanthin and Theophylline.

3.3 Removal of pharmaceuticals in purification steps

Production of pharmaceuticals is often in small quantities and discontinuously. It is estimated, on the basis of general experience in batch productions, that about 0.2% of the active substance is discharged with the flushing water for each batch (Oranjewoud, 1999).

The (batch) production process may vary considerably, depending on the type of pharmaceutical company and the active substance. This will also cause the composition of the wastewater of such companies to change to a large extent, both from company to company as well as in time (Polderman, 1984). The range of pharmaceuticals which reaches the sewage treatment plant via households and hospitals will be much more constant in composition, although it comprises many different substances.

Residues of pharmaceuticals may have a negative effect on the purification in a biological sewage treatment plant (Polderman, 1984). The inhibiting action of residues of antibiotics, corticosteroids, cytostatics, sulfonamides and other pharmaceuticals on the purification process have been demonstrated (various references from Polderman, 1984). However, a large number of studies demonstrate that the active sludge in sewage treatment plants is capable of degrading very complex substances, provided it is given the time to adapt to this (Polderman, 1984). The inhibition disappears after the period of adaptation. It is probable that this adaptation is caused by a shift in the composition of species of the microflora in the purification sludge.

The inhibiting properties of antibiotics on biological sewage treatment plants in particular have been studied to a large extent. Liebmann (1961) studied the effect of different concentrations of Penicillin, Streptomycin, Tetracycline, Chlortetracycline and Oxytetracycline on the gas production of sludge. The strongest inhibition (25% less gaseous volume) occurred in the presence of 2 g of Streptomycin per kg of sludge. The researchers concluded from this that the toxicity, even for these high concentrations, is not as severe as expected. Other studies also demonstrated that antibiotics do not cause large problems. The relatively high resistance of the active sludge for toxic substances can be attributed to the varied composition of this sludge.

In a biological sewage treatment plant a certain percentage of the pharmaceuticals are, depending on the type of compound, also removed either by degradation or by adsorption to sludge. For example, removal percentages of 66 to 96% were reported for various betablockers and bronchospasmolytics during sewage water treatment (Hirsch *et al.*, 1996). Ternes (1998b) investigated a number of betablockers, blood lipid regulators, analgesics and the antiepileptic Carbamazepine and detected removal percentages varying from 7% for Carbamazepine up to more than 99% for Salicylic acid. However, in sewage treatment plants in which the incoming sewage water is mixed with rain water running off paved surfaces, rain fall may result in a considerable reduction in the removal efficiency (Ternes, 1998b).

It is not clear to what extent pharmaceuticals inhibit the purification process in the concentrations detected in the sewage water treatment plant influent due to toxic effects. But it is a fact that, if inhibition takes place, the inhibiting substance not only breaks down to a lesser extent, but that all other substances are also removed less effectively (Polderman, 1984). This is especially true for substances with low degradability properties.

As mentioned above, pharmaceuticals are generally not or only scarcely detected in drinking water. The filtration step with activated carbon applied to the process water for the preparation of drinking water therefore appears to effectively remove most of the pharmaceuticals and their metabolites.

4 Substances under study

In this chapter, for 21 selected substances an estimate of the concentrations to be expected in surface water in the Netherlands is made, based on consumption data.

The selection of substances to be studied, the calculation method and the results will be discussed consecutively. The possible risks of the selected substances will be elaborated in section 4.3.

4.1 Selection of substances under study

Within the framework of this study, for a limited number of pharmaceuticals consumption data were requested. Unfortunately, it was not possible to obtain a list of the most consumed active substances authorised in the Netherlands. A list of substances had to be submitted and for these substances alone insight into the consumption data was provided. Thus the selection was made on the basis of expected consumption, which does not necessarily always correspond with the actual consumption. In addition to consumption, a large number of other arguments played a role.

A total of 21 substances were selected, referred to in this report as the substances under study. A list of these substances under study plus argumentation for their selection is presented in table 4.1. This list of substances was drawn up on the basis of pharmaceuticalswhich have been authorised in the Netherlands (Nefarma, 1999). One or more of the following elements played a role in the selection of the substances to be studied:

- Active substance in pharmaceuticals that are used daily with a high daily dosage (pharmaceuticals for treatment of heart and vascular diseases and antiepileptics, among others) or are

otherwise used on a large scale (Acetylsalicylic acid, for example);

- Active substances which are used periodically in high daily doses (e.g. antibiotics);
- Active substances or types of pharmaceuticals which have been detected in other countries in sewage treatment plant influent or effluent, surface water and/or groundwater;
- Familiarity of the 'public' with the pharmaceutical (that contains the active substance);
- Active substances which have shown not to be easily degraded;
- Formation of stable metabolites;
- Active substances with high risk (cytostatics, among others);
- Active substances which may cause resistance development and/or allergic reactions (antibiotics);
- Active substances which occur in many authorised pharmaceuticals;
- For each type of effect one representative per type of pharmaceuticals (e.g. per type of antibiotic or per type of cytostatic).

The arguments stated in table 4.1 are the arguments that played a role at the moment of selection. We emphasise that the selection of substances under study on the basis of the criteria mentioned above (expected consumption, stability, toxicity), does not automaticly stand for the substances that actually cause problems.

The consumption data (=sales in the Netherlands) were requested via the company FarmInform. This company collects monthly sales data from the pharmaceutical industry. These data are processed by FarmInform and also passed onto the IMS Health Nederland. The information is used by the pharmaceutical industry for marketing purposes, among other things. The individual pharmaceutical manufacturers have given their approval for providing the consumption data.

As a result of recent literature data, this report would also have to focus on iodinated X-ray contrasting agents, antidepressants and pharmaceuticals for treatment of impotence. However, at that time no consumption data were requested for these pharmaceuticals.

Table 4.1 Selection of substances under study.

active substance	application	motivation
Fibrates		
Bezafibrate Gemfibrozil Clofibrate	cholesterol and triglyceride reducing pharma-ceuticals (blood lipid regulators)	This type of pharmaceutical is used for long periods, daily, in relatively high doses. In Germany, various fibrates were measured in sewage treatment plants, surface water and drinking water. A limited number of fibrates have been authorised in the Netherlands (active substances): Bezafibrate, Gemfibrozil, Clofibrate and Ciprofibrate. The recommended daily dosage is 600 mg/day, 1200 mg/day and 100 mg/day respectively. The Clofibrate metabolite, Clofibric acid, appears very slowly degradable and can be detected in many surface water bodies in various European countries. Moreover, Clofibric acid has been detected in drinking water in Germany in concentrations up to 270 ng/l. Bezafibrate and Gemfibrozil have both been detected in sewage treatment plant influent and effluent and in surface water in Germany, the concentrations of Bezafibrate being higher than those of Gemfibrozil. In Germany, Ciprofibrate was not included in the measurement program. Consumption data for Bezafibrate, Gemfibrozil and Clofibrate have been requested.
ß-blockers		
	Pharma-ceuticals for treatment of high blood pressure and other heart diseases	β-blockers are pharmaceuticals that are used in case of high blood pressure and other heart diseases. This means that they are used for a long period on a daily basis. In the Netherlands, a large number of active substances have been authorised as β-blockers. One of them has been selected.
Metoprolol		This active substance is used in several pharmaceuticals in relatively high concentrations (100 - 400 mg/day). It has been detected in sewage treatment plant effluent up to 2200 ng/l, in surface water also up to 2200 ng/l. So it appears to degrade slowly. Not detected in drinking water.
Antiepileptics		
		Pharmaceuticals for treatment of epilepsy are taken daily in high dosage. 12 active substances have been authorised in the Netherlands. Two substances were selected from these, to wit:
Carbamazepine	antiepileptic	This active substance has been detected in 24 of the 26 samples of surface water in Germany, up to 1100 ng/l, removal rates in the sewage treatment plant are low.
Valproic acid	antiepileptic	Many pharmaceuticals containing this active substance have been authorised in the Netherlands.

Table 4.1 Selection of substances to be studied (*continued*).

active substance	application	motivation
Analgesics		
	non-narcotic, antipyretic analgesics	Analgesics (pain relievers) are used frequently. They can also be obtained without prescription. The daily dose is relatively high. These active substances are incorporated in many different products. A number of active substances were selected that are incorporated in many products, were detected in surface water in other countries, are taken in high daily doses and/or are well known to the public.
Acetylsalicylic acid		Detected in surface water in Germany up to 340 ng/l, in sewage treatment plant effluent up to 1500 ng/l. Appears to break down well. Is generally well-known
Paracetamol		Detected in sewage treatment plant effluent in Germany in a concentration of 26000 ng/l. Appears to break down well. Is well known to the public.
Naproxen		Detected in surface water in Germany up to 390 ng/l, in sewage treatment plant effluent up to 520 ng/l.
Ibuprofen		Detected in surface water in Germany up to 530 ng/l, in sewage treatment plant effluent up to 3400 ng/l.
Diclofenac		Detected in surface water in Germany and Switzerland up to 1200 ng/l, in sewage treatment plant effluent up to 2100 ng/l.
Cytostatics		
		Cytostatics are pharmaceuticals used for treatment of cancer. This group of substances includes different types of substances, such as alkylating substances (Cyclophosphamide, Ifosfamide, Tamoxifen), antimetabolites (Fluoracil), anti-tumor antibiotics (Bleomycin, Mitomycin), topo-isomerase inhibitors (Etoposide) and other cytostatics (Cisplatin). Since these cytostatics interfere with cell growth and cell division, they form a potentially high-risk group. Three substances were selected.
Cyclophosphamide	cytostatic (alkylating drug)	Detected in hospital effluent up to 4500 ng/l, measured in several dozen ng/l in effluent of a sewage treatment plant in Germany, not detected in surface water, slowly degraded.
Bleomycin	cytostatic (antibiotic drug)	The estimated concentration in hospital effluent in Switzerland is 20 ng/l, measured in several dozen ng/l in effluent of a sewage treatment plant and in river water in Italy. Appears difficult to break down.
Cisplatin	cytostatic (alkylating drug)	In general it can be stated that the toxicity of Cisplatin is considerably higher than that of the usual cytostatics. Cisplatin is not metabolised. Estimated concentration in effluent of a hospital in Switzerland is 90 ng/l.

Table 4.1 Selection of substances to be studied (*continued*).

active substance	application	motivation
Antibiotics		
		There are several groups of antibiotics, the most important ones of the human pharmaceuticals being: tetracyclines, macrolids, penicillins, fluoroquinolones, nitrofuranes, cefalosporines and sulfonamides. Antibiotics are generally taken in a relatively high daily dosage for a period of 5-7 days. Antibiotics can cause resistance development and allergic reactions. One representative was selected from each group.
Doxycycline	antibiotic from the tetracycline group	Only a few tetracyclines are authorised in the Netherlands. Doxycycline is most incorporated in these products.
Erythromycin	antibiotic from the macrolid group	This active substance from the macrolid group has been detected in surface water (~1000 ng/l). Used in several products.
Amoxicillin	antibiotic from the broad spectrum penicillin group	Most important broad spectrum penicillin authorised in the Netherlands; used in several products. Very high concentration estimated in hospital effluent in Switzerland (200,000 ng/l).
Ciprofloxacin	antibiotic from the fluoroquino-lone group	Measured in high concentrations in hospital effluent in Switzerland (3000- 87000 ng/l). Suspected to be genotoxic.
Nitrofurantoin	antibiotic from the nitrofuran group	The only substance from this group authorised for human consumption. Mutagenity has been demonstrated in *E. coli* bacteria and rats. Excreted in active concentrations in urine.
Cefalexin	antibiotic from the cefalosporin group	In the Netherlands 20 active substances have been authorised from this group. The portion which is excreted unchanged via the faeces is therefore expected to be relatively high.
Sulfamethoxazole	antibiotic from the sulphonamide group	One of the few pharmaceuticals from this group that have been authorised in the Netherlands. Measurements in the environment have demonstrated that the substance is fairly stable.

4.2 Estimates of concentrations in the environment

For the 21 selected substances under study estimates were made of the concentrations in surface water according to the method from the EU Draft Guideline III/5504/94 and discussion paper CPMP/SWP/4447/00 (worst case calculation):

$$PEC\ (g/l) = \frac{A * (100 - R)}{365 * P * V * D * 100}$$

in which:

A (kg/year):	consumption per year (= sales in a certain area per year)
R (%):	percentage of loss by adsorption, evaporation and degradation in the sewage treatment plant and the environment
P:	number of inhabitants in a certain area
V (m^3/day):	quantity of waste water produced per person per day
D:	dilution factor for transition from waste water to surface water

The loss percentage (R) is determined at 0% for the worst-case calculations. The concentration is divided up in the expected concentration in brooks, canals and rivers, taking into consideration any differences in dilution for the transition from effluent to surface water (dilution factor D of 3, 10 and 100, respectively). For P the number of inhabitants of the Netherlands (15.6 million; CBS) is used, and for V, the wastewater produced per person, 130 litres/day is used (CBS). The consumption of Bleomycin sulfate was given in I.E., a measure for the activity of a substance. This has been converted into kg/year with the assumption that 1 mg of dry Bleomycin sulfate weight contains 1500 I.E., at minimum (Boekema *et al.*, 1997).

The results of the worst-case calculations are presented in table 4.2. For comparison, the measured concentrations mentioned in the literature have also been included in this table.

In the most recent draft versions of the EU directive for environmental risk assessment of pharmaceuticals, the limit value in the surface water has been set at 0.01 µg/l. It appears from the table that, with the exception of the concentrations of Bezafibrate, Clofibrate, Cefalexine and cytostatics in the big rivers, this limit is exceeded for all pharmaceuticals. These results contrast somewhat with the results of Webb (2000a), who found that only 16 of the 67 pharmaceuticals studied exceeded the limit when calculating the 'worst case' PECs according to a comparable method in England. This discrepancy may be caused by the fact that for the English situation other values are used for the different parameters, such as the number of inhabitants, the consumption per year and the waste water produced per day.

As may be expected, a comparison with the measured concentration shows that in most cases these (insofar as available) are clearly below the worst-case estimate. This is true for sewage treatment plant effluent as well as for surface water. Exceptions are Bezafibrate (for sewage treatment plants and surface water), Cyclophophamide (only sewage treatment plants) and Erythromycin (only surface water). An

explanation for this may be that the measurements are related to different countries, mainly Germany, where the consumption of these pharmaceuticals may be higher than in the Netherlands. It is also remarkable that the measured peak concentrations in most cases are higher than the estimated concentrations in big rivers.

Table 4.2 Worst case calculation of the concentration expected in sewage treatment plant influent and in streams, canals and rivers, as well as the concentrations measured in sewage treatment plant influent and surface water mentioned in the literature (in various countries). The values in the table relate to sales to hospitals, pharmacies and chemist's in 1999.

active substance	quantity (<kg/year)	conc. STP influent calculated (ng/l)	conc. STP influent measured (ng/l)	conc. brooks calculated (ng/l)	conc. canals calculated (ng/l)	conc. big rivers calculated (ng/l)	conc. surface water measured (ng/l)
Heart and vascular pharmaceuticals							
Bezafibrate	294	396	up to 4400	132	40	4	<25 – 3100
Clofibrate	225	303	-	101	30	3	<0.5 - ~40
Gemfibrozil	5678	7644	up to 5500	2548	764	76	<5 – 510
Metoprolol	10078	13568	-	4523	1357	136	<3 – 2200
Antiepileptics							
Carbamazepine	10813	14557	150 – 1760	4852	1456	146	<30 – 2100
Valproic acid	10540	14190	-	4730	1419	142	-
Analgesics							
Acetylsacylic acid	27978	37666	3200	12555	3767	377	<10 – 340
Paracetamol	223372	300720	26000	100240	30072	3007	-
Naproxen	17559	23639	~650	7880	2364	236	<5 – 400
Ibuprofen	48008	64632	to 12000	21544	6483	646	<5 – 530
Diclofenac	5596	7534	to 6220	2511	753	75	<1 – 1200
Cytostatics							
Cyclophophamide	92	124	<6 – 143	41	12	1	<10
Bleomycin (as sulphate)	<128	172	-	57	17	2	<5 – 17
Cisplatin	0	0	-	0	0	0	-

Table 4.2 Continued

active substance	quantity (<kg/year)	conc. STP influent calculated (ng/l)	conc. STP influent measured (ng/l)	conc. brooks calculated (ng/l)	conc. canals calculated (ng/l)	conc. big rivers calculated (ng/l)	conc. surface water measured (ng/l)
Antibiotics							
Doxycycline[1]	903	1216	-	405	122	12	<50
Erythromycin[1]	1487	2002	-	667	200	20	~1000
Amoxicillin[1]	17974	24198	-	8066	2420	242	-
Ciprofloxacin	1589	2139	-	713	214	21	-
Nitrofurantoin	725	976	-	325	98	10	-
Cefalexin[1]	63	85	-	28	8	1	-
Sulfamethoxazole[1]	4120	5547	-	1849	555	55	<10 - ~1000

1 These pharmaceuticals also have veterinary applications. The value presented refers to human consumption only.
- No measurement values available.

The values in the table relate to sales to hospitals, pharmacists and drugstores in 1999.

4.3 Risk assessment of substances under study

In this section the environmental risks of a number of substance groups and specific substances under study are explained briefly. For more detailed information we refer to the cited references and to chapter 5.

4.3.1 Cardiovascular pharmaceuticals

Pharmaceuticals for treatment of cardiovascular diseases, especially fibrates (blood lipid regulators) and betablockers, are among the types of pharmaceuticals for which presence in the environment has been studied most. A number of reasons can be given for this. In the first place, these pharmaceuticals are consumed in large quantities, on the one hand because the daily dose is high, on the other because the pharmaceuticals are used throughout the year. In addition, the frequent detection of Clofibric acid was one reason for carrying out more studies on the presence of blood lipid regulators and other cardiovascular pharmaceuticals in the environment. Clofibric acid is a metabolite of the pharmaceuticals Clofibrate, Etofibrate and Etofylinclofibrate, which was frequently detected in routine measurements of herbicides because of its similarity to the herbicide Mecoprop.

Although cardiovascular pharmaceuticals are detected up to µg/l in sewage treatment plant effluent, the concentrations in surface water are generally low except for a few peaks. A remarkable exception to this is Clofibric acid. The consumption of the pharmaceuticals of which Clofibric acid is a metabolite is not extremely high, but Clofibric acid appears to be poorly degradable and has been detected in nearly all matrices, influent and effluent of sewage treatment plants, in rivers, the North Sea, groundwater and even drinking water up to concentrations of 270 ng/l (Stan *et al.*, 1993; Heberer, 1995; Stumph *et al.*, 1996; Kalbfus, 1997; Sacher *et al.*, 1997; Heberer *et al.*, 1998; Buser & Miller, 1998; Sacher *et al.*, 1998; Ternes, 1998b; Stumph *et al.*, 1999). It is one of the most reported substances in measurements of pharmaceuticals in the environment. As mentioned above, Clofibric acid has also been repeatedly detected in the Netherlands in the regular screening of Rhine water at Lobith and Meuse water at Eijsden. Mons *et al.* (2000) also demonstrated its presence in the Netherlands in sewage treatment plants effluent, in surface water and in the water during the treatment process for drinking water production. Maximum concentrations measured were 70 ng/l.

Hignite & Azarnoff (1977) already detected Clofibric acid in 1977 during measurements of pharmaceuticals in the influent and effluent of a sewage treatment plant in Kansas. They concluded that only 20% of the Clofibric acid was broken down in the sewage treatment plant. Ternes (1998b) found a removal percentage of 51% in the sewage treatment plant, while Stumph *et al.* (1999) reported removal percentages between 6-50% for sewage treatment plants in Brazil. These numbers indicate the poor degradability of Clofibric acid. The fact that Clofibric acid is also found in drinking water indicates that the purification step with active carbon is not entirely sufficient to remove all Clofibric acid.

The acute ecotoxicity of Clofibric acid is not very high. The EC_{50} is about 100 mg/l for various water organisms (Henschel *et al.*, 1997). For Clofibric acid ethyl ester, which is probably a metabolite of Clofibric acid, an $EC_{10,\ 21\ days}$ of 8.4 µg/l is mentioned for reproduction of the water flea *Daphnia magna* (Kopf, 1997). Clofibric acid is suspected of being a hormone disrupting substance (Stahlschmidt-Allner, 1996). There are no indications that Clofibric acid accumulates in organisms (Kalbfus, 1997). However, Clofibrate was detected in fish at a few µg/kg of fresh weight (Kalbfus, 1997). For a well-founded ecological risk assessment, however, more toxicity data, especial chronic ones, and data on specific toxicity are needed.

4.3.2 Antiepileptics

Antiepileptics are used daily in high doses. Studies on the occurrence of antiepileptics in the environment have been mainly focused on Carbamazepine. Carbamazepine was the pharmaceutical which was detected most frequently and in the highest concentrations during a study by Ternes (1998b). The pharmaceutical was found in all sewage

treatment plants and in the receiving surface water with a maximum concentration of 6.3 µg/l. Sacher *et al.* (1997), Sacher *et al.* (1998) and Möhle *et al.* (1999) also demonstrated the substance in high concentrations in various matrices. A concentration of no less than 2.5 mg/l was measured in the effluent of a pharmaceutical company (Sacher *et al.*, 1997). Moreover, the substance has also been demonstrated sometimes in the regular screening of Rhine water at Lobith and Meuse water at Eijsden. Mons *et al.* (2000) also detected Carbamazepine in the Netherlands in focused measurements in sewage treatment plant effluent (up to 870 ng/l) and in 10 of the 11 surface water samples studied. The pharmaceutical was, with a peak concentration of 310 ng/l, also the one demonstrated in the highest concentration in surface water. The drinking water purification step with active carbon however, appeared appropriate to remove all Carbamazepine.

The high concentrations in the environment indicate that Carbamazepine is poorly degradable. Ternes (1998b) detected a removal percentage of only 7% in sewage treatment plants.

No data were found on the ecotoxicity of Carbamazepine. Therefore it is not possible to estimate the risk of Carbamazepine to the environment.

Data on the exotoxicity of other antiepileptics (Fenobarbital, Valproic acid and its analog 2-n-valproic acid) indicate that these are not acutely toxic.

4.3.3 Analgesics

Analgesics or pain relievers are frequently used in high daily doses. Many analgesics can also be obtained without a prescription.

One of the best-known analgesics is Acetylsalicylic acid. This pharmaceutical has been regularly detected in sewage water treatment plants, but is degraded effectively there. Ternes (1998b) found a removal percentage of 81% in sewage treatment plants. The pharmaceutical is not very toxic to humans and the environment. Thus the environmental risks appear minor.

In addition to Acetylsalicylic acid, studies have mostly been focused on Diclofenac, Indometacine, Ketoprofen, Ibuprofen and Propyphenazone (AWWR, 1996; Stumph *et al.*, 1996; Buser *et al.*, 1998; Ternes, 1998b; Möhle *et al.*, 1999; Buser *et al.*, 1998; Stumph *et al.*, 1999). Although the concentrations in sewage treatment plant influent are very high (up to µg/l) and a number of pharmaceuticals are also detected in surface water in peak concentrations of a few hundred ng/l, they can no longer be demonstrated in drinking water. This shows that they can be rather effectively degraded or removed otherwise. For Diclofenac, Buser *et al* (1998) found a removal percentage of almost 50% in sewage treatment plants. Partly on the basis of data on concentrations in surface water they concluded that photodegradation is the most important route for Diclofenac to be broken down in surface water. Buser *et al.* (1999)

demonstrated that Ibuprofen is also easily broken down. Two metabolites were detected: Ibuprofen-OH and Ibuprofen-COOH. Effect concentrations for Ibuprofen are in the order of several dozen mg/l.

Although Paracetamol is an analgesic that is used in large quantities, hardly any studies have been carried out on the presence of the substance. Mons *et al.* (2000) could not detect the substance in sewage treatment plant effluent, in surface water, in treated surface water or in drinking water in the Netherlands (detection limit 100 ng/l), although it must be noted here that the recovery rate was very low (< 20%). Ternes (1998b) also could not detect Paracetamol in the effluent of a sewage treatment plant (detection limit 200 ng/l).

The analgesics Acetylsalicylic acid, Salicylic acid and Paracetamol are generally not or only slightly toxic (EC_{50} >10 mg/l).

4.3.4 Cytostatics

Cytostatics are pharmaceuticals that are used for treatment of cancer. The use of cytostatics is low due to their specific application.

The common characteristic of cytostatics is that they inhibit or kill (tumour) cells in their growth by interfering with the cell's metabolism. However, the way this effect is achieved can vary to a large extent (Boekema *et al.*, 1997).

Cytostatics are not only used for treatment of cancer, they are in many cases also cancer inducing and moreover highly toxic. Therefore, the substances are collected separately and removed by incineration. The urine and faeces of patients are in most cases also collected and removed separately. Therefore, the concentrations to be expected in the environment will be low.

With respect to the risks to the environment, cytostatics were mainly studied for their presence and degradability, in particular by the University Hospital of the University of Freiburg in Germany (Kümmerer *et al.*, 1996; Steger-Hartmann *et al.*, 1996; Kümmerer *et al.*, 1997; Steger-Hartmann *et al.*, 1997). The pharmaceuticals referred to are Cyclophosphamide and Iphosphamide. It appears that neither can be broken down biologically.

Little is known about the ecotoxicity of cytostatics. It appears, on the basis of toxicity checks within biodegradation tests that Cyclophosphamide and Iphosphamide are not very toxic to bacteria (Kümmerer *et al.*, 1996). For Bleomycin, Mitomycin and Flouracil, however, effects on bacteria are already observed starting at a concentration of several tens of µg/l (Hartmann *et al.*, 1998; Backhaus & Grimme, 1999). Hartmann *et al.* (1998) studied a few cytostatics for their genotoxicity and found LOEC values of 0.05 mg/l (Bleomycin) and 1.25 mg/l (Cisplatin). In both cases, these toxicity values exceeded the theoretically calculated effluent concentrations of the pharmaceutical in question.

It is not possible to make a good estimate of the risks of cytostatics to the environment on the basis of the present knowledge. Although the necessary precautions are taken to prevent the emission of cytostatics into the environment, this substance group certainly deserves attention, not in the last place due to their specific effect mechanisms and their poor degradability.

4.3.5 Antibiotics

The quantity of antibiotics which is used as veterinary drugs and/or animal feed additive is many times higher than the quantity used as human pharmaceutical (Hirsch, 1998). Despite their frequent use as a pharmaceutical, most antibiotics are rarely detected in the aquatic environment. Hirsch *et al.* (1998) studied 18 different antibiotics and metabolites. Only 5 of these could be detected in sewage treatment plant effluent as well as in surface water. No antibiotics could be detected in the studied groundwater samples. Penicillins and tetracyclines could also not be detected in water samples, either due to their high sensitivity to hydrolysis, or due to the fact that they can not be detected because they are bound to suspended matter or sediment (tetracyclines are known to bind strongly to sediment and soil). Mons *et al.* (2000) demonstrated the antibiotics Sulfamethoxazole and Erythromycin in sewage treatment plant effluent and in surface water in an inventory study in the Netherlands in concentrations of several tens of ng/l. The pharmaceuticals could no longer be detected in drinking water.

A relatively large quantity of ecotoxicity data has been found for antibiotics. Bacteria are especially very sensitive, as may be expected. Effects can already be demonstrated starting at a few µg/l. In addition, algae and cyanobacteria are also very sensitive to antibiotics. Based on their own studies and data from the literature, Holten Lütshøft *et al.* (1999) conclude that algae are more sensitive to antibiotics than are crustaceans and fish. This has been confirmed by Lanzky & Halling-Sørensen (1997). It can not be excluded that the environmental effects on higher organisms (crustaceans and fish) will probably take place mainly through indirect effects on algae.

Furthermore, it appears that the cyanobacterium *Microcystis aeruginosa* is about two or three orders of magnitude more sensitive to antibiotics than the other two investigated species of algae, the saltwater species *Rhodomonas salina* and the freshwater species *Selenastrum capricornutum* (Holten Lützhøft *et al.*, 1999; Halling-Sørensen, 2000). Harrass *et al.* (1985) demonstrated that the cyanobacterium *Microcystis aeruginosa* is about a factor of ten more sensitive to the antibiotic Streptomycin than is the freshwater algae *Selenastrum capricornutum*. Therefore for better risk evaluation of antibiotics it is advisable to also include cyanobacteria as a test organism in the testing battery.

A group of antibiotics on which relatively many studies have been carried out, mainly concerning their genotoxicity, are the

fluoroquinolones. Fluoroquinolones are frequently used antibiotics with a high anti-bacterial activity. Genotoxicity has been detected for this group of antibiotics (Mersch-Sundermann *et al.*, 1994). A few fluoroquinolones appeared to be very genotoxic in the SOS-Chromotest, meaning they caused a high induction of the SOS repair system. Sparfloxacin, the most genotoxic fluoroquinolone, appeared to be 50 times more genotoxic than the positive control in the SOS-Chromotest (4-nitroquinoline-N-oxid) and about 3000 times that of benzo(a)pyrene, a well known mutagen and carcinogen. Ciprofoxacin and Norfloxacin are also highly genotoxic, followed by Rosoxacin, Ofloxacin, Fleroxacin and Enoxacin. Pipemic acid, Cinoxacin and Nalidixic acid are only weak genotoxics. Mersch-Sundermann *et al.* (1994) demonstrated that genotoxicity increases in accordance with any increase in antibacterial activity. Hartmann *et al.* (1998) and Hartmann *et al.* (1999) demonstrated that the genotoxicity which was detected in the *Umu*-C test of the waste water of a large Swiss hospital and five German hospitals was mainly caused by antibiotics from the fluoroquinolone group, especially Ciprofloxacin.

Fluoroquinolone carboxylic acids break down in sunlight in aqueous solutions (Burhenne *et al.*, 1997a,b). Moreover, they can be broken down by fungi in the soil (Martens *et al.* 1996).

In addition, it must be mentioned that the increase in consumption of antibiotics also increases the spreading of resistance genes among pathogenic bacteria, as well as others. This phenomenon is considered by many as a big problem for public health in the near future.

It may be concluded that too little data are available on antibiotics to make a well-founded ecotoxicological risk assessment. It involves both data on presence in the environment and data on chronic toxicity (Health Council, 1998).

4.3.6 Antidepressants

Virtually nothing is known about the presence of antidepressants in the environment. However, studies on the ecotoxicity of anti-depressants were done by different people (Calleja *et al.*,1993; Fong, 1998; Fong *et al.*,1998; Lilius *et al.*,1994; Lilius *et al.*,1995 and Stoyanov *et al.*, 1987).

One important group of antidepressants, the 'Selective Serotonin Reuptake Inhibitors' (SSRIs), which includes the pharmaceuticals Fluoxetin (Prozac), Fluvoxamin (Luvox) and Paroxetin (Paxil), among others, is remarkable due to its very high ecotoxicity. Serotonin is involved in the transmission of signals in the nerves of both vertebrates and invertebrates. In addition, serotonin is involved in many physiological processes (Daughton & Ternes, 1999). SSRIs increase the effect of serotonin because they prevent serotonin from being re-uptaken after it has taken effect. Therefore, the neurotransmission will continue.

Fong (1998) and Fong *et al.* (1998) studied the effects of SSRIs on the reproduction of mussels. Already at low concentrations these pharmaceuticals appeared to stimulate the reproduction of mussels. The pharmaceutical that was the most powerful stimulator was Fluvoxamin, which already caused stimulation of the reproduction in males at 318 ng/l. SSRIs appeared to be the most powerful stimulators of the reproduction in mussels ever found.

It is not clear at what concentrations SSRIs are present in the environment. The results of the ecotoxicological studies indicate, however, that disruption of the ecosystem may already take place at very low concentrations of SSRIs.

4.3.7 Iodinated X-ray contrasting agents

Iodinated X-ray contrasting agents, including Iohexol, Iopamidol, Iopromide, Iotrolan and Diatrizoate are used for diagnostic purposes. By means of the X-ray contrasting agents, soft tissues can be visualised using X-rays. The agents are used in high dosage. More than 3000 tonnes annually are used worldwide (Kalsch, 1999). However, they are poorly degraded in humans: 95% is excreted unmetabolised (Daughton & Ternes, 1999). They have been detected in high concentrations in the environment, with median values up to 490 ng/l for Iopamidol and 230 ng/l for Diatrazoate in surface water, with locally a peak concentration of no less than 100 µg/l Diatrozate (Ternes & Hirsch, 2000). Physical chemical data (water solubility, octanol/water distribution coefficient and vapour pressure) indicate that iodinated X-ray contrasting agents remain in the water phase, do not absorb to sludge or sediments and do not accumulate in organisms (Steger-Hartmann *et al.*, 1998).

Iodinated X-ray contrasting agents are not easily degraded in sewage treatment plants and in the environment (Steger-Hartmann *et al.*, 1998; Steger-Hartmann *et al.*, 1999; Kalsch, 1999). Kalsch (1999) studied the biodegradability of Diatrizoate and Iopromide. Diatrizoate was slowly degraded after an adaptation period and two metabolites were detected. These metabolites turned out to dissolve well and to be stable under aerobic conditions. In anaerobic conditions, the metabolites were broken down. It was also shown that Iopromide breaks down slowly in both water sediment systems and in river water into two metabolites. Also for other iodinated X-ray contrasting agents it was reported that they break down slowly. In addition, they appear to be sensitive to photodegradation (Steger-Hartmann, 1998).

Acute ecotoxicological effects were not detected in concentrations up to 10 g/l in tests with bacteria, algae, crustaceans and fish. Chronic effects on the water flea *Daphnia magna* were also not detected up to the highest tested concentration of 1 g/l (Steger-Hartmann *et al.*, 1998). From a comparison of the expected environmental concentrations and the low (acute) ecotoxicity, it may be stated that even though iodinated X-ray contrasting agents are present in the environment in high concentrations and although they are poorly degradable in water, their acute risk to the environment will most likely be low. Since there are

insufficient chronic toxicity data available (the substances are only tested on one trophic level), no conclusion can be drawn with regard to the possible long-term risks to the environment.

4.3.8 Pharmaceuticals for treatment of impotence

Different pharmaceuticals for treatment of impotence have been used throughout the years. However, the introduction of many new pharmaceuticals, one of which is Viagra (Sildenafil citrate), has seriously increased the focus on this type of pharmaceuticals. These pharmaceuticals have a very specific effect. For example, Viagra inhibits the enzyme phosphodiesterase which, by an indirect mode of action, causes the muscles to relax and the blood circulation to improve. Hardly anything is known about its possible ecotoxicological effects. However, the fact that the pharmaceutical interferes with a general enzyme such as phosphodiesterase is reason enough to be concerned about the possible unintended effects of this pharmaceutical on non-target organisms. Moreover, the use of the pharmaceutical is expected to increase in the future, partly because it can be obtained via the Internet without a prescription (Daughton & Ternes, 1999).

5 Risks

5.1 Determining the risks

The following data are required for determining the risk of pharmaceuticals to humans and the environment:

1. The exposure time;
2. The (eco) toxicity of the pharmaceutical;
3. The concentration to be expected.

Continuous consumption of pharmaceuticals results in continuous emission of pharmaceuticals from households via domestic sewer water and sewage treatment plants into surface water throughout the entire year. Although a person's individual consumption may differ largly from time to time, the composition of the cocktail of pharmaceuticals leaving the sewage treatment plant is expected to be fairly constant throughout the year. Thus we are talking about long-term exposure to low concentrations of a large number of widely varying compounds.

Data on the toxicity for aquatic and terrestrial organisms are scarce (Römbke *et al.*, 1996; Halling-Sørensen *et al.*,1998; Daughton & Ternes, 1999; Webb, 2000a; Jørgensen & Halling-Sørensen, 2000). The ecotoxicity data available are mainly related to short-term tests (<72 hours) with standard organisms (bacteria (Microtox™ test), algae and water flea).

For humans there are many data of short-term exposure to high concentrations (such as when a pharmaceutical is used). However, data on long-term exposure of humans to low concentrations of pharmaceuticals are scarce.

Based on the literature, it may be stated that the concentrations are expected to be low, on the order of magnitude of a few ng/l in drinking

water and surface water and a few µg/l in the influent and effluent of sewage treatment plants (see supplement 4). Based on an average water consumption of two litres per day (Richardson & Bowron, 1985), the expected dose is no more than 1 µg/day. Webb (2000a) calculated that, assuming a worst-case estimate, the exposure via drinking water during an entire lifetime (70 years) is less than a daily dose for most pharmaceuticals. The risk to humans appears minor if considered this way.

However, considering the limited information it is difficult to make an exact estimate of the risks of pharmaceuticals in surface water, groundwater and drinking water to humans and the environment. However a number of aspects can be indicated, on the basis of the concentration data, which could *possibly* play a role at low concentrations, to wit:

- ecotoxicity;
- mutagenity, genotoxicity, carcinogenicity;
- resistance development in micro-organisms;
- allergic reactions in humans;
- endocrine effects.

Substances with an endocrine (hormonal) effect are discussed extensively in other publications, as already indicated in section 2.1, and are therefore not covered by the scope of this study. The other risks are elaborated in more detail in sections 5.2 through 5.6.

5.2 Ecotoxicity

The ecotoxicity data found in the literature are presented in supplement 6. A total of 456 entries were found for 76 substances and 6 metabolites. For some of the substances this involves several levels of effect (for example an EC_{10}-, EC_{50}- and EC_{90}-value) for the same organism, derived from the same basic data. For the main part, it involves acute toxicity data. Chronic toxicity data were found for 25 substances. This involves data for *Vibrio fischeri* in an adapted chronic test design of the Microtox™ test (38), for *Daphnia magna* (reproduction and lethality; 18), for the zebra fish *Brachydanio rerio*; (early life stage test; 6) and for aquatic plants (*Lythrum salicaria*; 20). The effect concentrations found are on the order of magnitude of a few to a few tens of µg/l. This is around or below the concentration level detected in the surface water. Thus, negative effects of pharmaceuticals on organisms in the surface water cannot be ruled out.

Figure 5.1 shows how the data are distributed among the different groups of organisms. It appears that by far the most data are related to tests with bacteria and crustaceans.

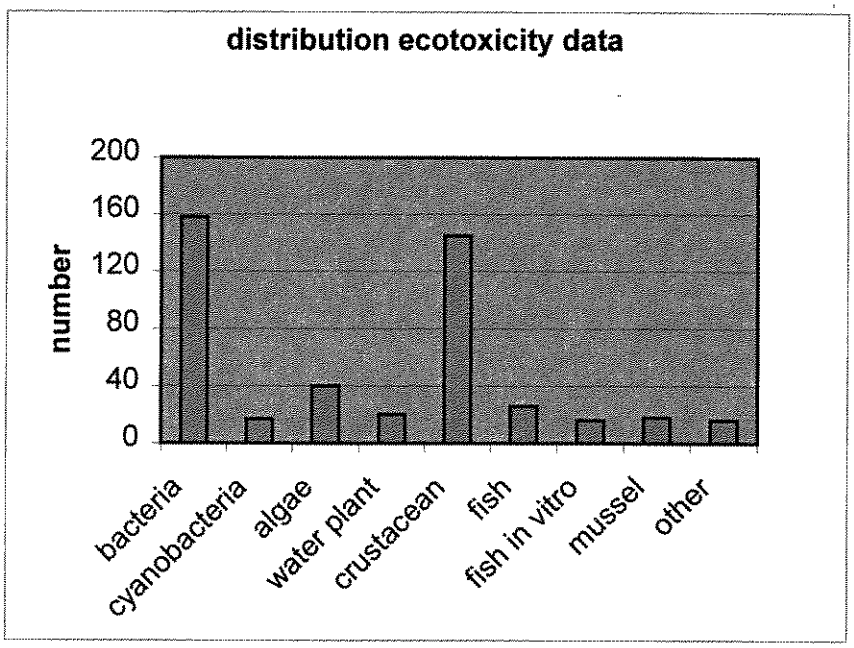


Figure 5.1 Distribution of the ecotoxicity data among the different types of test organisms.

Figures 5.2 and 5.3 present the further distribution of the data among different types of tests with bacteria and crustaceans. The bacterial tests involve mainly acute or chronic toxicity for the bacterium *Vibrio fischeri* in the Microtox™ test, tests in which the growth inhibition of in most cases the bacterium *Pseudomonas putida* is measured, and genotoxicity tests. The data on crustaceans (145 entries) involve principally acute toxicity for *Daphnia magna* (58.6%).

In addition to data in supplement 6, Predicted No Effect Concentrations (PNEC) are given in Webb (2000a) for 67 pharmaceuticals. Most of these pharmaceuticals are also used in the Netherlands. The PNEC values are derived from ecotoxicity data, taken into account a safety factor of 1000 for acute data, 100 if one NOEC value is known and 10 if chronic NOEC values are known for three trophic levels. In this calculation the lowest of the ecotoxicity data that is found is used. Since it is not stated which organism, test parameter and test duration are involved, the data in Webb (2000a) are not included in supplement 6. The ecotoxicity data used for determination of the PNEC value will be presented in Webb (2000b, in prep.).

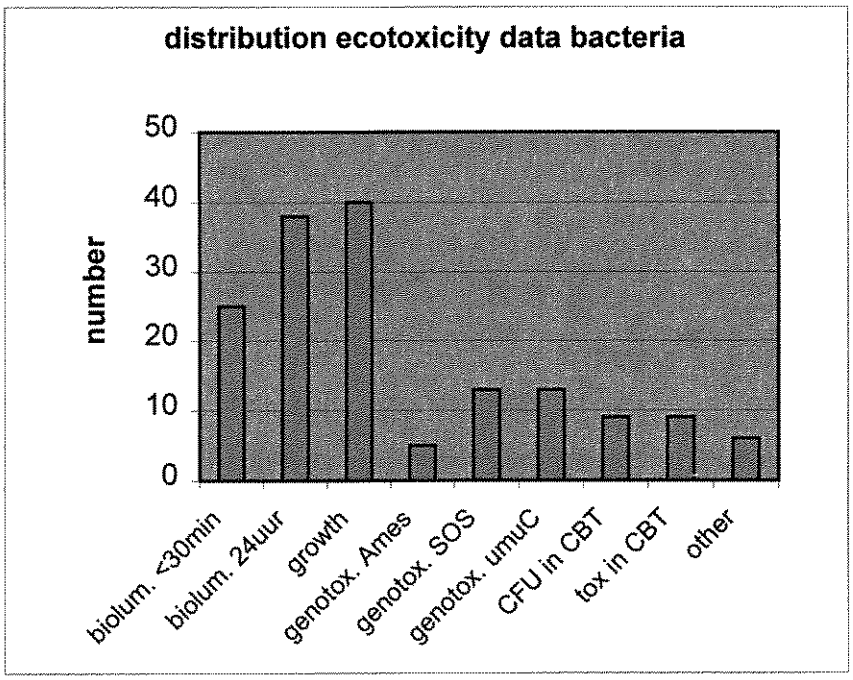


Figure 5.2 Distribution of ecotoxicity data on the bacteria. Biolum. = bioluminiscence; genotox. = genotoxicity; CFU in CBU = Colony Forming Units in Closed Bottle test; tox in CBT = toxicity in Closed Bottle Test.

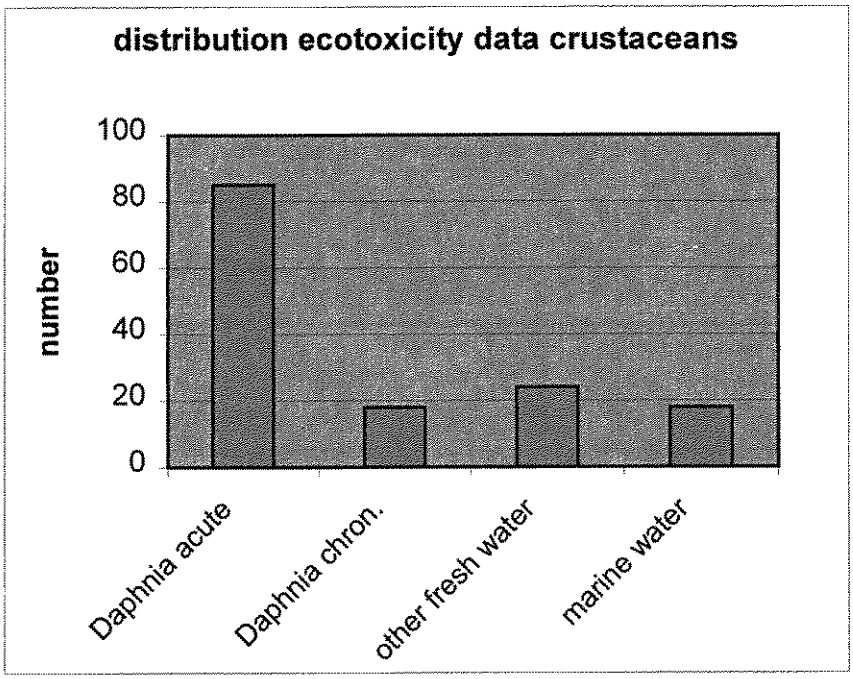


Figure 5.3 Distribution of the ecotoxicity data on crustaceans.

For acute EC_{50}- and LC_{50}-values, classification criteria have been established in EU directive 67/548/EEC. The acute toxicity data (EC_{50} and LC_{50}-values) from supplement 6 are summarised and assessed in table 5.1. The frequency distribution of the data collected by Webb is presented in table 5.2.

Table 5.1 Summary of the available acute ecotoxicity data (only the EC_{50} and LC_{50}-values) of the human pharmaceuticals from supplement 6.

ecotoxicity range	classification	number	frequency (%)	cumulative (%)
<0.1 mg/l	extremely toxic	9	7.0	7.0
0.1-1 mg/l	very toxic	6	4.7	11.7
1-10 mg/l	toxic	23	18.0	29.7
10-100 mg/l	harmful	31	24.2	53.9
100-1000 mg/l	not toxic	43	33.6	87.5
>1000 mg/l	not toxic	16	12.5	100.0
total		128		

Table 5.2 Summary of the available acute ecotoxicity data (only the EC_{50} and LC_{50}-values) of the human pharmaceuticals collected by Webb (from: Webb, 2000a).

Ecotoxicity range	classification	number	frequency (%)	cumulative (%)
<0.1 mg/l	extremely toxic	2	1.9	1.9
0.1-1 mg/l	very toxic	8	7.5	9.3
1-10 mg/l	toxic	22	20.6	29.9
10-100 mg/l	harmful	31	29.0	58.9
100-1000 mg/l	not toxic	37	34.6	93.5
>1000 mg/l	not toxic	7	6.5	100.0
total		107		

The classification of the data from Webb (2000a) and the data collected in this study show great similarities. This is not surprising since they are partly based on the same references. The difference is found mainly in the <0.1 mg/l class, the class of the very toxic substances. This involves especially EC_{50}-values for cyanobacteria, which appear to be extremely sensitive. The data with an EC_{50}-value <0.1 mg/l are displayed in table 5.3. It refers to the toxicity of various antibiotics for the bacterium *Pseudomonas putida* and the cyanobacterium *Microcystis aeruginosa*. In addition to table 5.3, mussels appear to be extremely sensitive to the antidepressant Fluvoxamine (Luvox). Spawning was induced in males at a concentration as low as 0.3 µg/l.

Table 5.3 Acute ecotoxicity data for human pharmaceuticals which are classified as extremely toxic (EC_{50}-value <0.1 mg/l). Test parameter: growth inhibition; test duration 16 hours for the bacterium *Pseudomonas putida* and 7 days for the cyanobacterium *Microcystis aeruginosa*

pharmaceutical	antibiotic group	EC_{50}-value growth inhibition (mg/l)	Reference
Pseudomonas putida			
Ofloxacin	fluoroquinolones	0.010 average (n=2)	Kümmerer *et al.* (2000)
Ciprofloxacin	fluoroquinolones	0.080 average (n=2)	Kümmerer *et al.* (2000)
Microcystis aeruginosa			
Amoxicillin	penicillins	0.0037	Holten Lützhøft *et al.* (1999)
Ciprofloxacin	fluoroquinolones	0.005	Holten Lützhøft & Halling-Sørensen (unpublished); from: Halling-Sørensen (2000)
Spiramycin	macrolids	0.005	Halling-Sørensen (2000)
Benzylpenicillin (Penicillin G)	penicillins	0.006	Halling-Sørensen (2000)
Streptomycin	others	0.007	Halling-Sørensen (2000)
Chlortetracycline	tetracyclines	0.05	Halling-Sørensen (2000)
Tetracycline	tetracyclines	0.09	Halling-Sørensen (2000)

The basic assumption is that the supply of pharmaceuticals in the field situation will be fairly constant in time. In a field situation there is therefore no short-term exposure, but a long-term one to a more or less constant concentration. Therefore, for a more realistic estimate of the possible risks to the environment chronic toxicity data are necessary.

In ECETOX (1993), a comparison is made between the ratio acute EC_{50} / chronic NOEC for different types of organisms, in both fresh and salt water. The toxicity data used for this are from the ECETOC Aquatic Toxicity (EAT) database. This database contains evaluated toxicity data of 368 chemical substances for 122 aquatic species in fresh and salt water. For 19 general chemicals (no pharmaceuticals) from this database which are used for comparison of the ratio between the acute EC_{50} / chronic NOEC, this ratio varied between 1.25 and 28.3. This means that the chronic NOEC-value in this case is about 30 times lower than the acute EC_{50}-value.

However, these data cannot be applied to pharmaceuticals just like that, since:

a) pharmaceuticals often have specific effect mechanisms which could have an unintended similar effect on vertebrates in the aquatic environment;

b) continuous exposure to (very) low concentrations of these substances occurs and;

c) the test methods being used for chemicals (acute and chronic toxicity tests) are not always equally useful for testing pharmaceuticals. To illustrate this, we refer to the example of Ethinyloestradiol, of which the acute toxicity (0.84 mg/l) differs from the lowest measured NOEC (0.001 µg/l) by a factor of 800,000.

In addition, in a field situation there will always be simultaneous exposure to several substances (pharmaceuticals AND other toxic substances). The combined effect of this cocktail is very difficult to predict.

Under the influence of toxic substances the species composition of natural micro-organisms may change, with sensitive species disappearing. In contrast to the described resistance (see section 5.4) this is achieved by acclimatisation of micro-organisms, which involves a shift in sensitivity within a species.

It has been demonstrated that residues of some types of antibiotics can temporarily inhibit natural bacterial processes in sediment (Anonymous, 1995).

It can be concluded that with the current knowledge for most human pharmaceuticals it is not possible to make a proper estimate of the ecotoxicological risk of human pharmaceuticals to the environment.

5.3 Genotoxicity and carcinogenicity

Genotoxic effects refer to all damage of genetic material. This may consist of minor or larger mutations (mutagenity) in genes, but also includes effects at the chromosome level. Carcinogenic effects refer to the development of tumours.

Genotoxic and carcinogenic effects both involve damage to hereditary material and therefore must be considered as serious. In principle, one single mutated cell can be sufficient to cause a tumour. However, a tumour is only developed after replication of the mutated cell. In addition, in order to develop a tumour the cell must have been mutated in such a way that it will begin to grow uncontrollable. It is well known that most mutations do not lead to development of tumours. In fact most mutated cells are not viable. Moreover, organisms have various repair mechanisms available to repair damaged genetic material from cells that do survive mutation. The only thing that is certain is that exposure to genotoxic and carcinogenic substances increases the chance of development of a tumour. Contact with such substances should therefore be avoided as much as possible. Some general aspects of genotoxic and carcinogenic processes are described in Van Genderen *et al.* (1994).

Effects on the genetic material have been found, among others, for:

- Cytostatics — mutagenic, genotoxic & carcinogenic (Aherne *et al.*, 1990; Van der Heide & Hueck-Van der Plas, 1982; Grahame-Smith & Aronson, 1992)
- Nitrofurans — (5-nitrofuranderivatives) mutagenic (among others, Anonymous, 1989)
- Sulfamethazine — carcinogenic (Barragry, 1994)
- Oxytetracycline — genotoxicity, combined with cytotoxicity (Giuliani *et al.*, 1996)

It is still unclear what the meaning of detection of genotoxicity in wastewater and drinking water is and how possible risks must be interpreted (Giuliani *et al.*, 1996). A possible relation between genotoxicity in, for instance, drinking water and the occurrence of tumours wil be very hard to demonstrate.

5.4 Antibiotics and development of resistance in micro-organisms

Development of resistance especially plays a role while using antibiotics. From the beginning of the use of these type of pharmaceuticals there has been concern about the possible development of resistant bacteria. This involves the so-called acquired or secondary resistance. This resistance can be acquired in different manners:

1. By genetic adaptation of micro-organisms. Two types of adaptations can be differentiated for this:
   a) By natural selection of bacteria (within one species) that by mutation have become insensitive to certain antibiotics. If, by using an antibiotic, the sensitive bacteria decrease in number, the resistant mutants will get the upper hand.
   b) Micro-organisms that are resistant to more than one antibiotic can have resistance factors (the 'R-factor') in their genetic material which can be transferred to non-resistant organisms. By this, these non-resistant organisms will suddenly become permanently insensitive. The R-factor often contains resistance genes to several antibiotics. This is referred to as cross-resistance. That means that a micro-organism is not only resistant to a certain antibiotic, but also to related substances. The cross resistance may be complete, meaning insensitivity to all related substances, or incomplete, meaning insensitivity to a certain antibiotic and reduced sensitivity to the related antibiotics. Complete cross-resistance occurs with penicillins, cefalosporins, macrolids, tetracyclines and a number of aminoglycosides. Partial cross-resistance occurs, among other pharmaceuticals, between tetracyclines and Chloroamphenicol, penicillins and cefalosporins and between macrolids and the lincomycine group. (Anonymous, 1989).

2. Resistance can also be caused by acclimatisation of the micro-organisms, meaning reduction of the sensitivity of micro-organisms after long term exposure. This resistance usually disappears after the administration of the antibiotic has stopped.

In particular the transfer of resistance genes has worried people. It is feared that the resistant bacteria will pass their resistance genes on to human bacteria. As a result of this the antibiotics will lose their effectiveness. Considering the serious consequences, much research has recently been carried out on resistance and transfer of resistance. The opinions on the possible risks are divided (Jagers op Akkerhuis *et al.*, 1995; Wilson, 1994; Anonymous, 1995; Zuidema & Klein, 1993, among other publications).

In order to prevent problems with resistance, in the Dutch hospitals a clear tendency has arisen to reserve new antibiotics for situations in which older pharmaceuticals are no longer effective (van Klingeren, 1990). In addition, the number of antibiotics for veterinary use has been restricted. When using antibiotics in animal feed, the substances are rotated (Jagers op Akkerhuis *et al.*, 1995; van Gool, 1990).

It can be concluded that the extent of the risks regarding transfer of resistance genes is still open for discussion.

5.5 Allergic reactions in humans

An other potential risk of the use of pharmaceuticals is the development of allergic reactions. An allergic reaction has a number of important characteristics (Grahame-Smith & Aronson, 1992):

- There is no dose-response relationship. Even very small quantities can cause a response once the allergy has developed. The reaction disappears when the contact with the substance is ceased;
- There is often a delay between the exposure and the response;
- The allergy manifests itself in a type of immunological response, for example fever, skin rash, a shift in the composition of the blood cells and asthma attacks.

Allergic reactions especially arise from the use of antibiotics. The allergy incidence for various antibiotics is: penicillins (10%), cephalosporins (5%), tetracyclines (5%); sulfonamides (13%) and Trimethoprim (3%) (Barragry, 1994).

Although it is estimated that 10 to 15% of the population is allergic to one or several antibiotics, few cases have been reported (Wilson, 1994). Reasons for the absence of registered cases of allergy caused by antibiotics may be that it is difficult to determine the cause of the allergy as well as to analyse the very low concentrations of pharmaceuticals that can already cause an allergic reaction.

Most of the cases reported are related to Penicillin allergy and are characterised by dermatitis (inflammation of the skin). In addition, an anaphylactic shock was observed in a number of cases (a certain

hypersensitivity response). Although rare, this has a very serious negative effect of the use of penicillin. The incidence is about 1 out of 2500 – 10000 patients.

The dose of Penicillin necessary to cause an allergic reaction is very low (Wilson, 1994). Minimal quantities (1 to 10 molecules) of Penicillin are capable of causing allergic reactions. However, for primary sensibilisation, somewhat higher concentrations are necessary (Adkinson, 1980).

The exent of the risk of allergic reactions due to the presence of pharmaceuticals in surface water or drinking water is still under discussion. Although very small quantities can cause allergic reactions, a direct relation between the presence and the expression of an allergic reaction has not been demonstrated.

6 Conclusions and recommendations

6.1 Conclusions

- Human pharmaceuticals cover a very diverse group of substances. The following pharmaceuticals were selected for further study, based on the expected high consumption, (bio)degradability, the available ecotoxicological data, the selection of substances in foreign studies and the representativeness of the type of pharmaceuticals for their class of substances:
    * Cardiovascular pharmaceuticals (blood lipid regulators and β-blockers)
    * Antiepileptics
    * Analgesics
    * Cytostatics
    * Antibiotics
    * Antidepressants
    * Iodinated X-ray contrasting agents
- Three emission routes by which human pharmaceuticals end up in the aquatic environment can be distinguished: the post-production industrial route, the post-usage domestic route and in the from unconsumed pharmaceuticals. Quantitatively, the domestic route makes the largest contribution. In this route, the human pharmaceuticals and their metabolites are, after consumption, excreted via urine and faeces and and are then discharged in the surface water after treatment in a sewage treatment plant. In the production of pharmaceuticals, the residual material is collected

carefully and recovered. The final residue is usually disposed of with the first flushing water as hazardous waste and incinerated in waste incinerator installations. The experience is that in batch productions about 0.2% of the active substance is discharged into the sewer with the second (and consequent) flushing water. In the Netherlands, 8,3% of the prescribed pharmaceuticals are not consumed. The majority of the unused pharmaceuticals (58%, i.e. 4.8% of the total amount of pharmaceuticals sold) are collected separately by handing them in to pharmacies. However, one third of the liquid pharmaceuticals handed in to the pharmacy still ends up in the sewer. About 3% of the unconsumed pharmaceuticals end up in the sewer via the consumer.

- The use of human pharmaceuticals leads to contamination of surface water, groundwater and incidentally drinking water. Measurement data for the Netherlands are available on a very limited scale. Of the thousands of active substances, only a very limited number of pharmaceuticals, approximately 85 active substances and 10 metabolites, are described in the international public literature with respect to the presence in and risks to the aquatic environment.
- As expected, the concentrations decrease along the emission route of wastewater from households, companies and hospitals, sewage water, sewage treatment plant effluent, surface water, groundwater and drinking water. The concentrations of human pharmaceuticals in surface water are between the detection limit and a few hundreds of ng/l, with several substances peaking above the µg/l. In influents and effluents from sewage treatment plants the concentrations are higher. Human pharmaceuticals are not, or only scarcely, present in drinking water (a few ng/l).
- Two substances, being the antiepileptic Carbamazepine and Clofibric acid, a stable metabolite of several blood lipid regulators, have been detected in nearly all matrices in relatively high concentrations. The presence of Clofibric acid, but not of Carbamazepine, was also demonstrated in drinking water.
- Based on the knowledge of possible adverse side effects of the use of pharmaceuticals, the expectation is that human health will not be affected due to consumption of drinking water with pharmaceuticals in the concentrations that have been detected. There is an extremely large margin between the maximum therapeutic dose and the sporadic concentration shown in drinking water (a factor of 10^6).
- Aquatic organisms in the surface water will be exposed to (very) low concentrations of several human pharmaceuticals as well as metabolites over a long period of time, possibly throughout their lives.
- There is still too little (public accessable) information available on the presence and the possible effects of low concentrations of human pharmaceuticals and their resulting metabolites in the water environment to enable a well-founded estimate of the risks for the water environment.

- By far, most ecotoxicity data are related to acute toxicity tests with bacteria and crustaceans. Chronic toxicity were only found on a limited scale. Furthermore, it is not inconceivable that pharmaceuticals may have a negative effect on non-target (aquatic) organisms even in low concentrations, just because of their specific effect mechanisms. There were no data on specific effect mechanisms found in the public literature.
- This lack of knowledge concerning the presence in the aquatic environment as well as chronic and specific toxicity of the initial substances and their metabolites, but above all the possible specific pharmacological effect of pharmaceuticals on non-target organisms, justifies further investigation of the possible negative effects on water organisms caused by human pharmaceuticals.
- The accepted acute toxicity tests are expected to be insufficient for detection of potential chronic and specific effects for aquatic organisms as a result of the presence of human pharmaceuticals in the (aquatic) environment. Chronic (toxicity) tests may give a more realistic estimate of the possible risks to the environment, although these tests also cannot give a definitive answer, as yet, on specific effect mechanisms. Except for tests that measure the disruption of hormones, no tests are available yet which measure specific effect mechanisms. For an adequate risk assessment of effects of pharmaceuticals in the environment, such specific tests will have to be developed.
- In the authorisation policy of human pharmaceuticals in the Netherlands and the EU, only the possible side effects and negative effects on humans are determined. There is no legal basis yet and there are no official directives for determining the possible risks to the (aquatic) environment as a result of the consumption of human pharmaceuticals. At the moment, a draft directive is being worked on within the EU. A question mark can be placed at the expected effectiveness of this draft directive for protection of the (aquatic) environment. In the first phase, calculation of the concentration of human pharmaceuticals in the (aquatic) environment is sufficient. If the expected environmental concentration does not exceed a certain limit value (0.01 µg/l) no ecotoxicological information will have to be submitted according to the law. However, it is not inconceivable that pharmaceuticals also may have a negative effect on non-target (aquatic) organisms in lower concentrations than this proposed limit value, because of their specific effect mechanisms. If the calculated concentration is higher than this limit value, a crude ecotoxicological risk assessment will have to be made. In this case, a PNEC is calculated mostly on the basis of acute toxicity divided by an uncertainty factor of 1000. If the PEN/PNEC ratio is higher than 1, a detailed additional ecotoxicological risk assessment is required.
- In 'worst case' estimates of the expected environmental concentrations of human pharmaceuticals in the Dutch surface water, it appears that the concentrations of substances under study, with the exception of the concentrations of Bezafibrate, Clofibrate,

Cefalexine and cytostatics in the large rivers, exceed the limit value of the provisional proposed limit value of the EU (0.01 µg/l). These estimates of the original substances are made on the basis of the consumption numbers (as human pharmaceutical) in the Netherlands and in this estimate the metabolization in humans or degradation, adsorption or evaporation in a sewage treatment plant as well as in surface water have not been taken into account.

- When comparing the 'worst case' estimates with the actually measured concentrations in surface water, it appears that the measured concentrations of initial substances in almost all cases clearly are below the 'worst case' estimates. Bezafibrate and Erythromycin are exceptions. An explanation for this could be that the measurements are related to foreign countries, especially Germany, where the consumption of these pharmaceuticals as well as the discharge situation may differ from those in the Netherlands.
- The knowledge of the risks to the environment of the different substance groups of 'human pharmaceuticals' can be summarised as follows:

type of pharmaceutical	consumption	concentration in surface water	biodegradability	availability ecotoxicological data
blood lipid regulators/β-blockers	+[1]	+	-	a, b[2]
antiepileptics	+	+	-	a, b
analgesics	++	-	+	a, b
cytostatics	--	--	--	a, c
antibiotics	+	-	-	a, b, c
antidepressants	?	?	?	D
Iodinated X-ray contrast media	?	++	--	a, b

1 ++ = very high, + = high, - = low and -- = very low
2 a = acute toxicity, b = chronic toxicity, c = genotoxicity, d = specific pharmacological effect

- This study of the literature provides good insight into the potential problem areas and possible problem substances within the substance group of 'human pharmaceuticals' for the aquatic environment, but does not answer the question of which substances are actual problems and which must be given priority attention.

6.2 Recommendations

With regard to the future, the following ecotoxicological, policy and technical research recommendations would help to gain a better overview of the potential side effects of the use of human pharmaceuticals on the aquatic environment, or at least help to focus attention on potential side effects.

- Prioritisation of problem substances.

Considering a lack of ecotoxicological data, potential problem substances will, in the first instance, have to be selected on the basis of the consumption of pharmaceuticals in the Netherlands. This should not only involve the active substances themselves but also their most important metabolites.Possible points of departure may be the substances reported on in the international literature and the information regarding possible side effects for people in the event of long-term use that is issued when the pharmaceuticals are authorised. Efforts to establish links with internationally selected substances may have the negative consequence of the focus remaining on the same substances all the time without any insight being created into the (environmental) relevance of these substances with regard to other human pharmaceuticals used but not yet researched in the Netherlands. Any reported side effects for humans may in some cases only give an indication of the possible relevance to the (aquatic) environment. A worst-case exposure estimate may serve as a first step for a general assessment of the risks. This would provide a basis for a more detailed elaboration of the risk assessment on the basis of metabolic degradation in humans and biological degradation, adsorption and evaporation in a sewage treatment plant or in surface water.

- Chemical monitoring.

  When in a worst-case estimate for a pharmaceutical an exposure concentration is calculated which is greater the detection limit of the analysis method, a chemical measurement campaign can provide additional insight into the actual concentrations which occur in the various matrices of sewer water, sewage treatment plant effluents, surface water, groundwater and drinking water.

- Generic risk analysis for the aquatic environment.

  The measured concentrations of pharmaceuticals will be combined with ecotoxicological measurement data to provide an indication of the environmental risk. The ecotoxicological research should, however, link up with the period of exposure in the environment and the time required for the effect to become noticeable. Because water organisms in surface water will be continuously exposed to (very) low concentrations of various pharmaceuticals, chronic (toxicity) tests would appear to be the most suitable. A combination of a number of chronic toxicity tests will allow a wide-spectrum risk analysis to be carried out that is independent of the specific effect mechanisms of the various pharmaceuticals.

- Specific risk analysis for the aquatic environment.

  Due to the often very specific pharmacological effect mechanisms of pharmaceuticals, it is conceivable that possible specific effects will occur even at very low concentrations. A possible risk analysis should be explicitly linked to the type of effect mechanism of a group of pharmaceuticals, as for example the effect on the hormone or immune system. Such biological testing methods are currently not, or only partially, available. It is recommended that an assessment is made of which specific pharmacological effect mechanisms can affect aquatic organisms and that specific biological test methods are developed which

can be used in the future when screening the active substances and their metabolites. These newly developed testing methods can also be used in the future for the biological monitoring of aquatic systems in addition to the collection of chemical data.

- Resistance development.

  It is also desirable that attention is paid to the consequences of low concentrations of antibiotics on water organisms, such as resistance development.

- Attention to (local) discharge of pharmaceuticals.

  In the production of pharmaceuticals consideration may be given to (further) minimising the amount of residual substances in the tanks at the end of the production process. In hospitals, etc., their use may be reserved as much as possible. For unconsumed pharmaceuticals, it should be considered to promote and improve the collection system for unconsumed pharmaceuticals in order to prevent these substances from ending up in the (aquatic) environment.

- International co-operation.

  Considering the complexity of a suitable method for assessing the risk pharmaceuticals pose to water organisms, as well as the comparable character of investigations and research requests in the countries around us, international co-operation and fine-tuning within the EU would obviously be a good idea. The international results could be used in the future in the further elaboration of a definitive European directive for the environmental risk assessment in relation to human pharmaceutical authorisation.

- Legislation and regulation.

  Further development of a European directive which can be used for the environmental risk assessment of pharmaceuticals will have to be carried out by the authorised agencies.

7 Bibliography

Adkinson, N.F. (1980). Immunological consequenses of antimicrobials in animal feeds. In: The effects on human health of subtherapeutic use of antimicrobials in animal feeds. National Academy of Science NAS. Washington D.C.: p301-316.

Aherne, G.W., J. English & V. Marks (1985). The role of immunoassay in the analysis of microcontaminants in river samples. Ecotoxicology and Environmental Safety 9(1): 79-83.

Aherne, G.W., A. Hardcastle & A.H. Nield (1990). Cytotoxic drugs and the aquatic environment: estimation of bleomycin in river and water samples. Journal of Pharmacy and Pharmacology 42: 741-742.

Al-Ahmad, A., F.D. Daschner & K. Kümmerer (1999). Biodegradability of Cefotiam, Ciprofloxacin, Meropenem, Penicillin G and Sulfamethoxazole and inhibition of waste water bacteria. Archive of Environmental Toxicology 37: 158-163.

Anonymus (1989). Repertorium diergeneesmiddelen: overzicht voor dierenartsen, 5e editie 1989/1990. Vereniging van Fabrikanten en Importeurs van Diergeneesmiddelen in Nederland FIDIN, Amsterdam. 264p.

Anonymus (1993). Stoffen en Normen. Overzicht van belangrijke stoffen en normen in het milieubeleid 1993-1994. Directoraat-Generaal Milieubeheeer Ministerie van Volkshuisvesting Ruimtelijke ordening en Milieubeheer, Den Haag. 458p.

Anonymus (1995). Aquaculture and the environment in the european community. European Commission Directorate-General for Fisheries. Luxembourg. 87p.

Anonymus (2000). Pharmaceuticals in the Environment. March 9, 2000, Hotel Sofitel, Brussels. Georganiseerd door Technological Institute, Section on Evironmental Technologie (TI KVIV), België.

Assche, van J. (2000). The fate of expired pharmaceuticals in Belgium. Presentatie op het internationale seminar 'Pharmaceuticals in the Environment' March 9, Hotel Sofitel, Brussels. Georganiseerd door Technological Institute, Section on Evironmental Technologie (TI KVIV), België.

AWWR (1996). Ruhrwassergute 1995. Ruhrverband & Arbeitsgemeinschaft der Wasserwerke an der Ruhr (AWWR). Essen, Duitsland.

Ayscough, N.J., J. Fawell, G. Franklin & W. Young (2000). Review of human pharmaceuticals in the environment. Research Contractor: WRc-NSF Ltd., Marlow, Buckinghamshire. R&D Technical Report P390. WRc Report no. EA 4761. Published by the Environmental Agency, Bristol, England.

Backhaus, T. & L.H. Grimme (1999). The toxicity of antibiotic agents to the luminescent bacterium *Vibrio fischeri*. Chemoshpere 38(14): 3291-3301.

Barragry, T.B., with the assistance of Thomas Power (1994). Veterinary Drug Therapy. Leo & Febiger, Malvern, Pennsylvania, USA. 1076p.

Belfroid, A.C., A.J. Murk, P. de Voogt, A.J. Schäfer, G.B.J. Rijs & A.D. Vethaak, met bijdragen van J.H.N. Meerman, E.G. van der Velde & J. de Boer (2000). Hormoonontregelaars in water. Oriënterende studie naar de aanwezigheid van oestrogeen-actieve stoffen in watersystemen en afvalwater in Nederland. Rijksinstituut voor Integraal Zoetwaterbeheer en Afvalwaterbehandeling (RIZA), Lelystad en Rijksinstituut voor Kust en Zee (RIKZ), Middelburg. RIZA-rapportnummer 99.007, RIKZ-rapportnummer 99.024.

Berking, S. (1991). Effects of the anticonvulsant drug Valproic acid and related substances on developmental processes in hydroids. Toxic. In Vitro 5(2): 109-117.

Blasius, H. & H. Cranz (1998). Arzneimittel und recht in Europa. Wissenschaftliche Verlagsgesellschaft mbH Stuttgart. 164p.

Blom, A.Th.G., J.C.M.J. de Bruijn & J.G.A.M. de Jong (1995). Verspilling. Faculteit Farmacie, Universiteit Utrecht, Utrecht.

Boekema, A.G., N.J. Dam, A. Direcks, W. Duchenne – van den Berge & P.P.A. Razenberg (1997). Zakboekje Cytostatica 2. Werking en bijwerkingen. Integraal Kankercentrum Stedendriehoek Twente, Enschede.

Brambilla, G., C. Civitareale & L. Migliore (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(1): 114-118.

Burhenne, J., M. Ludwig, P. Nikoloudis & M. Spiteller (1997a). Photolytic degradation of fluoroquinolone carboxylic acids in aqueous solution. Primary photoproducts and half-lives. Environ. Sci. Pollut. Res. 4: 10-15.

Burhenne, J., M. Ludwig & M. Spiteller (1997b). Photolytic degradation of fluoroquinolone carboxylic acids in aqueous solution. Isolation and structural elucidation of polar photometabolites. Environ. Sci. Pollut. Res. 4: 61-71.

Buser, H.-R., M.D. Müller & N. Theobald (1998a). Occurrence of the pharmaceutical drug clofibric acid and the herbicide mecoprop in various swiss lakes and in the North Sea. Environmental Science and Technology 32(1): 188-192.

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

Calleja, M.C., G. Persoone & P. Geladi (1993). The predictive potential of a battery of ectoxicological tests for human acute toxicity as evaluated with the first 50 MEIC chemicals. ATLA (21): 330-349.

Cannavan, A., S.A. Hewitt, W.J. Blanclhflower & D.G. Kennedy (1996). Gas chromatographic-mass spectrometric determination of sulfamethazine in animal tissues using a methyl/trimethylsilyl derivative. Analyst (Cambridge, U.K.) 121: 1457-1461.

Canton, J.H. & C.J. van Esch (1976). The short-term toxicity of some feed additives to different freshwater organisms. Bulletin of Environmental Contamination & Toxicology 15(6): 720-725.

CBG (1999). Lijst van farmaceutische producten. 2e en 3e kwartaal 1998. College ter Beoordeling van Geneesmiddelen (CBG), Den Haag. Uitg. Koninklijke Vermande, Lelystad.

CBS (1997). Vademecum gezondheidsstatistiek Nederland 1997. Centraal Bureau voor de Statistiek (CBS), Ministerie van Volksgezondheid, Welzijn en Sport. SDU uitgeverij, Den Haag; CBS-publicaties, 1997.

Daughton, C.G. & T.A. Ternes (1999). Pharmaceuticals and Personal Care Products in the environment: agents of subtle change? Environmental Healthe Perspectives 107(6): 907-938.

Delupis, di G.D., A. Macri, C. Civitareale & L. Migliore (1992). Antibiotics of zootechnical use: effects of acute high and low dose contamination on Daphnia magna Straus. Aquatic Toxicology 22: 53-60.

Derksen, J.G.M. & L.R.M. de Poorter (1997). Geneesmiddelen in oppervlaktewater. Aanwezigheid en risico's. In opdracht van Samenwerkende Rijn- en Maaswaterleidingbedrijven (RIWA), Amsterdam. Eindredactie: RIWA projectgroep Stofstudies. Vertrouwelijk.

DIA (2001). Manual DIA workshop on Environmental Risk Assessment of non-GMO Pharmaceuticals. 12-13 February 2001. London, UK.

EMEA (2001). *Draft* CPMP discussion paper on environmental risk assessment of non-genetically modified organism (non-gmo) containing medicinal products for human use. DIA workshop on Environmental Risk Assessment of non-GMO Pharmaceuticals. 12-13 February 2001. London, UK.

ECETOX (1993). Aquatic toxicity data evaluation. Technical Report No. 56. European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOX), Brussels.

Elvers, K.T. & S.J.L. Wright (1995). Antibacterial activity of the anti-inflammatory compound Ibuprofen. Letters in Applied Microbiology 20: 82-84.

European Commision (1994). 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 4. European Commission, Directorale-General Industry, III/E/3 Pharmaceuticals Service, Ad Hoc Working Party on environmental risk assessment for non GMO containing medicinal products, Brussels.

Falter, R. & R.-D. Wilken (1999). Determination of carboplatinum and cisplatinum by interfacing HPLC with ICP-MS using ultrasonic nebulisation. The Science of the Total Environment 22: 167-176.

FDA (1998). Guidance for industry. Environmental assessment of human drug and biologics applications. U.S. Department of Health and Humna Services, Food and Drug Administration (FDA). Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). July 1998, CMC 6, Revision 1.

Fong, P.P. (1998). Zebra mussel spawning is induced in low concentrations of putative serotonin reuptake inhibitors. Biol. Bull. 194: 143-149.

Fong. P.P., P.T. Hulminski & L.M. D'Urso (1998). Induction and potentation of parturition in fingernail clams (*Sphaerium striatinum*) by Selective Serotonin Re-Uptake Inhibitors (SSRIs). The Journal of Experimental Zoology 280: 260-264.

Franke, S., S. Hildebrandt, J. Schwarzbauer, M. Link & W. Francke (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 Analytic Chemistry 353: 39-49.

Gärtner (1998). Rechtliche Regelungen zu den Umweltauswirkungen von Arzneimitteln. In: B. Toussaint (ed.). Arzneimittel in Gewässern. Risiko für Mensch, Tier und Umwelt? 4. Juni 1998, Landesmuseum Wiesbaden. Hessische Landesanstalt für Umwelt.

Genderen, J. van, Th.H.M. Noij & J.A. van Leerdam (1994). Inventarisatie en toxicologische evaluatie van organische microverontreinigingen aangetoond in Rijn, Maas, IJsselmeer en Haringvliet alsmede in het daaruit bereide drinkwater. Samenwerkende Rijn- en Maaswaterleidingbedrijven RIWA, Amsterdam. 259p.

Gezondheidsraad (1998). Commissie antimicrobiële groeibevorderaars. Antimicrobiële groeibevorderaars. Rijswijk, Publicatie nr. 1998/15.

Gezondheidsraad (1999). Hormoonontregelaars in ecosystemen. Beraadsgroep Ecotoxicologie. Den-Haag. Publicatie 1999/3.

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

Grahame-Smith, D.G. & J.K. Aronson (1992). Oxford textbook of clinical pharmacology and drug therapy. Oxford University Press, Oxford. 756p.

Gool, S. van (1990). Diergeneesmiddelen, wie wordt er eigenlijk beter van? Stichting Natuur en Milieu, Utrecht. 43p.

Haberer, K & T.A. Ternes (1996). Bedeutung von wasserwerksgängigen Metaboliten für die Trinkwasserversorgung. Wasser·Abwasser 137(10): 573-577.

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

Halling-Sørensen, B. (2000). Algal toxicity of antibacterial agents used in intensive farming. Chemosphere 40: 731-739.

Harrass, M.C., A.C. Kindig & F.B. Taub (1985). Response of blue-green and green algae to Streptomycin in unialgal and paired culture. Aqua. Toxicol. 6: 1-11.

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

Hartmann, A., E.M. Golet, S. Gartiser, A.C. Alder, T. Koller & R.M. Widmer (1999). Primary DNA damage but not mutagnicity correlates with Ciprofloxacin concentrations in German hospital wastewaters. Environmental Contamination and Toxicology 36: 115-119.

Heberer, Th. (1995). Identification and quantification of pesticide residues and environmental contaminants in ground and surface water applying cpillary gas chromatography - mass spectrometry. TU Berlin thesis (in German). 437p.

Heberer, T. & H.-J. Stan (1994). Polare Umweltkontaminanten im aquatischen System. Vorkommen und Identifizierung mittels GC-MS. GIT Fachz. Lab. 8: 718-719.

Heberer, T. & H.-J. Stan (1996a). Determination of trace levels of Dichlorprop, Mecoprop, Clofibric acid, Naphthylacetic acid in soil by gas chromatography/mass spectrometry with selected-ion monitoring. Journal of AOAC international 79 (6):1428-1433.

Heberer, T. & H.-J. Stan (1996b). Vorkommen von polaren organischen Kontaminanten in Berliner Trinkwasser. Vom Wasser 86: 19-31.

Heberer, T. & H.-J. Stan (1997). Determination of Clofibric acid and N-(phenylsulfonyl)-Sarcosine in sewage, river, and drinking water. International journal of international environmental analytical chemistry 67: 113-124.
Heberer, T. & H.-J. Stan (1998). Arzneimittelrückstände im aquatischen system. Wasser & Boden 50 (4): 20-25.
Heberer, T., S. Butz & H.J. Stan (1995). Int. J. Environ. Anal. Chem. 58: 43-53.
Heberer, T. & U. Dünnbier, Ch. Reilich & H.-J. Stan (1997). Detection of drugs and drug metabolites in groundwater samples of a drinking water treatment plant. Fresenius Environmental Bulletin 6: 438-443.
Heberer, T., K. Schmidt-Bäumler & H.-J Stan (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 hydrochim. Hydrobiol. 26 (5): 272-278.
Heide, E.F. van der & E.H. Hueck-van der Plas (1982). Geneesmiddelen en Milieu. Studie- en Informatiecentrum TNO voor Milieu-Onderzoek. 54p.
Heide, E.E. van der & E.H. Hueck van der Plass (1984). Geneesmiddelen en milieu. Pharmaceutisch weekblad 119: 936-947.
Henschel, K.-P., A. Wenzel, M. Diedrich & A. Fliedner (1997). Environmental harzard assessment of pharmaceuticals. Regulatory toxicology and pharmacology 25: 220-225.
Herrmann (1993). Effects of the anticonvulsant drug Valproic acid and related substances on the early development of the zebra fish (*Brachydanio rerio*). Toxic. in Vitro 7(1): 41-54.
Hignite, C. & D.L. Azarnoff (1977). Drugs and drug metabolites as environmental contaminants: chlorophenoxy-isobutryrate and salicylic acid in sewage water effluent. Life Sciences 20: 337-342.
Hirsch, R. (1998). Antibiotika in der Umwelt. In: B. Toussaint (ed.). Arzneimittel in Gewässern. Risiko für Mensch, Tier und Umwelt? 4. Juni 1998, Landesmuseum Wiesbaden. Hessische Landesanstalt für Umwelt.
Hirsch, R., T.A. Ternes, K. Haberer, & K.L. Kratz (1996). Nachweis von Betablockern und Bronchospasmolytika in der aquatischen Umwelt. Vom Wasser 86: 263-274.
Hirsch , R., T.A. Ternes, K. Haberer, A. Mehlich, F. Ballwanz & K.L. Kratz (1998). Determination of antibiotics in different water compartments via liquid chromatography-electrospray tandem mass spectrometry. Journal of Chromatography A: 213-223.
Hirsch, R.,T. Ternes, K. Haberer & K.-L. Kratz (1999). Occurrence of antibiotics in the environment. The Science of the Total Environment 225:109-118.
Hirsch, R., T.A. Ternes, A. Lindart, K. Haberer & R.-D. Wilken (2000). A sensitive method for the determination of iodine containing diagnostic agents in aqueous matirces using LC-electrospray-tandem-MS detection. Fresenius Journal of Analytical Chemistry 366: 835-841.
Holten Lützhøft, H.-C., B. Halling-Sørensen & S.E. Jørgensen (1999). Algal toxicity of antibacterial agents applied in Danish fish farming. Archives of Environmental Contamination and Toxicology 36: 1-6.
Jagers op Akkerhuis, G.A.J.M., L. den Boer & G.A. Pak (1995). Toevoegingen aan veevoer, Verantwoord of verdacht?. Centrum voor Landbouw en Milieu CLM, Utrecht. 79p.
Jørgensen, S.E. & B. Halling-Sørensen (2000). Drugs in the environment. Editorial. Chemosphere 40 (special issue): 691-699.

Kalbfus, W. (1997). Belastung bayerischer Gewässer durch Lipidsenker. In: Bayerisches Landesamt für Wasserwirtschaft. Stoffe mit endokriner Wirkung im Wasser. Münchener Beiträge zur Abwasser-, Fischerei- und Flussbiologie Band 50, Oldenbourg, München: 190 -198.

Kalbfus, W. & W. Kopf (1997). Ansätze zur ökotoxikologischen Bewertung von Pharmaka in Oberflächengewässern. 51. Fachtagung Bayerisches Landesamt für Wasserwirtschaft, 1996. Munich, Deutschland.

Kalsch, W. (1999). Biodegradation of the iodinated X-ray contrast media diatrizoate and iopromide. The Science of the Total Environment 225: 143-153.

Kamstra, A. & J.W. van der Heul (1995). Afvalwater van Viskwekerijen. Dienst Landbouwkundig Onderzoek Rijksinstituut voor Visserijonderzoek RIVO-DLO, IJmuiden. 64p.

Klingeren, B. van (1990). Microbiologische risico's van veterinair antibioticumgebruik. PAON-cursus Veterinaire Farmaca: nieuwe ontwikkelingen en residu-problematiek. Zeist.

Knoll (1995). BASF Pharma safety data sheet: Ibuprofen. Issue/revision data 6/4/95. Knoll Pharmaceuticals, Nottingham, England.

Kopf, W. (1997). Wirkung endokriner Stoffe in Biotests mit Wasserorganismen. Münchener Beiträge zur Abwasser-, Fischerei- und Flussbiologie. Band 50, Stoffe mit endokriner Wirkung im Wasser

Krämer, I. & H.M. Wendel (1988). Wachtsumverhalten ausgewählter Mikroorganismen in Zytostatika-Zubereitungen. In: Krankenhauspharmazie 9: 439-442.

Kuiper (1982). Diergeneesmiddelen en veevoederadditieven. In: Syllabus Voedingsmiddelentoxicologie. Vakgroep Toxicologie. Landbouw Universiteit Wageningen.

Kümmerer K., T. Steger-Hartmann, A. Baranyai & I. Bürhaus (1996). Evaluation of the biological degradation of the antineoplastics Cyclophosphamide and Ifosfamide with the Closed Bottle Test (OECD 301 D). Zbl Hyg. 198: 215-225.

Kümmerer, K., T. Steger-Hartmann & M. Meyer (1997). Biodegradability of the anti-tumour agent Ifosfamide and its occurrence in hospital effluents and communal sewage. Water Resources 31(11): 2705-2710.

Kümmerer, K., A. AL-Ahmad & V. Mersch-Sundermann (2000). Biodegradability of some antibiotics, elimination of the genotoxicity and affection of wastewater bacteria in a simple test. Chemosphere 40: 701-710.

Kümmerer, K. (2000). Occurrence, fate and effect of pharmaceuticals in the environment. Presentatie op het internationale seminar 'Pharmaceuticals in the Environment' March 9, Hotel Sofitel, Brussels. Georganiseerd door Technological Institute, Section on Evironmental Technologie (TI KVIV), België.

Kyak, P.J. (1994). Confirmation of chloramphenicol residues in bovine milk by gas chromatography/mass spectrometry. J. AOAC Int. 77: 34-40.

Lanzky, P.F. & B. Halling-Sørensen (1997). The toxic effect of the antibiotic Metronidazole on aquatic organisms. Chemosphere 35(11): 2553-2561.

Lilius, H., B. Isomaa & T. Holmström (1994). A comparison of the toxicity of 50 reference chemicals to freshly isolated rainbow trout hepatocytes and *Daphnia magna*. Aquatic Toxicology 30: 47-60.

Liebmann, H. (1961). Erfahrungen bei der Beseitigung und Reinigung von Krankenhausabwässern, mit besonderer Berücksichtigung der Beeinflussung der Klärprozesse durch Antibiotika. In: Liebmann, H., red. Die Reiningung von Abwässern aus Schlachthöfen und Krankenhäusern. Verlag R. Oldenburg, München. 163-173.

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

Linders, J.B.H.J., J.W. Jansma, B.J.W.G. Mensink & K. Otermann (1994). Pesticides: benefaction of pandora's box? A synopsis of the environmental aspects of 243 pesticides. National Institute of Public Health and Environmental Protection, RIVM, Bilthoven, Holland. Report no. 679101014. 204p.

Lindner, K, T.P. Knepper, F. Karrenbrock, O. Rörden, H.J. Brauch, F.T. Lange & F. Sacher (1996). Erfassung und Identifizierung von trinkwassergängigen Einzelsubstanzen in Abwässern und im Rhein. Abschlußbericht. ARW/VCI-Forschungsvorhaben. Internationale Arbeitsgemeinschaft der Wasserwerke im Rheineinzugsgebiet IAWR, Rhein-themen 1. 180p.

Macri, A., A.V. Stazi & G.D. Di Delupis (1998). Acute toxicity of Furazolidone on *Artemia salina*, *Daphnia magna* and *Culex pipiens molestus* larvae. Ecotoxicology and Environmental Safety 16: 90-94.

Martens, R., H.G. Wetzstein, F. Zadrazil, M. Capelari, P. Hoffman & M. Schmeer (1996). Degradation of the fluoroquinolone enrofloxacin by wood-rotting fungi. Applied Environmental Microbiology 62: 4206-4209.

Meer, L. van der, P.J. Meijer & G.C. Duvoort (1992). Aanwijzing klein chemisch afval uit huishoudens. Publicatiereeks afvalstoffen nr. 1992/20. Ministerie van Volkshuisvesting, Ruimtelijke Ordening en Milieubeheer, Directoraat-Generaal Milieubeheer (VROM/DGM).

Mersch-Sundermann, V., K.-H. Hauff, P. Braun, L. Wenqing & H. Hof (1994). DNA damage caused by antibiotic drugs: Quinolones. International Journal of Oncology 5: 855-859.

Migliore, L., C. Civitareale, G. Brambilla & G.D. Di Delupis (1997). Toxicity of several important agricultural antibiotics to *Artemia*. Water Research 31(7): 1801-1806.

Migliore, L., S. Cozzolino & M. Fiori (2000). Phytotoxicity to and uptake of Flumequine used in intensive aquaculture on the aquatic weed, *Lythrum salicaria* L. Chemosphere 40: 741-750.

Mons, M.N., J. van Genderen & A.M. van Dijk-Looijaard (2000). Inventory on the presence of pharmaceuticals in Dutch water. RIWA, VEWIN & Kiwa. Kiwa Research & Consultancy, Nieuwegein.

Montforts, M.H.M.M. & J.B.H.J. Linders (1997). Ecotoxicologische beoordeling diergeneesmiddelen Fase I. De Nederlandse procedure. A. Verspreiding via bemesting volgens EMEA/CVMP/055/96-final note for guidance. Rijksinstituut voor Volksgezondheid, Centrum voor Stoffen en Risicobeoordeling (RIVM-CSR).

Möhle, E., S. Hilbert, J.W. Metzger, W. Merz (1997). Identifizierung umweltrelevanter Stickstoffverbindungen inm Abwasser. Poster auf der Jahrestagung 1997 der Fachgruppe Wasserchenie der Gesellschaft Deutsher Chemiker (GDCh) 5 bis 7 Mai 1997 in Lindau.

Möhle, E., S. Holvart, W. Merz & J.W. Metzger, (1999). Bestimmung von schwer abbaubaren Verbindungen im Abwasser - Identfizierung von Arzneimittelrückständen. Vom Wasser 92: 207-223.

Nefarma (1998). Farmafeiten 95/96. Http://www.nefarma.nl/feiten/index.htm, 11/11/98. Oorspronkelijke bron IMS en OECD Health Data, 1995.

Nefarma (1999). Repertorium 98/99. Overzicht van door het College ter beoordeling van geneesmiddelen geregistreerde informatieteksten van farmaceutische spécialités. Nefarma, Utrecht. Sdu, Den Haag.
Nickell, L.G. & A.C. Finley (1954). Growth modifers. Antibiotics and their effects on plant growth. Agr. Food Chem. 2: 178.
Oranjewoud (1999). Effecten van cytostatica in afvalwater. Documentnr. 843-10. In opdracht van Pharmachemie.
Pendland, S.L., S.R. Pisoitellie, P.C. Schreckenberger & L.H. Danziger (1994). In vitro activities of Metronidazole and its hydroxy metabolite against *Bacteriodes* spp.. Antimicrob. Agents. Chemother. 38(9): 2106-2110.
Polderman, A.K.S. (1984). Afvalverwerking in de farmaceutische industrie. Pharmaceutisch Weekblad 119: 951-963.
Pursell, L., O.B. Samuelsen & P. Smith (1995). Reduction in the in-vitro activity of Flumequine against *Aeromonas salmonicida* in the presence of the concentration of Mg2+ and Ca2+ ions found in seawater. Aquaculture 135: 245-255.
Richardson, M.L. & J.M. Bowron (1985). The fate of pharmaceutical chemicals in the aquatic environment. Journal of Pharmacy and Pharmacology (37): 1-12.
Roij, Th.A.J.M. de & P.H.U. De Vries (1982). Milieutoxicologische aspecten van het gebruik van veevoederadditieven en therapeutica. Persistentie in dierlijke excreta en milieu. Ministerie van Volksgezondheid en Milieuhygiëne VROM. Serie Bodembescherming 4: 1-134.
Rosenberg, D., I. Rehmann & C. Gloege (1994). Der Verbleib von Iopromid in der Umwelt, Schering Report SPA 08/94 (niet openbaar). Uit: Steger-Hartmann *et al.* (1998). Vom Wasser 91: 185-194.
Rote Liste (1996). Arzneimittelverzeichnis des BPI. Hrsg: Bundesverband der pharmazeutischen Industrie e.V., ECV Editor Cantor Verlag für Medizin und Naturwissenschaften GmbH.
Römbke, J., Th. Knacker & P. Stahlschmidt-Allner (1996). Umweltprobleme durch Arzneimittel. Literaturstudie. Texte 60-96. Umweltbundesamt, Berlin.
Sacher, F, E. Lochow, D. Bethmann, H.J. Brauch (1997). Vorkommen von Arzneimittelwirkstoffen in Oberflachenwassern. Poster auf der Jahrestagung 1997 der Fachgruppe Wasserchenie der Gesellschaft Deutsher Chemiker (GDCh) 5 bis 7 Mai 1997 in Lindau.
Sacher, F., E. Lochow, D. Bethmann & H-J. Brauch (1998). Vorkommen von Arzneimittelwirkstoffen in Oberflächenwässern. Vom Wasser 90: 233-243.
Sanyal, A.K., D. Roy, B. Chowdhury & A.B. Banerjec (1993). Ibuprofen, a unique anti-inflammatory compound with antifungal activity against dermatophytes. Letters in Applied Microbiology 17: 109-111.
Seel, P. (1998). Arzneimittel in Gewässern - neue Umweltchemikalien. In: Arzneimittel in Gewässern. Risiko für Mensch, Tier und Umwelt? B. Toussaint (Ed.). Fachtagung, 4. Juni 1998, Landesmuseum Wiesbaden.
SFK (1998). Data en feiten 1998. Kostenontwikkeling van de farmaceutische hulp. September 1998. Stichting Farmaceutische Kengetallen (SFK), Den Haag. 65p.
Spindler, P. (2000). Global trends in environmental legislation for nog-GMO pharmaceutical for use in humans. Presentatie op het internationale seminar 'Pharmaceuticals in the Environment' March 9, Hotel Sofitel, Brussels. Georganiseerd door Technological Institute, Section on Evironmental Technologie (TI KVIV), België.
Stahlschmidt-Allner, P. (1996). ECT Ökotoxikologie, Flörsheim, Duitsland. In: Der Spiegel 26/1996.

Stan, H.J., T. Heberer & M. Linkerhägner (1994). Vorkommen von Clofbrinsäure im aquatischen system - Führt die therapeutische Anwendung zu einer Belastung von Oberflächen-, Grund- und Trinkwasser?-. Vom Wasser 83: 57-68.

Stan, H.J. & T. Heberer (1997). Pharmaceuticals in the aquatic environment. *Analusis* Magazine 25 (7): 20-23.

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

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

Steger-Hartmann, T., R. Länge & H. Schweinfurth (1998). Umweltverhalten und ökotoxikologische Bewertung von iodhaltigen Röntgenkontrastmitteln. Vom Wasser 91: 185-194.

Stoyanov, I.S., I.G. Nicolov, I.N. Chernozemsky & I. Stoichev (1987). Assessment for mutagenicity of 10 pharmaceutical products following Ames, micronucleus and sperm morphology testing. Toxicity Assessment: An International Quarterly 2: 207-215.

Stumpf, M., T.A. Ternes, K. Haberer, P. Seel & W. Baumann (1996). Nachweis von natürlichen und synthetischen Östrogenen in Kläranlagen und Fließgewässern. Vom Wasser 87: 251-261.

Stumpf, M., T.A. Ternes, K. Haberer, P. Seel & W. Baumann (1996). Nachweis von Arzneimittelrückständen in Kläranlagen und Fließgewässern. Vom Wasser 86: 291-303.

Stumpf, M., T.A. Ternes, K. Haberer & W. Baumann (1998). Isolierung von Ibuprofen-Metabolieten und deren bedeutung als kontaminanten der aquatischen Umwelt. Vom Wasser 91: 291-303.

Stumpf, M., T.A. Ternes, R.-D. Wilken, S.V. Rodrigues & W. Baumann (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.

Tally, F.P. & C.E. Sullivan (1981). Metronidazole: in vitro activity, pharmacology and efficacy in anaerobic bacterial infections. Pharmacotherapy 1(1): 28-38.

Ternes, T.A. (1998a). Arzneimittelrückstände in Gewässern und Kläranlagen. In: B. Toussaint (ed.). Arzneimittel in Gewässern. Risiko für Mensch, Tier und Umwelt? 4. Juni 1998, Landesmuseum Wiesbaden. Hessische Landesanstalt für Umwelt.

Ternes, T.A. (1998b). Occurrence of drugs in German sewage treatment plants and rivers. Water Research 32 (11): 3245-3260.

Ternes, T.A., R. Hirsch, J. Mueller & K. Haberer (1998a). Methods for the determination of neutral drugs as well as betablockers and β_2-sympathomimetics in aqeous matrices using GC/MS and LC/MS/MS. Fresenius Journal of Analytic Chemistry 362: 329-340.

Ternes, T.A., M. Stumpf, B. Schuppert & K. Haberer (1998b). Simultaneous determination of antiseptics and acidic drugs in sewage and river water. Vom wasser 90: 295-309.

Ternes, T.A. & R.W. Hirsch (2000). Occurrence and behaviour of iodinated contrast media in the aquatic environment. Environmental Science and Technology (in press).

Thomulka, K.W., D.J. McGee & J.H. Lange (1993). Detection of bioharzardous materials in water by measuring bioluminescence reduction with the marine organism *Vibrio fischeri*. Journal of Environmental Science and Health A28: 2153-2166.

Toussaint, B. (ed.) (1998). Arzeneimittel in Gewässern. Risiko für Mensch, Tier und Umwelt? 4. juni 1998, Landesmuseum Wiesbaden. Georganiseerd door: Hessische Ministerium für Umwelt, Energie, Jugend, Familie und Gesundheit; Wirtschaftsförderung Hessen Investitionsbank AG; Wasser Agentur Hessen & Hessische Landesanstalt für Umwelt.

US EPA (1999). Search in Ecotoxicology Database System (US EPPAA MED-Duluth): http://www.epa.gov/medecotx/ecotox/home.htm.

Vethaak, A.D., G.B.J. Rijs, B. Van der Burg & A. Brouwer (eds.) (2000). Endocrine-disrupting compounds: wildlife and human health risks. Proceedings of a symposium 27 October 1998, The Hague. Rijksinstituut voor Kust en Zee (RIKZ), Middelburg.

Vlaardingen, P.L.A. van & M.H.M.M. Montforts (1999). Geneesmiddelen in het milieu. Twee verkennende studies samengevat. RIVM rapport nr. 734301 017. Rijksinstituut voor Volksgezondheid en Milieu (RIVM), Bilthoven.

Waggott, A. (1981). Trace organic substances in the river Lee. In: W.J. Cooper (Ed.). Chemistry in water reuse. Ann. Arbor Publishers. p55-99.

Wal, J-M., G. Bories, S. Mamas & F. Dray (1975). Radioimmunoassay of Penicilloyl groups in biological fluids. FEBS Letters 57: 9-13.

Watts, C.D., M. Craythorne, M. Fielding & C.P. Steel (1983). Identification of non-volatile organics in water using field desorption mass spectrometry and high performance liquid chromatography. In: Angeletti, G. & A. Bjorseth (ed.). Analysis of organic micropollutants in water. D.D. Riedel Publishing Co., Dordrecht. 120-131.

Webb, S.F. (2000a). Risk assessment approaches for pharmaceuticals. In: Pharmaceuticals in the environment. International Seminar Day, March 9, 2000. Hotel Sofitel Brussels Airport. Technological Institute, Section on Environmental Technology, Antwerpen.

Webb, S.F. (2000b). A data-based perspective on the environmental risk assessment (ERA) of human pharmaceuticals. M.Phil. Thesis, Open University, UK [in preperation].

Westphal, R. (1990). Berekeningsmodel 'VerdunWS.pro' t.b.v. de bepaling van verdunningsfactoren. RIZA-notitie.

Wienbeck, H. & H. Koop (1990). Untersuchungen zum Formalinabbau in Kreislaufanlagen. Arch. FischWiss. 40(1/2): 153-166.

Wilson, R.C. (1994). Antibiotic residues and the public health. In: Crawford, L.M. & D.A. Franco. Animal drugs and human health. Technomic Publishing Company, Lancaster, Pennsylvania: 63-80.

Wollenberger, L., B. Halling-Sørensen & K.O. Kusk (2000). Acute and chronic toxicity of veterinary antibiotics to *Daphnia magna*. Chemosphere 40: 723-730.

Yates, I.E. & J.K. Porter (1982). Appl. Environ. Microbiol. 44: 1072-1075.

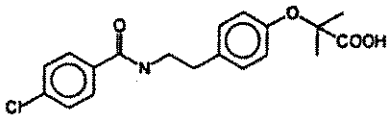
Zuidema, M. & A.E. Klein (1993). Bacteriële antibiotische resistentie en bodemkwaliteit. Technische Commisie Bodembescherming (TCB), Den Haag. Rapportnr. TCB R01(1993). 47p.

Supplements

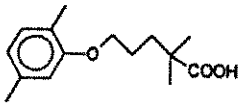
Supplement 1
Structural formulas of various human pharmaceuticals

Fibrates

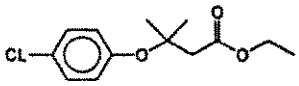
Bezafibrate



Gemfibrozil



Clofibrate



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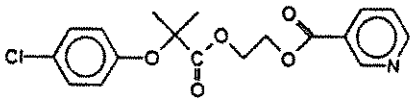
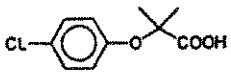
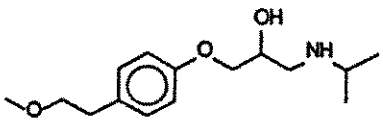


Clofibric acid



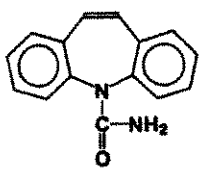
Betablockers

Metoprolol



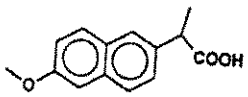
Antiepileptics

Carbamazepine

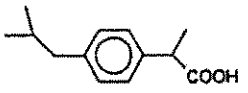


Analgesics

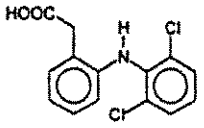
Naproxen



Ibuprofen

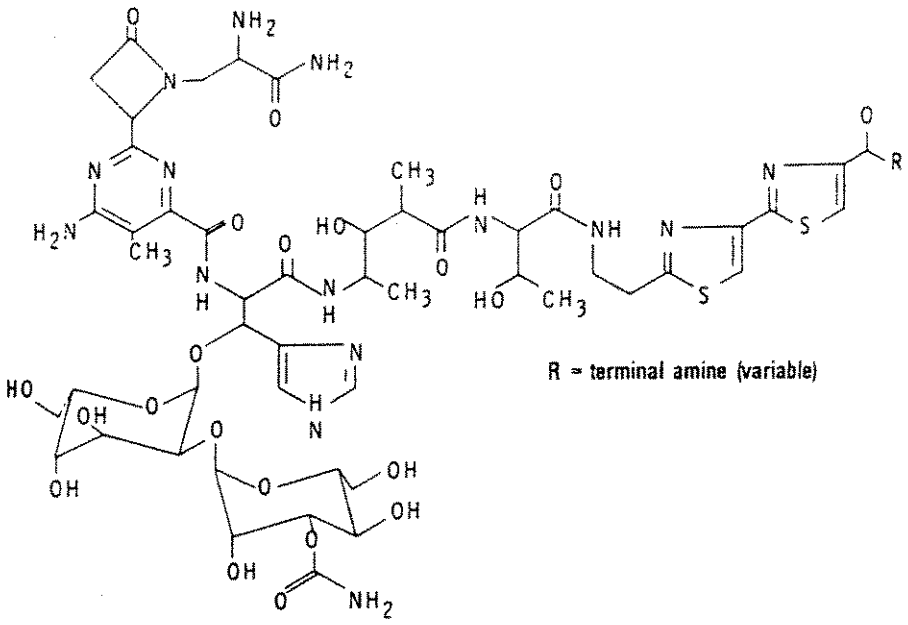


Diclofenac

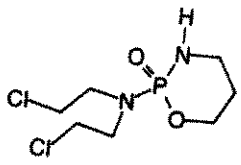


Cytostatics

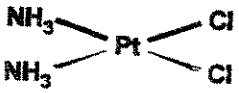
Bleomicin



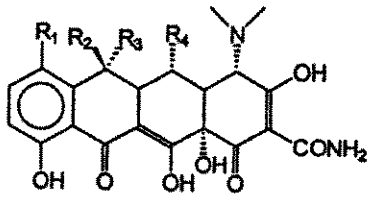
Cyclophosphamide



Cisplatin

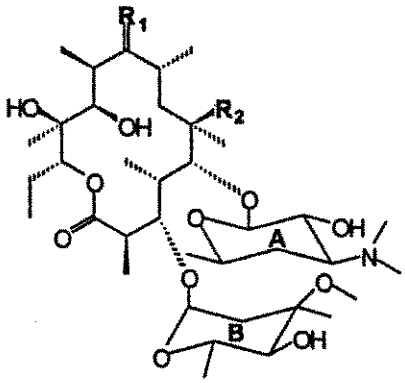


Doxycycline



R_1 = H; R_2 = H; R_3 = CH_3; R_4 = OH

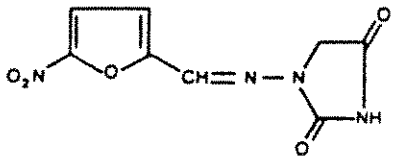
Erythromycin



A = desosamine
B = cladinose (3-O-methylmycarose)

R_1 = O; R_2 = OH

Nitrofurantoin



Supplement 2
European draft directives for environmental risk assessment within the authorisation procedure of human pharmaceuticals

This supplement contains:

1. European Commission (1994). 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 4*. European Commission, Directorate-General Industry, III/E/3 Pharmaceuticals Service, Ad Hoc Working Party on environmental risk assessment for non GMO containing medicinal products, Brussels.
2. EMEA (2001). *Draft* CPMP discussion paper on environmental risk assessment of non-genetically modified organism (non-gmo) containig medicinal products for human use. DIA workshop on Environmental Risk Assessment of non-GMO Pharmaceuticals. 12-13 February 2001. London, UK.

EUROPEAN COMMISSION
Directorate-General
INDUSTRY

III/E/3
Pharmaceuticals Service

III/5504/94 Draft 4

AD HOC WORKING PARTY ON ENVIRONMENTAL RISK ASSESSMENTS FOR NON GMO CONTAINING MEDICINAL PRODUCTS

Title: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.

Discussion in working party	February - July 1994
Transmission to CPMP	July 1994
Transmission to interested parties	July 1994
Deadline for comments	October 15 1994
Resubmission to working party	
Final approval by CPMP	

N-2.8 Rue de la Loi 200, B-1049 Brussels.
Telephone: direct line 296 1806, standard 299 11.11, Telefax:296 1520 , Telex COMEU B 21877, Telegraphic address COMEUR Brussels

ASSESSMENT OF POTENTIAL RISKS TO THE ENVIRONMENT POSED BY MEDICINAL PRODUCTS FOR HUMAN USE (EXCLUDING PRODUCTS CONTAINING LIVE GENETICALLY MODIFIED ORGANISMS) :

PHASE 1 ENVIRONMENTAL RISK ASSESSMENT

1. Introduction and Background

The use and disposal of medicinal products can have an adverse effect on the environment and, consequently, present a risk to human health arising from indirect exposure. This is recognised in article 4.6 of Directive 65/65/EEC, as amended. Therefore, from 1. January 1995, an application for marketing authorisation for a medicinal product for human use must be accompanied by, "... if applicable, reasons for any precautionary and safety measure to be taken for the storage of the medicinal product, its administration to patients and for the disposal of waste products, together with an indication of any potential risks presented by the medicinal product for the environment". The article applies irrespective of the procedure used, i.e. national, decentralised or centralised.

Normally for medicinal products, the identification of potential risks to the environment will be achieved by means of an environmental risk assessment (ERA), conducted in two phases. For most medicinal products, it is anticipated that only the first phase of the evaluation will be necessary.

The purpose of this document is to give guidance on the following:

- the applications for marketing authorisation of medicinal products for human use which should be accompanied by an environmental risk assessment
- the data requirements for the Phase I assessment of ecotoxity
- the conclusions of the Phase I assessment
- the circumstances under which an applicant should proceed to a Phase II assessement

Guidance on the Phase II assessment, which applies to medicinal products for both human and veterinary use, is available in a separate document (III/5505/94). Chapter 1 is of particular relevance to products for human use.

The European Commission has already issued a technical guidance document entitled Risk Assessment of Notified New Substances which was prepared to assist those carrying out risk assessments of new substances notified under Directive 67/548/EEC, as amended. Some sections of this document are not applicable to medicinal products, as the emphasis is on manufacture, rather than use and disposal Nevertheless, it contains much useful information

which may be helpful to applicants in the preparation of an environmental risk assessment for a medicinal product, including sections on :

- principles of risk assessment
- assessment of human exposure levels
- approaches to the assessment of ecotoxicity, environmental exposure and environmental risk characterisation
- reasonable worst case and statistical approaches
- general processes of release, dispersion and elimination
- estimation of relevant parameters in the aquatic, soil and atmospheric compartments

2. The Scope of the Environmental Risk Assessment

According to Article 4.6 of Directive 65/65/EEC, as amended, the subject of the ERA is the medicinal *product*, i.e. the product as a whole, including the adjuvants/excipients in the formulation, the immediate container and the packaging, as well as the active constituent itself. In addition, Article 4.6 relates to those risks to the environment arising from use, storage and disposal of the medicinal product, rather than those arising from synthesis and manufacture of the active substance and the product.

Whilst it is accepted that most excipients can be described as inert, and are chosen specifically for their lack of pharmacological or toxicological effect, nevertheless it is possible that some may warrant attention in relation to their potential for harmful environmental effects and this should be discussed in the ERA, where relevant.

3. Applications which require an Environmental Risk Assessment

- All applications for marketing authorisations for medicinal products containing a New Active Substance received after 1 January 1995.
- Any application for a medicinal product containing a live vaccine received after 1 January 1995.
- Subsequent renewal of marketing authorisations granted for the above categories.

These restrictions are provisional and may need to be revised later. Any decision not to conduct an environmental risk assessment should be justified by the applicant.

Specific environmental issues relating to live vaccines will be addressed in a separate guideline.

Products consisting of or containing live genetically modified organisms are subject to separate requirements with respect to the evaluation of environmental risk, as laid down in Article 6 of Regulation No. 2309/93.

4. The Role of The Applicant's Expert

Due to the wide diversity of the information to be handled in a Phase I ecotoxicity assessment , an expert suitably qualified to give an overview of all the data together with an evaluation of the category of risk , will be required.

In general terms, the assessment of environmental risk involves the consideration of :

- the assessment of effects (identification of the intrinsic hazardous properties of the substance and the elucidation of dose/response or concentration/effects characteristics where appropriate)
- the assessment of exposure for the different environmental compartments
- risk characterisation, i.e. comparison of information on hazardous properties and effective dose levels/concentrations with exposure levels in order to characterise the degree of risk posed to the environment

Risk characterisation will lead to one of the following conclusions :

1. the product is of no immediate concern; no further data is required;
2. the product may be of concern and further data will be required immediately;
3. the product may be of concern and further data will be required when use reaches a certain level;
4. the product is of concern and recommendations should be made for risk reduction.

Following a Phase I assessment , it is unlikely that the expert will reach a category 4 decision and give an opinion on measures necessary to reduce the risk of an adverse environmental impact, since this will normally come after more refined estimations of predicted environmental concentrations have been made, often with additional studies in a Phase II assessment. It is likely that the expert's expression of concern in categories 2 & 3 will also lead to a more detailed Phase II assessment.

The expert should also consider all of the user information texts and make a statement on the relevance and suitability of the advice regarding the administration and disposal of the medicinal product.

5. Environmental Exposure Assessment

5.1 General Approach.

The assessment of environmental exposure involves the identification of emission sources, the estimation of emission rates and the subsequent distribution and elimination process. The purpose of the Phase I assessment for medicinal products is to provide a first estimate of the distribution among the environmental compartments water, soil and air as well as of the respective concentrations within them, i.e. a crude estimate of the Predicted Environmental Concentrations (PEC).

These first estimates will establish whether or not there is a need for a Phase II assessment. In general, Phase II assessments will not be required for medicinal products which are used in relatively small quantities and released diffusely into the environment thus leading to negligible environmental concentrations.

The Phase I assessment is based on data on the release of the substance(s) under consideration into the environment and certain physico-chemical properties of the active substance and/or its main metabolites. Other relevant information includes the use pattern of the product, the expected extent of use, the concentration of the substance(s) under consideration in urine and faeces, the degradation process under typical conditions and sewage handling and disposal practices. Consequently, experimentally-derived data on environmental effects (e.g. LC_{50}, fish toxicity) are usually not required in Phase I, but must form part of a Phase II assessment.

During the development of the medicinal product it will become apparent whether or not a Phase I assessment provides adequate reassurance regarding potential adverse environmental effects, and the decision whether or not to move to a more detailed Phase II evaluation should be made at this stage.

5.2 Data Requirements

In Phase I the estimate of the release into the environment is based on the following information:

- amount placed on the market per time unit
- use pattern
- excretion and metabolite pattern in humans (generally available from clinical studies)

Furthermore, the prediction of the environmental concentration requires information on physico-chemical properties allowing a first, crude, prediction of the environmental fate:

- water solubility
- n-octanol/water partition coefficient ($P_{o/w}$ or $\log_1 P_{o/w}$)
- dissociation constant (if applicable)
- hydrolysis
- vapor pressure (estimate)

Generally this information should be provided on the drug substance and its main metabolites

(Normally >20% of the dose, possibly less in cases of known or suspected special ecotoxic effects)

The data requirements and issues relating to a Phase II Environmental Risk Assessment are the subject of a separate Guideline.

5.3 General Processes Affecting Environmental Exposure

5.3.1 Release into the environment

The environmental exposure arising from the *use* of the medicinal product is the main consideration for the exposure assessment in Phase I. Manufacture and production are subject to other regulations, while the release into the environment due to *disposal* and waste treatment will generally be considered diffuse. However, in cases where the mammalian toxicity data or the nature of the product already provide an indication of possible concern (e.g. due to mutagenic or carcinogenic properties) the disposal of the drug product should be included in the Phase I assessment.

The exposure consideration should be restricted to the designated use pattern of the product as defined in the SPC. Indirect release, such as might occur from landspreading of sewage sludge, should also be considered

The emission pattern will generally be a diffuse release into waste water systems due to the excretion of the active substance itself and/or its metabolites by patients. Other patterns may occur (e.g. emission of inhalation anaesthetics or propellants into the atmosphere).

5.3.2 Environmental Fate (Distribution & Elimination Processes)

After emission, distribution of the substance will occur to an extent dependent on the magnitud of the advection, dispersion and diffusion processes.

Regarding sewage concentrations, many medicinal products are used intermittently, consequently there will be considerable dilution from the addition of sewage from the untreated population.

For active substances or their metabolites excreted into waste water this normally means dilution in the waste water streams and subsequently in surface waters.

A consideration of the pattern of use will also be important here.

Subsequent to the release into an environmental compartment and dispersion therein, a substance will distribute between the different compartments (water, air, soil, sediment and biota). This distribution process can be assessed using the above mentioned physico-chemical parameters. The octanol/water partition coefficient is generally used as an indicator of bioconcentration, but can also be useful in the assessment of sorption to sediment and soil particles. The vapour pressure and/or Henry's constant allow an assessment of the relative emission into the air compartment.

While distribution refers to the physical process of transfer from one phase to another (e.g from water to sediment particles or to the atmosphere), elimination means the reduction in concentration of substances by chemical or biochemical process Thus, elimination of a substance may occur by hydrolysis and photolysis.

5.4 Estimation of Environmental Concentrations

5.4.1 Concentration in Water

In general the active substance and its metabolites will at first be found in the water compartment due to human excretion. Information on metabolism - and thus on the compounds introduced into the environment, will be available from clinical trials. Metabolism often leads to substances which are more hydrophilic and less toxic. During product development, Structure-Activity Relationships, SAR, may have been established which will be useful in this context, especially if quantitative.

These data may already be available and described elsewhere in the submission dossier, e.g. in Part II & Part III, in other cases, the applicant may need to generate some of them to help the expert reach a conclusion in Phase I.

In most cases no specific data for the emission and environmental conditions in a particular environment or region will be available. A first estimate of the predicted environmental concentration in surface waters receiving the discharge of sewage treatment facilities can then be obtained using the following formula:

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

where

A [kg/yr] = predicted amount used per year in the EU country of highest dosage

R [%] = removal rate (due to loss to sludge particles, volatization, hydrolysis or biodegradation)

P = number of inhabitants of the country

V [$m^{3/day}$] = volume of waste water per capita and day (generally 0.15 to 0.20 m^3)

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

In the Phase I assessment under worst-case conditions, R should always be counted as zero, and A/P should be maximum.

Generally an active substance and its metabolites or degradation products will be considered as being of no immediate concern in the water compartment if the crude estimated value for PEC is 0.001 µg/l or below in surface water. This threshold value has been chosen for the following reasons:

- It is hundred times lower than the general limit value for pesticides in drinking water. Thus there is little concern about the respective substances reaching groundwater or surface water which is used for production of drinking water.
- It is considered unlikely that drug substances will produce toxic effects on aquatic organisms at such a low concentration.

5.4.2 Concentration in Soil

It is generally assumed that for medicinal products there is insignificant exposure of the soil compartment. Exposure may occur mainly via landspreading of sewage sludge. The partitioning between the aqueous phase in a waste water treatment plant and sludge particles follows the formula:

$$K' = \frac{Css \quad \text{(conc. of substance adsorbed to particles)}}{Cww \text{ (conc. of substance in the aqueous phase)}}$$

The equilibrium constant K' is related to the adsorption constant (related to organic carbon) K_{oc} by:

$K' = K_{oc} \times$ % organic carbon content/100

For the purposes of Phase I assessment, as a first approximation, K_{oc} may be taken to be equal to $P_{o/w}$.

Sewage sludge contains a relatively high proportion of organic matter (up to 40% organic carbon). The concentration in soil can be roughly estimated using the following formula:

$PEC_{soil} = C_{ss} \times 1.7 \times 3000^{-1}$ (mg/kg for arable land)

$PEC_{soil} = C_{ss} \times 1.0 \times 1500^{-1}$ (mg/kg for grass land)[1]

A threshold for PEC_{soil} of 10ppb (µg/kg) can be considered, below which there is no immediate concern about the occurence of a substance in soil as with veterinary medicinal products.

5.4.3 Concentration in Air

The concentration of active substances or their metabolites in the air compartment are generally assumed to be low due to their low vapour pressures, low production volumes and significant dilution.

For example, in the case of propellants for inhalation aerosols the potential risk for depletion of the ozone layer and / or 'greenhouse' effects should be considered.

6. SUMMARY OF ACTION LIMITS

Usually, if the substances under consideration in a Phase I environmental risk assessment fulfil the following criteria then further investigations (e.g. in the form of a Phase II assessment) will not be considered necessary :

- estimated PEC in soil < 10µg/kg
- estimated PEC in surface water < 0.001µg/l

However, it may not be relevant to apply these limits to substances of known, 'special' toxic or adverse environmental effects, or where such effects are suspected on the basis of Stucture/ Activity Relationships. Stricter criteria would apply in these cases, and the expert will be required to consider other, more appropriate, action limits. A dose (concentration) - response (effect) assessment would normally be required. For example, it may be more appropriate in Phase I to relate the Predicted Environmental Concentration to the Lethal Concentration for certain appropriate animal species, e.g. a requirement that PEC < 1% Acute LC_{50} or a Predicted No Effect Concentration.

Conversely, regarding bioaccumulation potential, it is accepted that a persistent chemical is not necessarily a toxic one, nor will it necessarily have adverse environmental effects, and the expert will be expected to comment accordingly.

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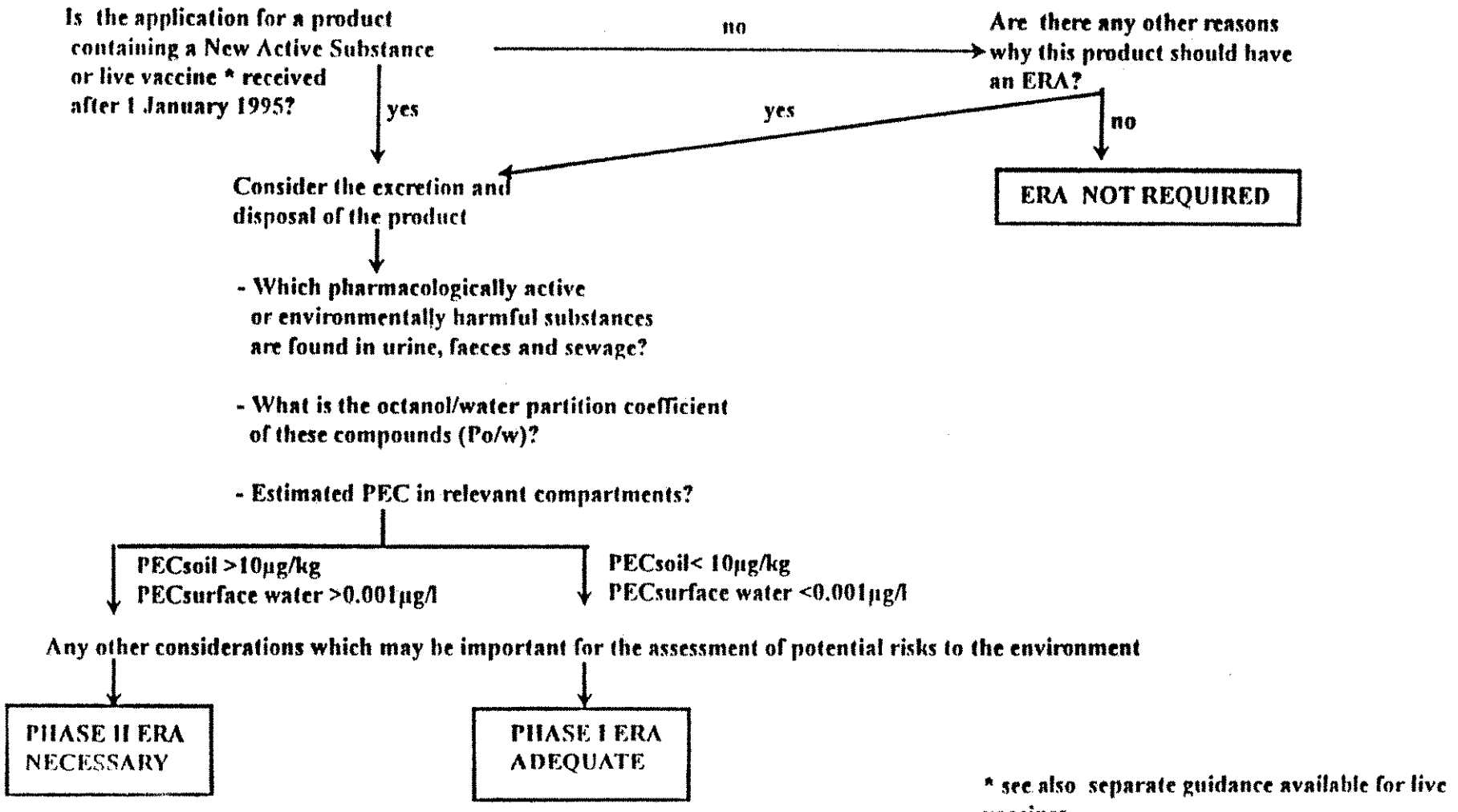
[1][Risk Assessment of Notified New Substances Technical Guidance Document]

GENERAL CRITERIA FOR FIRST PHASE ECOTOXICITY ASSESSMENT
(Human medicinal products, excluding GMO-containing products)



* see also separate guidance available for live vaccines

The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

London, 25 January 2001
CPMP/SWP/4447/00 draft corr.

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

DISCUSSION PAPER ON ENVIRONMENTAL RISK ASSESSMENT OF NON-GENETICALLY MODIFIED ORGANISM (NON-GMO) CONTAINING MEDICINAL PRODUCTS FOR HUMAN USE

DISCUSSION IN THE SAFETY WORKING PARTY	June 1999 - November 2000
TRANSMISSION TO THE CPMP	January 2001
RELEASE FOR CONSULTATION	January 2001
DEADLINE FOR COMMENTS	July 2001

Any comments should be sent to the EMEA, SWP Secretariat (fax no +44 20 7 418 8613), before the end of *July 2001.*

7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Tel. (+44-20) 74 18 84 00 Fax: (+44-20-) 74 18 86 13
E_Mail: mail@emea.eudra.org http://www.eudra.org/emea.html

DISCUSSION PAPER ON ENVIRONMENTAL RISK ASSESSMENT OF NON-GENETICALLY MODIFIED ORGANISM (NON-GMO) CONTAINING MEDICINAL PRODUCTS FOR HUMAN USE

1 INTRODUCTION

Council Directive 65/65/EEC recognises that an application for the marketing authorisation for a medicinal product for human use must be accompanied, if applicable, by reasons for any precautionary and safety measure to be taken for the storage of the medicinal product, its administration to patients and for the disposal of waste products, together with an indication of any potential risks represented by the medicinal product for the environment. This discussion paper is applicable for non-Genetically Modified Organism (non-GMO) containing medicinal products that apply to Council Directive 65/65/EEC; it is applicable for proprietary medicinal products for human use intended to be placed on the marked in the European Union, and subsequent renewals of such products.

This discussion paper is not applicable for medicinal products containing or consisting of Genetically Modified Organisms; applicants are referred to the *Note for guidance on Environmental risk assessment for human medicinal products containing or consisting of GMOs* (CPMP/III/5507/94).

This discussion paper presents

- Commonly accepted principles for the environmental risk assessment of medicinal products when administered to patients.
- Labelling provisions: an outline of the information that applicants could provide on precautionary and safety measures to be taken, for the purpose of reducing any risks to the environment, with regard to the administration to patients, and to storage and disposal of waste products.

2 GENERAL PRINCIPLES OF ENVIRONMENTAL RISK ASSESSMENT OF MEDICINAL PRODUCTS WHEN TAKEN BY PATIENTS

Assessment of potential risks to the environment is a step-wise, tiered procedure that may be terminated when sufficient information/data are available to either suggest that the medicinal product is unlikely to represent a risk to the environment or else to identify and sufficiently characterise the potential risks. If relevant experimental data (e.g. metabolism) can be obtained from other parts of the dossier, these should be used in the assessment, and such studies therefore need not to be repeated. If, based on the available information and data, the applicant concludes that the medicinal product is unlikely to represent a risk to the environment and that therefore it would not be necessary or useful to generate additional experimental data, the applicant should justify this decision. When the medicinal product exhibits potential risks to the environment, the applicant should propose appropriate precautionary and safety measures to be observed when the product is administered to patients and/or for the disposal of waste products. These measures should be included in the Summary of Products Characteristics (SPC) (Figure 2).

Since for medicinal products the benefit for humans has relative precedence over any environmental risks, the environmental risk management procedures adopted for industrial chemicals and pesticides (i.e. prohibiting or restricting their use if an unacceptable risk to the environment is evident) is neither possible nor desirable in this case. Precautionary measures through product labelling are therefore the recommended risk management procedures for medicinal products, when concerns for the environment are present.

Article 4.6 of Directive 65/65/EEC, as amended, requires the applicant to indicate any potential risks exhibited by the medicinal product for the environment. Although it is expected that emphasis will be given to the main substance(s) being excreted (parent compound and/or metabolite(s), as determined by human excretion profile), the assessment should consider any substance of concern in the medicinal product. It should be noted that Article 4.6 relates to those risks to the environment arising from use, storage and disposal of the medicinal product rather than to those arising from synthesis and manufacture of the product. Manufacture and production are subject to other regulations.

Whilst it is accepted that most excipients can be described as inert, and are chosen specifically for their lack of pharmacological or toxicological effect, it is nevertheless possible that some may warrant attention in relation to their potential for harmful environmental effects. This should be discussed in the Environmental Risk Assessment Report, where relevant.

3 ENVIRONMENTAL EXPOSURE ASSESSMENT: OVERALL CONSIDERATIONS OF ENVIRONMENTAL COMPARTMENTS OF POTENTIAL CONCERN

Of the different environmental compartment(s) (aquatic, atmospheric, and/or terrestrial), mainly those of potential concern need to be considered. The environmental exposure considerations should, however, not be restricted to the designated use pattern as defined in the Summary of Product Characteristics (SPC). For example, indirect release, such as might occur from land spreading of sewage sludge, should also be considered.

It is generally assumed that for medicinal products emission patterns will mainly consist of a diffuse release into waste water systems due to excretion of the active substance and/or its metabolites by patients (see Figure 1). Other patterns may occur in special situations, e.g., emission of inhalation anaesthetics or propellants into the atmosphere. As it can be assumed that in most cases there is only an insignificant exposure of the compartments soil and air, these compartments need generally not to be considered in the first step of an assessment.

The concentrations of active substances and/or their metabolites in the air compartment are generally assumed to be low due to their low vapour pressure, low production volumes and significant dilution. However, specific environmental concerns should be considered, for example, in the case of propellants for inhalation aerosols, where the potential risk for depletion of the ozone layer and/or 'greenhouse' effects has to be looked at. Matters relating to the replacement of chlorofluorocarbons (CFC) are referred to in the Note for Guidances on *Replacement of Chlorofluorocarbons (CFC) in Metered Dose Inhalation Products* (CPMP/III/5378/93) and *Matters Relating to the Replacement of CFC's in Medicinal Products* (CPMP/III/5462/93).

Where relevant, assessments of exposures and effects in non-aquatic environmental compartments should be conducted on a case-by-case basis.

3.1 Environmental exposure assessment: initial considerations

The exposure assessment is based mainly on data on the release of the substance(s) under consideration into the environment and on certain physico-chemical properties of the substance. Other relevant information includes the use pattern of the product (e.g., seasonal vs. continuous use; population-based vs. hospital based use), the expected extent of use (e.g., short-term vs. chronic use, magnitude of patient population), the concentration of the substance(s) under consideration in urine and faeces, the degradation processes under typical environmental conditions and sewage handling and disposal practices.

Subsequent to the release into one environmental compartment and dispersion therein, a substance will be further distributed between the different additional compartments (water, air, soil, sediment and biota). This distribution process can be estimated using the above

mentioned physico-chemical parameters. The octanol/water partition coefficient is generally used as an indicator of bioconcentration, but can also be useful in the assessment of sorption to sediment and soil particles. The vapour pressure and/or Henry's constant allow an assessment of the relative emission into the air compartment.

While distribution refers to the physical process of transfer from one phase or compartment to another (e.g. from water to sediment particles or to the atmosphere), elimination means the reduction in concentration of substances by chemical or biochemical processes. Thus, elimination of a substance may occur by hydrolysis, photolysis or biodegradation (or a combination thereof).

The prediction of environmental concentrations requires information on the physico-chemical properties allowing a first, crude, prediction of the environmental fate. Data on the following should be provided, if applicable:

- Molecular weight
- Water solubility
- N-octanol/water parturition coefficient (K_{OW}, $P_{O/W}$, $\log_{10}P_{O/W}$ etc.)
- Estimate of vapour pressure
- Dissociation constant for acids or bases
- Hydrolysis rate
- Other degradation processes, e.g., oxidation, and photolysis.

Other data, which may be useful in refining crude PEC's include information relating to removal and passage from one environmental compartment into another, e.g.,

- Biodegradation
- Adsorption to sewage sludge
- Adsorption to soil particles

This information should preferably be provided for the substance being assessed. When such information is not available for the substance itself, information from similar substances through structure-activity relationships may be useful, but the reliability of such data has to be discussed by the applicant.

3.2 Environmental exposure assessment: the substance(s) to be evaluated

The substance(s) to be included in the environmental risk assessment should generally be determined based on the excretion profile in man. The main excretory moiety should generally be assessed. In most cases, however, it is sufficient to consider just the active entity (the parent compound, or the active metabolite for pro-drugs), especially when a crude PEC is calculated under worst case conditions (i.e., no removal, low water consumption per capita) in the relevant environmental compartment, and the PEC value obtained gives no reason for concern and for further environmental effect analysis.

3.3 Environmental exposure assessment: aquatic compartment

Based on the common environmental exposure pattern of medicinal products for human use, the risk assessment for the water compartment generally needs to be considered as the first step (Figure 1).

3.4 Environmental exposure assessment: crude predicted environmental concentrations in the aquatic compartment

The initial step of assessment should be to estimate the environmental concentration in that part of the aquatic compartment receiving the discharge of sewage treatment facilities.

In most cases it is sufficient to predict the concentration of the active moiety of a medicinal product at the point of entry into the aquatic environment as defined in the following formula

for crude calculation of the Predicted Environmental Concentration in surface water ($PEC_{SURFACE\ WATER}$):

$$PEC_{SURFACE\ WATER}\ [g/l] = (A \times (100 - R)) / (365 \times P \times V \times D \times 100)$$

where,

A (kg) = Predicted amount used per year in the relevant geographic area in any of the next five years. This area may be a single EU country (the EU member state with a maximum ratio of A/P should be used), or another, relevant area for national/multinational applications

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

P = Number of inhabitants of the geographic area considered (EU member state(s))

V [m^3] = Volume of wastewater per capita and day (generally 0.15 to 0.30 m^3 in the EU).

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

This crude calculation of PEC in surface water assumes

- the predicted amount used per year is evenly distributed over the year,
- the medicinal product is used evenly throughout the geographic area,
- the sewage system (sewage treatment plants) is the main gate for the entry of the medicinal product into the environment,
- there is no metabolism

Case-specific alterations in these assumptions may justify modifications of the formula for the calculation of the $PEC_{SURFACE\ WATER}$.

The applicant should choose and justify appropriate and realistic values for the parameters used in this formula (A, R, P, V and D).

3.5 Environmental exposure assessment: action limits and conclusions from the calculation of crude predicted aquatic concentration

If this crude PEC value (crude predicted concentration of the substance in surface water) is below 0.01 µg/l, and no other environmental concerns are apparent, it may be assumed that the medicinal product is unlikely to represent a risk for the environment following its prescribed usage in patients.

If this crude PEC value is above 0.01µg/l, a crude environmental effect analysis should be performed as described below (section 4).

These action limits may not be universally applicable, e.g.:

- for substances with known or suspected special ecotoxic effects, lower PEC action limits would be appropriate, e.g. for estrogens, or genotoxic substances, while
- substances of known low ecotoxic potential may warrant higher PEC action limits, e.g. paracetamol.

In every case, the applicant should justify the action limits applied and all action taken or not taken.

3.6 Environmental exposure assessment: prediction of concentrations in non-aquatic compartments

When indicated, predicted concentrations in other compartments should be calculated by using methodologies as described in the Guideline *Environmental Risk Assessment for Veterinary Medicinal Products other than GMO-Containing and Immunological Products* (EMEA/CVMP/055/95).

4. CRUDE ENVIRONMENTAL EFFECT ANALYSIS

The purpose of this analysis is to predict the concentration of the substance for which adverse effects are not expected to occur in the environmental compartment of concern, i.e. to estimate the predicted no-effect concentration (PNEC).

If the calculated PEC is below the threshold of concern, environmental effect analysis and further testing is not needed.

4.1 Crude environmental effect analysis: aquatic compartment

If a $PEC_{SURFACE\ WATER}$ has been calculated and has been shown to exceed the action limit, the tiered testing should be continued with a determination of $PNEC_{WATER}$, as described below.

For the first assessment approach, a standard acute toxicity test set on fish, daphnia and algae may be used to determine the $PNEC_{WATER}$. The lowest value of the respective LC_{50} or EC_{50} should be used for risk evaluation. The applicant should justify the test species used

The PNEC is calculated by applying an assessment factor to the values resulting from tests on environmental organisms from the compartment of concern, e.g. LC_{50}, EC_{50} or NOEC. The assessment factor is an expression of the degree of uncertainty in the extrapolation from the test data on a limited number of species to the real environment. In general, the more extensive the data and the longer the duration of the tests, the smaller is the degree of uncertainty and the size of the assessment factor.

The assessment factor is determined by the nature of the available toxicity data and accounts for

- extrapolation from acute to chronic toxicity (a factor 10)
- inter-species variations differences in sensitivity (a factor of 10)
- intra-species variability (a factor of 10)

Usually, an assessment factor of 1000, applied to the lowest $L(E)C_{50}$ value, should be used when reviewing data from laboratory testing in at least three aquatic organisms.

For the establishment of a crude PNEC, the following basic formula should be used:

$$PNEC = EC / AF$$

where;

PNEC = Predicted no effect concentration

EC = Effect concentration determined as the lowest LC_{50} or EC_{50} from acute toxicity tests in several test organisms

AF = Assessment factor

Priority should be given to test methods adopted in, or being developed for, Annex V to Directive 67/548/EEC, or adopted as OECD test guidelines. Test methodologies accepted by the FDA may also be used.

Experimental studies should be performed according to Good Laboratory Practices (GLP).

4.2 Conclusions from the crude environmental effect analysis: aquatic compartment

If the ratio $PEC_{SURFACE\ WATER}$: $PNEC_{WATER}$ is below 1, further testing will be unnecessary, and it can be concluded that the medicinal product is unlikely to represent a risk to the environment.

If the ratio $PEC_{SURFACE\ WATER}$:$PNEC_{WATER}$ is above 1, further considerations are needed on a case-by-case basis, i.e., a more detailed assessment of the substance in the appropriate environmental compartment and using appropriate models should be conducted. The principles of such an assessment are described in the Guideline *Environmental Risk Assessment for Veterinary Medicinal Products other than GMO Containing and Immunological Products* (EMEA/CVMP/055/96). Further assessment may also include field studies.

5. PRECAUTIONARY AND SAFETY MEASURES TO BE TAKEN FOR THE STORAGE, ADMINISTRATION AND DISPOSAL OF THE MEDICINAL PRODUCT AND LABELLING

When the possibility of environmental risks cannot be excluded, precautionary and safety measures may consist of, but not be restricted to,

- Restricted clinical use, e.g. hospitals only
- Product labelling, SPC, PL, etc. for patient use, product storage and disposal
- Environmental monitoring (field studies)

Labelling should generally aim at minimising the quantity discharged into the environment by appropriate mitigation measures, e.g. through state-of-the-art hospital treatment plants.

Appropriate disposal of unused pharmaceuticals, e.g. when shelf life is expired, is considered important to reduce the exposure of the environment. In order to enhance environmental protection, it is therefore recommended that – even for medicinal products that do not require special disposal measures - package inserts (patient information leaflets) should include the following statement:

"Unused preparations or old preparations should be returned to pharmacies. Old preparations should not be disposed of via wastewater or the municipal drainage system. These measures will reduce pollution of the environment."

6. SCIENTIFIC ADVICE FROM THE CPMP

The applicant may request scientific advice from the CPMP -according to the EMEA procedures for such advice- on issues related to environmental risk assessment and on possible precautionary and safety measures to be taken with respect to the use, storage and disposal of a medicinal product.

7. REPORTING – THE ENVIRONMENTAL RISK ASSESSMENT REPORT

An Environmental Risk Assessment Report should always be prepared. It should be a self-standing document without unnecessary cross-referral to other parts of the dossier and should be presented in the Part I of the dossier.

The Environmental Risk Assessment Report should include an evaluation the applicability of the environmental assessment performed. In particular, the report should provide:

1. An estimate of the potential environmental exposure (PEC) with an assessment of the underlying assumptions

2. An assessment of possible risks to the environment from the point of view of use, and a presentation and evaluation of data in support of such risk evaluation,

3. An evaluation of precautionary and safety measures to be taken regarding the storage of the medicinal product, environmental release from use in patients, and disposal of unused products or waste materials derived from such products,

4. Proposals for labelling (SPC, PL etc.) which would reduce potential risks to the environment

The Environmental Risk Assessment Report should state the justifications if any of the above evaluations are not found to be applicable for the medicinal product.

The curriculum vitae of the author of the Environmental Risk Assessment Report should be provided.

8. LIST OF ABBREVIATIONS

CPMP Committee for Proprietary Medicinal Products
PNEC Predicted No-Effect Concentration
PEC Predicted Environmental Concentration
AF Assessment Factor
NOEC No Observed Effect Concentration
ERA Environmental Risk Assessment
SPC Summary of Product Characteristics
PL Package Leaflet
FDA United States Food and Drug Administration
OECD Organization for Economic Co-operation and Development
GLP Good Laboratory Practices

Figure 1:

Usual environmental exposure scenario for medicinal products when prescribed to patients:

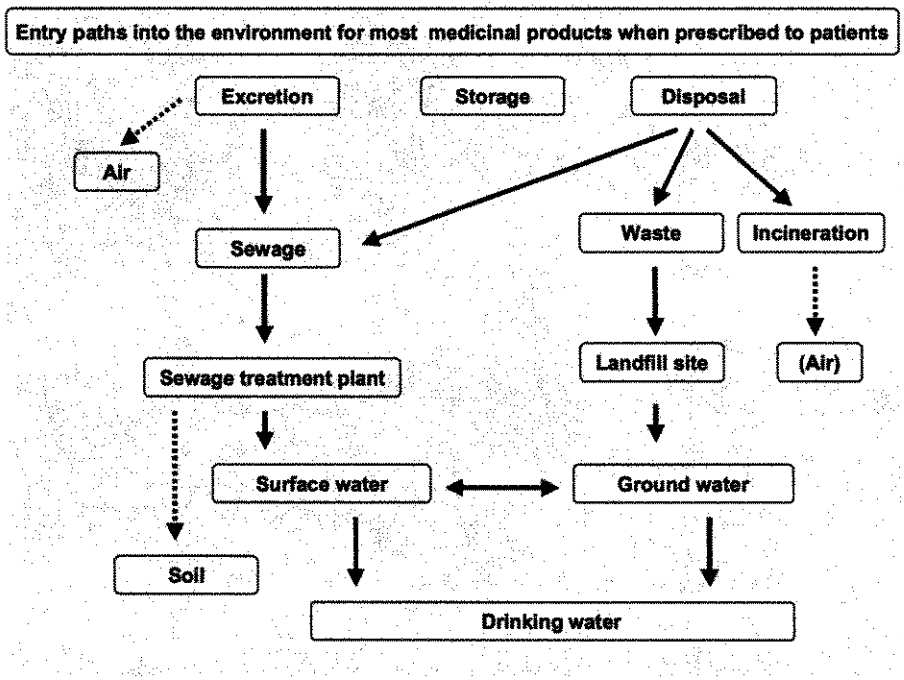
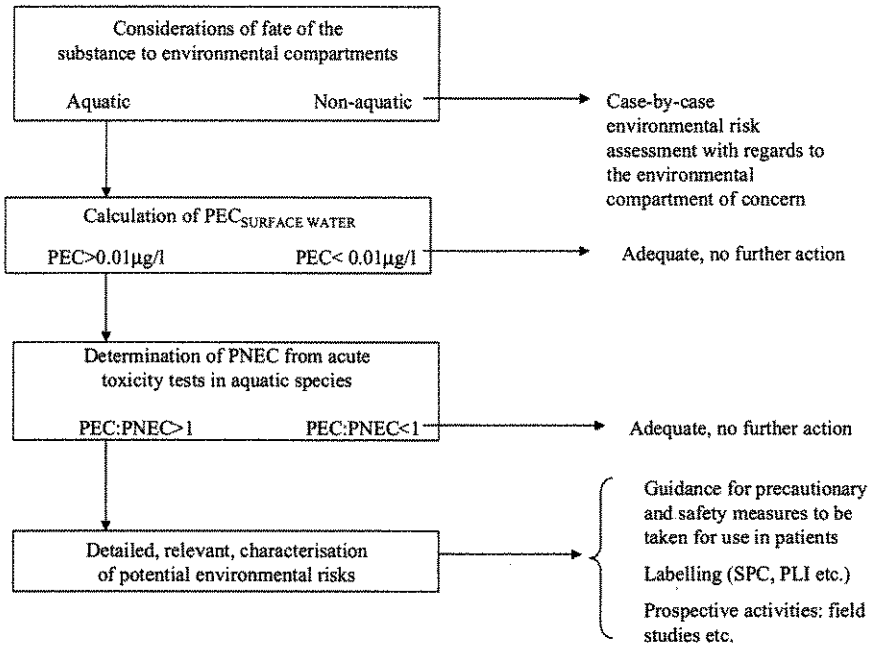


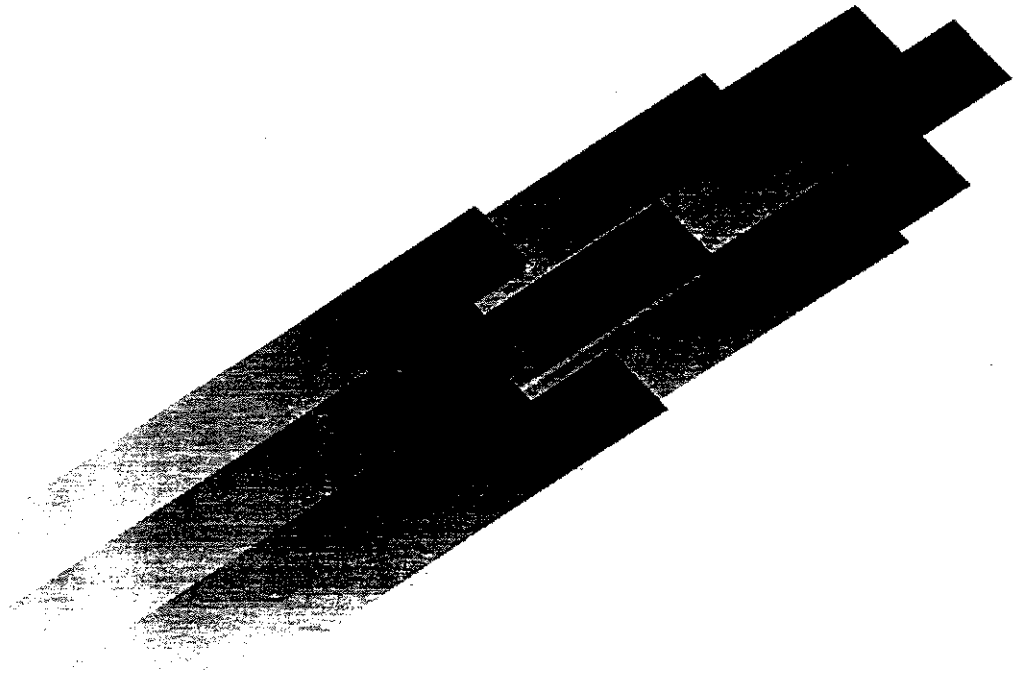
Figure 2:
Schematic decision tree for environmental risk assessment of non-GMO medicinal products.



Supplement 3
American directive for environmental risk assessment within the authorisation process of human pharmaceuticals

Guidance for Industry

Environmental Assessment of Human Drug and Biologics Applications



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
July 1998
CMC 6
Revision 1

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GUIDANCE FOR INDUSTRY[1]

Environmental Assessment of Human Drug and Biologics Applications

I. INTRODUCTION

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impacts of their actions and to ensure that the interested and affected public is informed of environmental analyses. The Food and Drug Administration (FDA) is required under NEPA to consider the environmental impacts of approving drug and biologics applications as an integral part of its regulatory process. FDA's regulations in 21 CFR part 25 specify that environmental assessments (EAs) must be submitted as part of certain new drug applications (NDAs), abbreviated applications, applications for marketing approval of a biologic product, supplements to such applications, investigational new drug applications (INDs) and for various other actions (see 21 CFR 25.20), unless the action qualifies for categorical exclusion.

Under the President's reinventing government (REGO) initiatives, announced in April 1995, FDA reevaluated and revised its environmental regulations to reduce the number of EAs required to be submitted by industry and, consequently, the number of findings of no significant impact (FONSIs) prepared by the Agency under NEPA. FDA issued for public comment a notice of proposed rulemaking on April 3, 1996 (61 FR 14922) (republished May 1, 1996 (61 FR 19476)), that proposed additional categorical exclusions for those actions that have been identified as normally not having a significant effect, individually or cumulatively, on the quality of the human environment. The final rule was published on July 29, 1997 (62 FR 40569), and became effective August 28, 1997. All applications or petitions requesting Agency action (e.g., NDAs, abbreviated new drug applications (ANDAs), INDs, biologics license applications (BLAs), supplements to such applications) must be accompanied by either an EA or a claim of categorical exclusion. Failure to provide (1) a claim of categorical exclusion or (2) an adequate EA, is sufficient grounds for ***refusing to file or approve*** the application (21 CFR 314.101(d)(4), 601.2(a) and (c), and 25.15(a)). An EA that is adequate for filing is one that addresses the relevant environmental issues. An EA adequate for approval is one that contains sufficient information to enable the Agency to determine whether the proposed action may affect significantly the quality of the human environment. This guidance provides information on when an EA should be submitted; it also makes recommendations on how to prepare EAs for submission of drug or biologics applications to the Center for Drug Evaluation and Research (CDER) and the Center for

[1] This guidance has been prepared under the direction of the Chemistry Manufacturing Controls Coordinating Committee, Center for Drug Evaluation and Research (CDER), and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration. This guidance represents the Agency's current thinking on environmental assessments. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

Biologics Evaluation and Research (CBER). Topics covered include (1) when categorical exclusions apply, (2) when to submit an EA, (3) the content and format of EAs, (4) specific guidance for the environmental issues that are most likely to be associated with human drugs and biologics, (5) test methods, (6) an applicant's treatment of confidential information submitted in support of an EA, and (7) master files for drugs and biologics.

This guidance, which is based on the July 1997 final rule, will remain in effect until superseded by new regulations or new guidance. The guidance is intended to supersede CDER's *Guidance for Industry For the Submission of an Environmental Assessment in Human Drug Applications and Supplements,* which was published in November 1995. Information in this guidance, along with information in the Code of Federal Regulations (CFR) at 21 CFR part 25 and 40 CFR parts 1500-1508 and the FDA *Environmental Assessment Technical Handbook* (NTIS Publication Number PB 87 175345/AS), which provides information on acceptable test methods, represents the core information available from CDER and CBER to assist industry in preparing an EA.

II. WHAT TYPES OF ACTIONS ARE SUBJECT TO CATEGORICAL EXCLUSION?

Certain classes of actions are subject to categorical exclusion and, therefore, ordinarily do not require the preparation of an EA because, as a class, these actions, individually or cumulatively, do not significantly affect the quality of the human environment (21 CFR 25.5(c)). However, as required under 21 CFR 25.21 and 40 CFR 1508.4, FDA will require "at least an EA" for any specific action that ordinarily would be excluded if extraordinary circumstances indicate that the specific proposed action may significantly affect the quality of the human environment.[2] See section III.C for additional information regarding extraordinary circumstances.

Submissions to CDER or CBER that ordinarily are excluded categorically under the regulations include actions on (1) NDAs, abbreviated applications, applications for marketing approval of a biologic product, and supplements to such applications if FDA's approval of the application does not increase the use of the active moiety; (2) NDAs, abbreviated applications, and supplements to such applications if FDA's approval of the application increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion (ppb); (3) NDAs, abbreviated applications, applications for marketing approval of a biologic product, and supplements to such applications for substances that occur naturally in the environment when the approval of the application does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment; (4) INDs; and (5) applications for marketing approval of a biologic product for transfusable human blood or blood components and plasma. An applicant is eligible

[2] Regulations would require an EIS (environmental impact statement) when "evaluation of data or information in an EA or otherwise available to the agency leads to a finding by the responsible agency official that a proposed action may significantly affect the quality of the human environment (21 CFR 25.22(b)).

to file a claim of categorical exclusion from the requirement to submit an EA if the action meets the criteria of at least one categorical exclusion.

A person submitting an application or petition of a type subject to categorical exclusion under 21 CFR 25.31 is not required to submit an EA if the person states that the action requested qualifies for categorical exclusion, citing the particular categorical exclusion that is claimed, and states that to the applicant's knowledge, no extraordinary circumstances exist (21 CFR 25.15(d)). An applicant ordinarily need not provide data to demonstrate that the action qualifies for categorical exclusion. CDER and CBER can rely on other information submitted in an application to evaluate the appropriateness of a claim for categorical exclusion. In the limited instances when it may be necessary, CDER or CBER will request additional information as needed to establish to their satisfaction that the criteria for categorical exclusion have been met.

III. WHEN IS AN EA REQUIRED?

Preparation of an environmental assessment ordinarily is required unless the proposed action qualifies for an exclusion under 21 CFR 25.30 or 25.31. An EA would also be required if extraordinary circumstances indicate that the specific proposed action may significantly affect the quality of the human environment (21 CFR 25.21).

Detailed information is provided below for the most common situations when actions would not qualify for categorical exclusion.

A. NDAs, Abbreviated Applications, and Supplements

Note: Section 1, below, should be used to assess increased use of a biological product as referenced in 21 CFR 25.31(a). Section 2 does not apply to biologics license applications (BLAs) because BLAs are not included in the categorical exclusion on which this section is based (21 CFR 25.31(b)). BLAs should be evaluated for whether they are eligible for categorical exclusion using 21 CFR 25.31(a) or (c) or other appropriate categorical exclusions found in 21 CFR 25.30 and 25.31.

NDAs, abbreviated applications, and supplements to such applications would not qualify for categorical exclusion if FDA's approval of the application increases the use of the active moiety ***and*** the estimated concentration of the substance at the point of entry into the aquatic environment will be 1 ppb or greater.

1. Increased Use

Increased use of an active moiety may occur if the drug will be administered at higher dosage levels, for longer duration, or for different indications than were previously in effect, or if the drug is a new molecular entity. The term *use* also encompasses disposal of FDA-regulated articles by consumers.

Attachment A contains examples of actions that would not be considered to increase the use of a drug and Attachment B contains examples of actions that would be considered to increase the use of a drug or biologic. These lists are not inclusive. An applicant is encouraged to contact the appropriate Center if any questions arise as to whether a particular action is considered to increase the use of a drug or biologic.

2. Estimating the Concentration of a Substance at the Point of Entry into the Aquatic Environment

The expected introduction concentration (EIC) of an active moiety into the aquatic environment should be calculated as follows:

EIC-Aquatic (ppb) = A x B x C x D where

A = kg/year produced for direct use (as active moiety)
B = l/liters per day entering POTWs*
C = year/365 days
D = 10^9 µg/kg (conversion factor)

* 1.214×10^{11} liters per day entering publicly owned treatment works (POTWs). Source: *1996 Needs Survey, Report to Congress.* Information regarding the *Needs Survey* is available on the Internet at http://www.epa.gov/owm. It is updated periodically.

This calculation assumes:

- All drug products produced in a year are used and enter the publicly owned treatment works (POTW) system.
- Drug product usage occurs throughout the United States in proportion to the population and amount of waste water generated.
- There is no metabolism.

The estimate of the kilogram/year active moiety should be based on or include (1) the highest quantity of the active moiety expected to be produced for direct use in any of the next five years. *Produced for direct use* means the quantity intended for use in humans during a given year (i.e., excludes any quantity produced for inventory buildup), (2) the quantity used in all dosage forms and strengths included in the application, and (3) the quantity used in an applicant's related applications. Related applications include those for other dosage forms using the same active moiety and for products using different forms of the active moiety (e.g., level of hydration, salt, free acid/base). All concentrations should be reported as the

concentration of active moiety, rather than the salt or complex.

The calculation of the expected introduction concentration (EIC) of an active moiety entering into the aquatic environment from patient use can consider the extent of metabolism of the active moiety to less pharmacologically active or inactive compounds, if that information is available. The pharmacological activity of metabolites relative to the active moiety should be considered when calculating the EIC. The weighted contribution of the metabolite to the EIC should be calculated (e.g., kg/year active moiety x 10% x 0.5 for a metabolite found at a level of 10% and that has half the pharmacological activity of the active moiety). If the pharmacological activity of the metabolite is unknown, it can be assumed to be the same as the active moiety.

An alternative calculation should be used if the drug product is intended for use in a specific geographic location (e.g., use an alternative value for the amount of liters per day entering POTWs — term B in the EIC calculation above). Moreover, if an alternative calculation is used to estimate localized use, or for any other reason, the calculation and the source and basis for the alternative calculation should be provided when filing an EA or a claim of categorical exclusion and would be subject to review.

B. Applications for Substances that Occur Naturally in the Environment

NDAs, abbreviated applications, applications for marketing approval of a biologic product and supplements to such applications for substances that occur naturally in the environment would not qualify for categorical exclusion under 21 CFR 25.31(c) when FDA's approval of the application alters significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment. This might be the case when the use and disposal occur in a geographic area where the substance does not naturally occur. However, the application may be eligible for a categorical exclusion under other provisions in 21 CFR 25.31.

In addition to drug and biologic products derived from natural sources or from biological systems, substances can be considered naturally occurring even if they are chemically synthesized. The Agency will consider the form in which the FDA-regulated article will exist in the environment when determining whether the drug or biologic is a naturally occurring substance. For example, a modified active moiety (e.g., salt) that does not occur naturally could be considered a naturally occurring substance if it is established that, in vivo and in the environment, the active moiety exists in a form that is found naturally.

Biological and biotechnological products will be similarly evaluated. For example, a protein or DNA comprising naturally occurring amino acids or nucleosides, but having a sequence different from that of a naturally occurring substance, will normally qualify as a

naturally occurring substance after consideration of metabolism. The same principle would apply to synthetic peptides and oligonucleotides and living and dead cells and organisms. CDER and CBER may rely on other information submitted in an application (e.g., information about metabolism, excretion, and stability; viability (if applicable); and physical and/or chemical characteristics of the product) in determining whether the FDA-regulated article would be considered a naturally occurring substance.

CDER and CBER will evaluate on a case-by-case basis the appropriateness of categorical exclusions claiming that the quantity of the naturally occurring substance that is expected to enter the environment as a result of an action will not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment.

C. Extraordinary Circumstances

As stated in 21 CFR 25.21 and 40 CFR 1508.4, FDA will require at least an EA for any specific action that ordinarily would be categorically excluded if extraordinary circumstances indicate that the specific proposed action could significantly affect the quality of the human environment. Extraordinary circumstance can be shown by data available either to the Agency or the applicant and can be based on the production, use, or disposal from use of the FDA-regulated article. Data available to the Agency can include public information, information submitted in the application, and data available to the Agency on the same or similar products.

1. Actions for which available data establish that there is a potential for serious harm to the environment at the expected level of exposure.

FDA considers harm to the environment to include not only toxicity to environmental organisms but also environmental effects other than toxicity, such as lasting effects on ecological community dynamics.

2. Actions that adversely affect a species or the critical habitat of a species determined under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Fauna and Flora to be endangered or threatened, or wild fauna or flora that are entitled to special protection under some other Federal law.

Actions that adversely affect a species or the critical habitat of a species determined under the Endangered Species Act to be endangered or threatened, wild fauna or flora listed in the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES), or wild fauna or flora that are entitled to special protection under some other Federal law or international treaty to which the United States is a party would be considered an extraordinary circumstance, and an EA should be submitted unless there are specific exemptions relating to the

pharmaceutical substances or FDA action. An example of an exception would be when a species is afforded special protection under Federal law or international treaty, but the pharmaceutical is derived only from nonwild specimens. If nonwild specimens are exempted from Federal law or treaty, the action would be eligible for categorical exclusion as indicated in section III.C.3.a. Both direct effects (e.g., pharmaceuticals derived from fauna or flora, see section III.C.3) and indirect effects (e.g., adverse effects from manufacturing site emissions) should be considered.

Under the U.S. Endangered Species Act (ESA), Congress declared, "[T]he United States has pledged itself as a sovereign state in the international community to conserve to the extent practicable the various species of fish or wildlife and plants facing extinction, pursuant to the Convention on International Trade in Endangered Species of Wild Fauna and Flora" (16 U.S.C. 1531(a)(4)(F)). Identification as an endangered or threatened species does not preclude the use of such fauna or flora. However, under the ESA, if a species has been determined to be endangered or threatened, a Federal agency is required to consult with the Secretary of Interior or the Secretary of Commerce to ensure that the agency's actions are not likely to jeopardize the continued existence of endangered or threatened species or their critical habitats (16 U.S.C. 1536).

3. Use of Fauna or Flora

FDA intends to examine closely the proposed actions for FDA-regulated articles obtained from fauna and flora and will use the extraordinary circumstances provision to require an EA in any instance in which it appears from an examination of the proposed action that the action may jeopardize the continued existence of a species. The following sections discuss CDER's and CBER's current position on when the use of fauna or flora normally would constitute an extraordinary circumstance for which an EA should be submitted to support the application.[3]

a. Cultivated Specimens

Actions involving drug or biologic products derived from cultivated plants (e.g., plantation, nursery stock) or bred or domestic animals (e.g., laboratory breed, cows, pigs) are not normally considered an extraordinary circumstance that would require an EA for an action that is normally categorically excluded (see section III.C.2 for a possible exception).

b. Wild Specimens

[3] FDA may clarify the environmental information that must be submitted to the Agency in marketing applications for specific drug or biologic products derived from plants or animals (e.g., paclitaxel, 61 FR 58694).

i. NDAs, abbreviated applications, applications for marketing approval of a biologic product, or certain supplements to such applications.

NDAs, abbreviated applications and applications for marketing approval of a biologic product where the drug or biologic product is derived from plants or animals taken from the wild, supplements to such applications that relate to changes in the source of the wild biomass (e.g., species, geographic region where biomass is obtained), or supplements to such applications that are considered to increase the use of an active moiety or biologic substance (see Attachment B) and which will cause more harvesting than what was described in the original EA would be considered an extraordinary circumstance, and an EA should be submitted.

ii. INDs

INDs generally involve relatively small quantities of a drug or biologic product and treatment of a limited number of patients. Many INDs never result in the filing of an NDA or application for marketing approval of a biologic product, which would allow for the wide-spread commercial sale of the product. CDER and CBER will evaluate INDs on a case-by-case basis where the drug or biologic product is derived from wild plants or animals to determine whether the extraordinary circumstance provision in 21 CFR 25.21 is invoked.

To facilitate Center review, when submitting a claim of categorical exclusion for actions where the drug or biologic product is derived from plants or animals, CDER and CBER request that the applicant provide the following information with the claim, or specifically identify where the information can be located (e.g., page number of application): (1) biological identification (i.e., common names, synonyms, variety, species, genus and family); (2) a statement as to whether wild or cultivated specimens are used; (3) the geographic region (e.g., country, state, province) where the biomass is obtained; and (4) a statement indicating whether the species is (a) determined under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) to be endangered or threatened, (b) entitled to special protection under some other Federal law or international treaty to which the United States is a party, or (c) the critical habitat of a species that has been determined to be endangered or threatened under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) or is entitled to

special protection under some other Federal law or international treaty to which the United States is a party. CDER and CBER will use this information to evaluate whether the claim of categorical exclusion is appropriate.

4. Production and Disposal Sites

FDA has found that regulated articles produced and disposed of in compliance with all applicable emission requirements do not significantly affect the environment and has determined it is unnecessary to review a company's compliance with Federal, State, and local environmental laws. In addition, both CDER and CBER routinely require as part of their safety evaluations that live organisms be inactivated following production and prior to release into the environment if there is a reasonable possibility that the living system may be harmful to the environment. Therefore, CDER and CBER will not routinely request submission of manufacturing and disposal information in an EA. However, if information available to the Agency or the applicant establishes that the general or specific emission requirements promulgated by Federal, State, or local environmental protection agencies do not address unique emission circumstances and the emissions may harm the environment, this would be sufficient grounds for requesting manufacturing or disposal information in an EA. Actions that threaten a violation of Federal, State, or local law or requirements imposed for the protection of the environment may constitute a significant impact (40 CFR 1508.27(b)(10)).

5. Significant Effects as Defined in 40 CFR 1508.27

The Council on Environmental Quality has provided a definition of "significantly" to aid in determining if an action may significantly affect the quality of the human environment. These examples should be considered when evaluating whether extraordinary circumstances exist that may warrant submission of at least an EA (See Attachment C).

IV. PREPARING AN EA FOR SUBMISSION TO CDER or CBER

A. Content and Format

This section describes the basic information that should be submitted in an EA if an EA is required. Attachment D contains an outline of the format for an EA. Alternative formats may be used, but the applicant should recognize that use of a standard format, such as described in this guidance, promotes efficiency in the review process.

1. Date

The EA should include the date the EA was originally prepared and the date(s) of any subsequent amendments.

2. Name of Applicant or Petitioner

The EA should identify the applicant who is submitting the application.

3. Address

The EA should contain the address where all correspondence is to be directed.

4. Description of Proposed Action

a. Requested Approval

The description of the requested approval should include the drug or biologic application number (if available), the drug or biologic product name, the dosage form and strength, and a brief description of the product packaging. For example, "XYZ Pharmaceuticals has filed an NDA pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for TRADE NAME (established name). 250 mg and 500 mg, packaged in OHDPE bottles. An EA has been submitted pursuant to 21 CFR part 25."

b. Need for Action

The EA should briefly describe the drug's or biologic's intended uses in the diagnosis, cure, mitigation, treatment, or prevention of disease.

c. Locations of Use

The EA should identify the location(s) where the product will be used. Depending on the type of product and its use, the locations of use are typically identified as hospitals, clinics and/or patients in their homes. If use is expected to be concentrated in a particular geographic region, this fact should be included.

d. Disposal Sites

Unless other disposal methods by the end user are anticipated, it is sufficient to state that at U.S. hospitals, pharmacies, or clinics, empty or partially empty packages will be disposed of according to hospital, pharmacy, or clinic procedures and/or that in the home, empty or partially empty containers will typically be disposed of by a community's solid waste management system, which may include landfills, incineration, and

recycling, although minimal quantities of the unused drug could be disposed of in the sewer system.

5. Identification of Substances that are the Subject the Proposed Action

The EA should contain information that allows for the accurate location of data about the substance in the scientific literature and for identification of closely related compounds. At a minimum, the information listed below should be provided, if available. For many biological products, format items 5.a.iii. b, c, and d will not apply. Other information, such as the international nonproprietary name (INN) or nonsystematic or semisystematic chemical names should be included if deemed useful in the identification of the compounds.

Usually this information need only be provided for the drug or biologic substance, but the same information also should be provided for the form of the active ingredient in the drug or biologic product if it is different from the drug or biologic substance (e.g., a salt formed in situ from a free base) or for a pharmacologically active related substance formed by conversion from a pharmacologically inactive parent compound (e.g., a prodrug product is converted to the pharmacologically active form).

a. Nomenclature

i. Established Name (U.S. Adopted Name-USAN)

ii. Brand/Proprietary Name/Tradename

iii. Chemical Names or Genus/Species of Biologic Product (e.g., virus)

- Chemical Abstracts (CA) Index Name (inverted form)
- Systematic Chemical Name (uninverted form)

b. Chemical Abstracts Service (CAS) registration number

c. Molecular Formula

d. Molecular Weight

e. Structural (graphic) Formula/Amino Acid Sequence

6. Environmental Issues

The type of information provided will vary depending on the environmental issues associated with the particular action. In general, the EA should include a succinct description of the environmental issues. The affected environment and the environmental effects and their significance should be discussed. Data and analyses to support the discussions should be provided as appropriate. Specific guidance is provided in section IV.B for the environmental issues that are most likely to be associated with human drugs and biologics. For environmental issues not specifically addressed in section IV.B (e.g., those included in sections III.C.4 and 5), applicants are encouraged to consult the appropriate Center prior to preparing the EA.

7. Mitigation Measures

Describe measures taken to avoid or mitigate any potential adverse environmental effects associated with the proposed action. If no adverse environmental effects have been identified, it should be so stated and indicated that, therefore, no mitigation measures are needed. See section IV.B.2.b for additional information regarding the discussion of mitigation measures for actions involving fauna and flora.

8. Alternatives to the Proposed Action

If no potential adverse environmental effects have been identified for the proposed action, the EA should state this. If potential adverse environmental effects have been identified for the proposed action, the EA "shall discuss any reasonable alternative course of action that offers less environmental risk or that is environmentally preferable to the proposed actions" (21 CFR 25.40(a)). The discussion should include the no-action alternative and measures that FDA or another government agency could undertake as well as those the applicant or petitioner would undertake. The EA should include a description of those alternatives that will enhance the quality of the environment and avoid some or all of the adverse environmental effects of the proposed action. The environmental benefits and risks of the proposed action and the environmental benefits and risks of each alternative should be discussed. See section IV.B.2.c for additional information regarding the discussion of alternatives for actions involving fauna and flora.

9. List of Preparers

The EA should include the name, job title, and qualifications (e.g., educational degrees) of those persons preparing the assessment and should identify any persons or agencies consulted. Contract testing laboratories should be included in the list of consultants, although this may be included in a confidential appendix. Curriculum vitae can be included in lieu of a description of an individual's

qualifications.

10. References

The EA should include a list of citations for all referenced material and standard test methods used in generating data in support of the EA. Copies of referenced articles that are not generally available and that are used to support specific claims in the EA document should be attached in a nonconfidential appendix.

11. Appendices

Both confidential and nonconfidential appendices can be included. See section IV.E for additional information about the treatment of confidential information. A list of the appendices should be included in the EA summary document with a designation of confidential or nonconfidential following each of the listings. Typically, the nonconfidential appendices include data summary tables and copies of referenced articles that are generally unavailable or that were used to support specific claims in the EA. Proprietary or confidential information, such as use estimates and test reports, should be included in the confidential appendices.

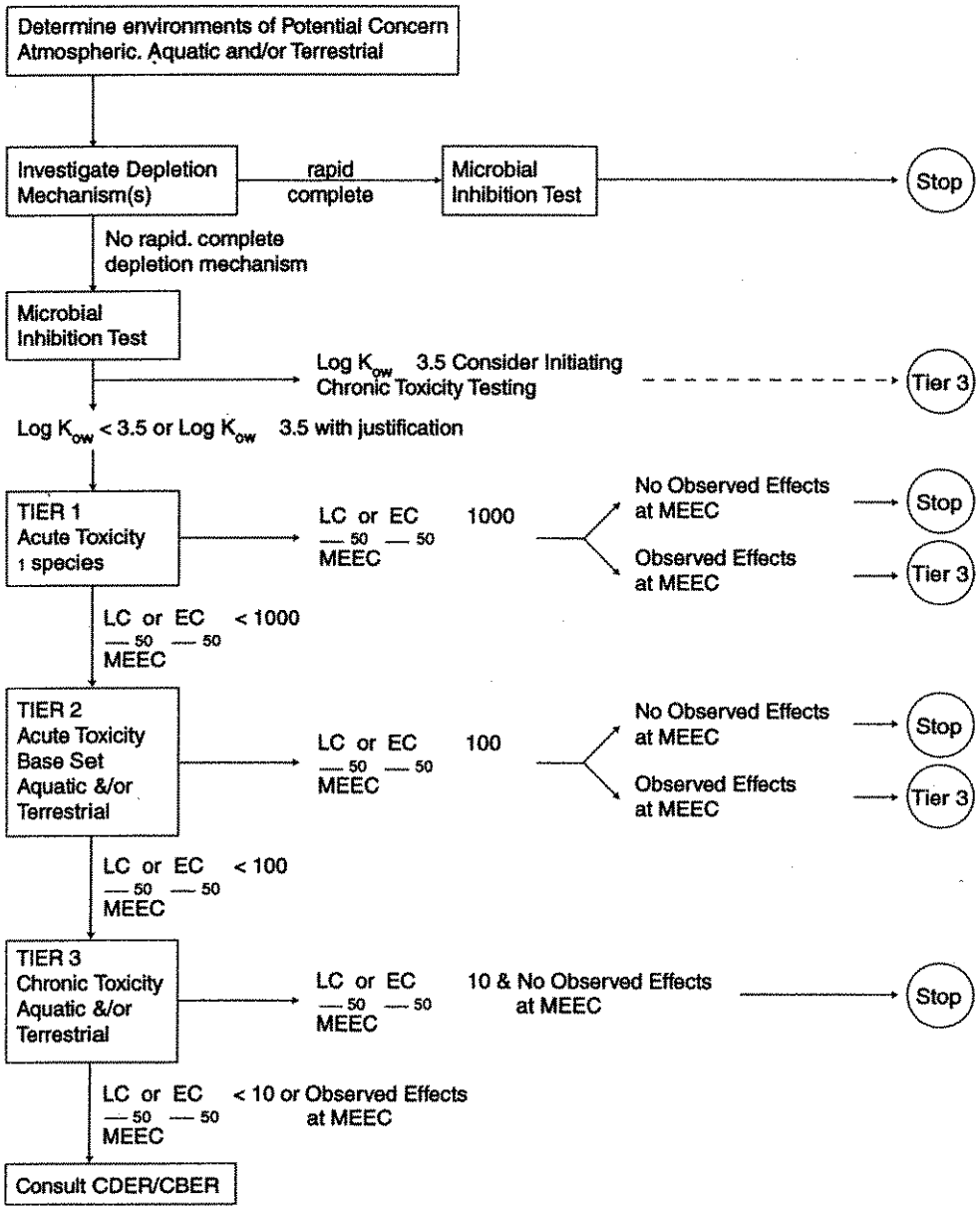
B. Specific Guidance — Environmental Issues

1. Assessing Toxicity to Environmental Organisms

If an EA is required, it normally should focus on characterizing the fate and effects of the compound of interest in the environment (1) when FDA's approval of the application increases the use of an active moiety and the estimated concentration of the active moiety at the point of entry into the aquatic environment is 1 ppb or greater (see section III.A); (2) when the substance occurs naturally in the environment and FDA's approval of the application alters significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment (see section III.B); or (3) in some cases, when data available to the Agency or applicant establish that at the expected level of exposure, there is the potential for serious harm to the environment (see section III.C.1). The provided information should focus on the fate and effects of the active moiety and/or structurally related substances (SRSs), rather than on excipients, for example.

The Centers encourage the use of a logical, tiered approach to testing so that adequate information is available to assess the potential environmental fate and effects of pharmaceuticals while minimizing the cost to industry. Figure 1 provides an illustration of a tiered approach. Alternative, scientifically justified approaches also can be used.

Figure 1
Tiered Approach to Fate and Effects Testing



Note: MEEC = EEC or EIC whichever is greater

Information submitted for fate and effects can include specific data generated on the test substance or relevant information on analogous compounds from the submitter or from peer-reviewed literature as appropriate. Actual experimental data regarding base parameters are generally preferable to computer modeling; however, in some circumstances computer modeling may be appropriate. FDA should be consulted if a company believes computer modeling is appropriate and wishes to use modeling in an EA.

a. Environmental Fate of Released Substances

i. Identification of Substances of Interest

The actual substances that will enter or exist in the environment (i.e., atmospheric, aquatic, terrestrial) can include the parent compound (i.e., drug or biologic substance) or SRSs such as the dissociated parent compound, metabolites, or degradants. The EA should list the drug or biologic substance and the predominant SRSs expected to enter or exist in the environment; provide the name, chemical structure and CAS number when possible; and provide a rationale for the decision as to which substance(s) will be studied. Predominant SRSs should be considered those greater than 10 percent of dose.

In most cases, fate (and effects) information should be provided on the parent (or active) drug or biologic substance, as representative of substances entering the environment. Such information is relevant to SRSs when the SRSs possess the same fundamental structure as the parent drug or biologic substance and are comparably or more polar. At a minimum, the EA should contain a discussion of the potential fate and effects of the predominant SRSs based on their structural differences and/or similarities to the parent compound (e.g., due to a functional group change, the metabolite should be more soluble than the parent compound, or the SRS is more polar). Computerized structure-activity relationship modeling programs may be useful in supporting extrapolation of fate and effects information from the parent (or active) drug or biologic substance to the SRS. Relevant available pharmacologic activity and toxicity information should be provided for the SRSs. Specific toxicity-activity information for SRSs may be included in a confidential appendix. Additional environmental information on a predominant SRS may be warranted, following consultation with the appropriate Center, if the fate of the compound is expected to differ from the parent compound, or there is an indication that the

SRSs effect on the environment would be substantially greater than from the parent drug or biologic substance.

ii. Physical and Chemical Characterization

The following tests should be conducted to determine if the compound is most likely to amass predominantly in aquatic, terrestrial, and/or atmospheric environments:

- Water Solubility
- Dissociation Constant(s)
- Octanol/Water Partition Coefficient
- Vapor Pressure or Henry's Law Constant

If there is a scientific basis for not performing a test, the justification should be included in the EA (e.g., water solubility was not determined because the compound is hydrolytically unstable). For a test compound that associates or dissociates in water, water solubility and the octanol/water partition coefficient may have to be determined at pH 5 and 9 as well as pH 7.

The octanol/water partition coefficient (K_{ow}) is an indicator of a nonionized compound's potential to adsorb to the organic fraction of soil, sediment, or biosolids (i.e., sludge) in addition to being an indicator of a compound's lipophilicity. It is not as good a predictor for inorganic chemicals, metal organic complexes, dissociating, ionic organic compounds, or compounds with other mitigating structural features such as molecular size. Further study of the sorption and/or desorption properties (K_{oc}) of a substance to biosolids should be considered if log K_{ow} is greater than 3 or other properties indicate that sorption or desorption may occur.

iii. Environmental Depletion Mechanisms

Depletion mechanisms should be investigated to determine if there is degradation of the compound in the environment(s) of interest. It is usually sufficient to provide basic supporting information that identifies the potential for a compound to be removed from the environment by a depletion mechanism (e.g., photolysis or hydrolysis based on information developed for analytical methods validation or from stability studies). It is unnecessary to go to

extraordinary effort to identify a depletion mechanism once the typical depletion mechanisms (i.e., hydrolysis, photolysis, biodegradation) have been investigated or to continue investigating other potential depletion mechanisms once one has been identified.

If the depletion mechanism is being used to reduce the expected introduction concentration or to eliminate effects testing, a formal, detailed analysis of the depletion mechanism should be provided (e.g., according to a standard test method, rate determination, analysis of expected exposure time in the environment).

Consideration should be given to the nature and extent of the degradation. If a rapid, complete depletion mechanism is identified (degradants are relatively simple, polar by-products), no testing to determine the environmental effects of the compound should be performed except for a microbial inhibition test or other appropriate test to assess the potential for the compound to disrupt waste treatment processes. Based on the estimated time prior to emission from a treatment facility, the following would be considered rapid depletion mechanisms:

Hydrolysis $t_{½}$ (pH 5-9):	≤ 24 hours
Aerobic Biodegradation $t_{½}$:	≤ 8 hours
Soil Biodegradation $t_{½}$:	≤ 5 days

Direct and indirect photolysis, although significant under laboratory conditions, may not be as rapid a depletion mechanism in the environment due to significant variation in light intensity (e.g., related to weather, latitude, depth penetration) and duration of exposure. Efforts to characterize photolysis as a depletion mechanism should take these factors into consideration.

iv. Environmental Concentrations

Expected Introduction Concentration (EIC): The environmental introduction concentrations into those environments (i.e., aquatic, terrestrial, atmospheric) where the substance(s) of interest is most likely to amass (see section IV.B.1.a.ii) should be estimated. A method of calculating the expected introduction concentration of a substance into the aquatic environment is described in section III.A.2. The calculation of the expected introduction concentration (EIC) entering into the aquatic environment from patient use, in addition to considering metabolism as described in section III.A.1, may include consideration of the environmental depletion

mechanisms that occur in the waste treatment process (e.g., adsorption, degradation, hydrolysis), if the information is available (see section IV.B.1.a.iii).

Some drug or biologic substance and/or active moiety may enter the terrestrial environment when biosolids from waste water treatment facilities, which contain adsorbed material, are applied to land. Application of biosolids to land is subject to regulation by the Environmental Protection Agency (EPA) or an appropriate State authority. Biosolids are generally subjected to some form of aerobic or anaerobic digestion in the waste treatment facility. The EIC for the terrestrial compartment should be estimated if, based on the available physical or chemical properties of the compound, significant quantities of the active moiety are expected to adsorb to biosolids. The calculation used will depend on the typical treatment, disposal, and application processes. Currently, approximately 6.8 million tons of biosolids (dry basis) are generated per year with 54 percent of that quantity being applied to land. The remaining biosolids are incinerated, landfilled or disposed of by other means. Depletion mechanisms (e.g., biodegradation, hydrolysis) that occur in the waste treatment process can be considered when calculating the EIC for the terrestrial compartment, if the information is available. Additional information regarding land application of biosolids is available from EPA's Office of Wastewater Management (on the Internet at http://www.epa.gov/owm/bio.htm).

The concentration expected in the atmospheric compartment need not be routinely calculated for pharmaceutical products administered through inhalation because, for the majority of these, the active moiety or other compound of interest is not released into the air. However, the EIC should be considered for products that are released primarily into the air (e.g., medical gases).

CDER and CBER have defined *use* to encompass disposal of FDA-regulated articles by consumers. Normally, the EIC from disposal need not be calculated since the majority of pharmaceutical products will be totally consumed, and any residual waste will typically be disposed of in landfills or at incineration facilities that are regulated by the EPA or appropriate State agencies. These agencies have considered the environmental impacts from the operation of these facilities in their licensing process and require controls (e.g., scrubbers, lined landfills, migration tests) to limit the release of materials into the environment. The EIC for disposal

should be calculated if significant quantities of material are expected to be disposed of other than by landfill, incineration or other procedures regulated by the EPA or appropriate State agencies.

Expected Environmental Concentration (EEC): The expected environmental concentration (EEC), sometimes referred to as the *predicted environmental concentration* (PEC), is the concentration of the active moiety or other compound of interest that organisms would be exposed to in the environment (e.g., surface water) after consideration of, for example, spatial or temporal concentration or depletion factors such as dilution, degradation, sorption and/or bioaccumulation. Adjustments to the expected introduction concentration may be made, based on spatial and temporal concentration or depletion factors, to provide an expected environmental concentration. Supporting information and/or discussion should be provided to explain the factors used in calculating the expected environmental concentration. The concentration should be provided for each environmental compartment (aquatic, terrestrial, atmospheric) expected to be affected based on the physical and/or chemical characterization of the compound of interest. In the majority of cases, the EEC for the aquatic environment would be expected to be significantly less than the EIC for the aquatic environment due to dilution. Based on dilution factors for POTWs available from the EPA, applying a dilution factor of 10 to the EIC-aquatic to estimate the EEC-aquatic is normally appropriate.

v. Summary

A summary discussion of the environmental fate of the substance(s) of interest should be provided for each environmental compartment based on the information and data provided in the EA, and the environmental compartment(s) in which the substance is expected to predominantly amass should be identified. In some circumstances, transport between environmental compartments should be considered when determining the fate of the substance(s) of interest in the environment.

Aquatic Environment: In general, pharmaceutical substances are expected to enter predominantly into the aquatic environment and, therefore, the focus of any effects studies most likely will be on aquatic organisms. If the substance(s) of interest rapidly degrades (see section IV.B.1.a.iii) or adsorbs completely and irreversibly to

biosolids, then fate and effects in the aquatic environment should not usually be considered.

Terrestrial Environment: In general, substances enter the terrestrial environment predominantly from biosolids removed from waste water treatment plants that are subsequently applied to land. Therefore, effects on the terrestrial environment are more likely if a compound adsorbs to biosolids (see section IV.B.1.a.ii). Biosolids are generally subjected to some form of aerobic or anaerobic digestion in the waste treatment facility; only a fraction of the biosolids may be applied to land, while the remainder is incinerated or land filled. Fate and effects testing in the terrestrial environment should be considered if testing indicates that the substance(s) of interest will significantly adsorb to biosolids (e.g., $K_{oc} \geq 1000$).

Atmospheric Environment: In general, substances that do not adsorb readily to soils, have a high vapor pressure, and have a low water solubility, are likely to volatilize significantly from the aquatic or terrestrial environments, although actual volatilization rates will depend on environmental conditions (e.g., dispersion away from the evaporation site) and on factors that can lessen or enhance the effective vapor pressure or behavior of the chemical at a liquid-air or solid-air interface. The atmospheric compartment may be of interest for medical gases. But, based on the polarity of the majority of compounds at relevant aquatic environmental conditions, it is unlikely that there would be substantive partitioning from the aquatic to the atmospheric environment for other pharmaceuticals. Any potential for a substance to volatilize and recycle into the aquatic or terrestrial environments should be discussed based on the information and data available for the substance.

b. Environmental Effects of Released Substances

Tiered approach to environmental effects testing (see below, Microbiological Inhibition Testing through Tier 3 Testing and Figure 1): If no rapid, complete depletion mechanism has been identified, it should be assumed that the compound will persist in the environment for some time and, therefore, the toxicity of the released substances to environmental organisms should be evaluated. The fate of the substance should be considered when designing the studies. For those compounds that enter the atmospheric environment, testing should be designed based on the extent to which the substance recycles into the aquatic or terrestrial environments. All toxicity test results for the drug or biologic substance

should be reported in terms of the quantity and/or concentration of the active moiety. When using this tiered approach to effects testing, it is important to design the test conditions appropriately so that a no-observed-effects concentration is determined.

Microbial Inhibition Testing: A microbial inhibition test or other appropriate test (e.g., respiration inhibition testing) should be performed to assess the substance(s) of interest's potential to inhibit microorganisms and subsequently disrupt waste treatment processes.

Assessment Factors: The assessment factors are intended to provide a consistent regulatory basis for determining when additional ecotoxicity testing should be performed (tiered approach). They are directly related to the amount of valid ecotoxicity data available. If the LC_{50} or EC_{50} or other appropriate test endpoint divided by the maximum expected environmental concentration (MEEC: EIC or EEC, whichever is greater) is less than the assessment factor, additional testing should be performed. The use of EC_{50} or test end point other than the LC_{50} should be limited to those test organisms for which the LC_{50} is not the test endpoint.

TEST TIER	ASSESSMENT FACTOR
1	1000 (see below)
2	100 (see below)
3	10 (see below)

Alternative scientifically justified approaches also can be used.

Tier 1 Testing: Acute ecotoxicity testing should be performed on a minimum of one suitable test organism (see base set for Tier 2 testing). If the EC_{50} or LC_{50} divided by the MEEC is greater than or equal to 1000, no further testing should be conducted unless sublethal effects are observed at the MEEC. If the EC_{50} or LC_{50} divided by the MEEC is less than 1000, Tier 2 testing should be performed. Sublethal effects (observed effects) at the MEEC indicate that chronic toxicity testing (Tier 3) should be performed. The use of the assessment factor of 100 could be used for Tier 1 testing if there is evidence (e.g., Tier 2 testing on a similar compound) to support that the single test organism used would be expected to be the most sensitive of the base set test organisms. If the compound is expected to partition to both the aquatic and terrestrial environments, usually testing of an aquatic test organism is sufficient since CDER has routinely observed lower toxicity results reported for aquatic test organisms as compared to terrestrial test organisms.

Tier 2 Testing: Acute ecotoxicity testing should be performed on the minimum base set of aquatic and/or terrestrial organisms. The aquatic base set usually consists of (1) a fish acute toxicity test, (2) an aquatic invertebrate acute toxicity test, and (3) an algal species bioassay. The terrestrial base set usually consists of (1) plant early growth tests, (2) earthworm toxicity tests, and (3) soil microbial toxicity tests. Usually only an earthworm toxicity study is indicated if the substance binds tightly to soil. A rodent acute toxicity is not included in the terrestrial base set since there is usually a significant quantity of mammalian (e.g., mouse, rat, dog, monkey, human) toxicity testing performed, both acute and chronic, to support the underlying applicacton and to demonstrate the safety of the drug or biologic product. Consultation with CDER or CBER is suggested prior to initiating any terrestrial studies.

If the EC_{50} or LC_{50} for the most sensitive organism in the base set divided by the MEEC is greater than or equal to 100, no further testing should be conducted unless sublethal effects are observed at the MEEC. If the EC_{50} or LC_{50} divided by the MEEC is less than 100, Tier 3 testing should be performed. Sublethal effects (observed effects) at the MEEC indicate that chronic toxicity testing (Tier 3) should be performed.

Tier 3 Testing: Chronic toxicity testing should be considered if the compound has the potential to bioaccumulate or bioconcentrate, if indicated based on Tier 1 and/or Tier 2 testing, or if there are other indications that the compound undergoes biotransformation to more toxic compounds.

Bioaccumulation, or bioconcentration, is a complex, dynamic process that depends on the availability, persistence, and physical and/or chemical properties of a compound in the environment. In general, pharmaceuticals tend not to be very lipophilic and are produced and/or used in relatively low quantities compared to industrial chemicals. In humans, the majority of pharmaceuticals are metabolized to some extent to SRSs that are more polar, less toxic, and less pharmacologically active than the parent compound. This suggests that there is a low potential for bioaccumulation or bioconcentration of pharmaceuticals; however, because of the length of time it takes to conduct chronic toxicity studies, applicants are encouraged to identify as early as possible compounds that are candidates for these studies.

A primary indicator of the potential for bioaccumulation is a compound's octanol/water partition coefficient (K_{ow}). A high octanol/water partition coefficient indicates that the compound will tend to be lipophilic. Chronic toxicity testing should be considered if log K_{ow} of a compound is greater

than or equal to 3.5 under relevant environmental conditions (e.g., pH 7), and a justification should be provided if chronic toxicity testing is not performed. Structural features (e.g., molecular size, polarity) that limit passage across biological membranes or the lack of bioavailability to environmental organisms (e.g., strong adsorption to soil) are mitigating factors that could be considered when determining if bioaccumulation (bioconcentration) would be a concern for compounds with a K_{ow} greater than or equal to 3.5. It may be important to obtain acute toxicity data for the organism to be tested to set the concentrations for the chronic studies properly. If the preparer of an EA is considering initiating chronic toxicity studies, consultation with CDER or CBER is recommended to ensure that such studies are appropriate and properly designed.

For chronic toxicity testing, if the EC_{50} or LC_{50} divided by the MEEC is greater than or equal to 10, no further testing should be conducted unless sublethal effects are observed at the MEEC. CDER or CBER should be consulted if the EC_{50} or LC_{50} divided by the MEEC is less than 10 or there are sublethal effects at the MEEC.

Test Methods and Test Organisms: Studies should be performed using test organisms and methods that have been identified by the FDA *Environmental Assessment Technical Handbook*, the EPA (40 CFR 797), the Organization for Economic Cooperation and Development (OECD), or other peer-reviewed literature, as appropriate, for use in environmental studies. If the drug or biologic product is intended to act upon an environmental organism (e.g., antiparasitic, antibiotic), information regarding the toxicity to the target organism(s) should be included.

c. Summary

A summary discussion of the environmental fate and effect of the substance(s) of interest should be provided. Discussion of the affected environments (aquatic, terrestrial, or atmospheric) should be included. The toxicity test results should be compared to the MEEC and the difference between the values discussed (e.g., in terms of the assessment factor, > 1000, > 100). It also may be appropriate to relate the toxicity test results to other estimated environmental concentrations (see section IV.B.1.a.iv).

2. Use of Fauna or Flora

If an EA is to be submitted for an action because the use of fauna or flora is the environmental issue (see section III.C.2 or 3), the EA should include specific information regarding the source of the fauna or flora, the mitigation measures associated with the harvesting of the resources, and a discussion of the reasonable

alternatives.

a. Use of Resources

Information relating to the source of the plant or animal, such as biological identification, government oversight of harvesting, geographic region where biomass is obtained, and harvesting methods and techniques should be included in the EA. The EA should include, but not be limited to, the following types of information:

- Biological identification (i.e., common names, synonyms, variety, species, genus, and family).
- A statement as to whether wild or cultivated specimens are used.
- The geographic region (e.g., country, state, province) where biomass is obtained and whether harvesting occurred on public or private land.
- A brief description of government oversight of the harvesting including, if applicable, the identity of the authority permitting harvesting and identity of authorities consulted regarding the harvesting. Submission of copies of permits or harvesting regulations relating to the specific species is helpful. For species covered under CITES, CDER or CBER could request copies of relevant permits.
- A brief description of the applicant's oversight of the harvesting.
- A statement indicating whether the species is (1) determined under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) to be endangered or threatened, (2) entitled to special protection under some other Federal law or international treaty to which the United States is a party, or (3) the critical habitat of a species that has been determined to be endangered or threatened under the Endangered Species Act or the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) or is entitled to special protection under some other Federal law or international treaty to which the United States is a party.
- A statement describing the part of plant or animal used and whether it is a renewable resource.

- A detailed description of the method of harvest including such information as the type of harvesting (e.g., clear cut, gleaning from timber stands destined for clear cutting, salvaging, pruning), frequency of harvest, whether the harvesting technique will affect the ecosystem (and if so, how), and whether the harvesting is conducted in accordance with government regulations or guidances (include citations to applicable regulations or guidances).

- Bulk weight or other appropriate measure of biomass needed to yield one kilogram of active moiety or biologic substance, the amount that has been harvested to date to support the proposed Agency action for the product, and the amount expected to be harvested in the future.

- The amount of biomass needed to produce the active moiety or biological substance used to treat the average patient. This should be provided in terms easy to understand (e.g., 2-3 trees per patient). The expected patient population and number of kilograms of active moiety or biologic substance needed per year should be provided.

- An estimate of the total number of plants or animals in the geographic region where the biomass is obtained.

- Any uses of the plant or animal other then for the proposed use (humans, food source, habitat for fauna).

- Plant or animal growth rate and/or life span and, if applicable, the rate of reproduction/regeneration.

- A discussion of whether the harvesting provides for sustained yield (e.g., percentage of sustainable harvest needed to supply annual needs based on the proposed use and any prior approved uses).

b. Mitigation Measures

Mitigation measures taken before (e.g., developing a process that uses a renewable part of a plant), during (e.g., limiting/selecting specimens to be harvested), and after harvesting (e.g., reforestation) should be included in the discussion of mitigation measures (see 40 CFR 1508.20).

c. Alternatives to the Proposed Action

A discussion must be provided of the reasonable alternatives that were considered when deciding which biomass source would be used to produce the active moiety or biologic substance (21 CFR 25.40(a)). All alternatives that were considered (e.g., other species, wild or cultivated sources, chemical synthesis) should be discussed. A brief discussion of the factors (e.g., environmental effects) that were considered in deciding whether or not the alternative would be used should be provided. The no-action (i.e., no approval) alternative should also be discussed. It should be indicated if any of the alternatives not currently used are planned for use in the future.

C. Data Summary Table

To facilitate review, the EA, if appropriate, should include a data summary table in a nonconfidential appendix (EA format item 11). Attachment E provides an example of a suitable data summary table.

D. Test Methods and Report Formats

Test methods and report formats are provided in the FDA *Environmental Assessment Technical Handbook*. Equivalent tests, such as those provided by the EPA (40 CFR 796 and 797), the Organization for Economic Cooperation and Development (OECD), or other validated, peer-reviewed methods can be used. Environmental fate studies should be compliant with either FDA's current Good Manufacturing Practice (cGMP) regulations (21 CFR 211.194) or FDA's Good Laboratory Practice (GLP) regulations (21 CFR part 58). The reports submitted in support of fate testing should include a description of the test method sufficient for a reviewer to determine the scientific merit of the methodology. Test performance and test reporting for environmental effects studies should meet FDA's GLP standards. Guidance on test reporting formats is included in the FDA *Environmental Assessment Technical Handbook* or 40 CFR parts 796 and 797. Raw test data (e.g., copies of notebook pages, HPLC chromatograms for each assay) should not be included in the EA.

E. Confidential and Nonconfidential Information

Some of the information that is submitted in an EA may be available elsewhere in an application or in a publicly available document. This information may be incorporated by reference in the EA (21 CFR 25.40(d)). However, the EA summary document, the document that contains the information recommended in section IV.A, should be a stand-alone document that contains a summary of the public information that is incorporated by reference and, to the extent possible, a summary of the confidential information that is either incorporated by reference or included in confidential appendices to the EA (21 CFR 25.51(a)). The EA will be made public by the FDA as required by regulations issued by

the Council on Environmental Quality. Therefore, the EA should contain, if appropriate, three distinct parts: (1) the EA summary document (see section IV.A), which is nonconfidential: (2) nonconfidential appendices: and (3) appendices with confidential information used to support the EA. Confidential data and information pertinent to the environmental review of a proposed action should be included in confidential appendices whenever possible to facilitate review of the EA. All confidential appendices should be at the end of the environmental assessment document. References to nonconfidential and confidential appendices may be included in the EA summary document, as appropriate. The EA summary document, nonconfidential appendices, and FONSI are made available for public inspection to the extent allowed by applicable laws (21 CFR 25.50(a) and (b)).

Attachment F provides general guidance as to which information can be included in confidential appendices of the EA. It is the applicant's responsibility to clearly identify the information in the EA that it believes is confidential.

F. Master Files for Drugs and Biologics

CDER and CBER do not take action on drug master files (DMFs) or master files (MFs) (i.e., they do not approve or disapprove submissions to a DMF (21 CFR 314.420(a)) or MF). Therefore, NEPA does not apply, and no EA needs to be submitted for a master file.

However, if an EA is required for the particular application, certain information that is included in a master file may be needed to address the relevant environmental issue(s). In these instances, the applicant seeking marketing approval should include the nonconfidential information in the EA summary document, rather than provide reference to the master file. The master file holder may be the applicant or an independent manufacturer who wants to limit the applicant's access to proprietary information. A master file reference may be provided for the confidential information, although this information must be summarized to the extent possible and included in the EA for public release. To expedite review of the EA, CDER and CBER prefer that copies of confidential information from master files be submitted in confidential appendices to the EA, whenever possible. If a letter of authorization is provided to reference confidential information in a master file, the specific type of information that is being referenced, the submission date, and page number where the information can be located should be stated. References to master files should be included in a confidential appendix since such references are considered confidential commercial information under the Freedom of Information Act (FOIA).

REFERENCES

1. FDA, "National Environmental Policy Act; Revision of Policies and Procedures: Final Rule," *Federal Register*, July 29, 1997 (62 FR 40569).

2. FDA, "National Environmental Policy Act; Proposed Revision of Policies and Procedures; Proposed Rule," *Federal Register*, April 3, 1996 (61 FR 14922); (republished May 1, 1996 (61 FR 19476)).

3. Rand, G., and S. Petrocelli, *Fundamentals of Aquatic Toxicology*, Hemisphere Publishing Corporation, 1987.

4. Zeeman, M., and J. Gilford, "Ecological Hazard Evaluation and Risk Assessment Under EPA's Toxic Substances Control Act (TSCA): An Introduction," *Environmental Toxicology and Risk Assessment, ASTM STP 1179*, Wayne G. Landis, Jane S. Hughes, and Michael A. Lewis, Eds., American Society for Testing and Materials, Philadelphia: 1993, pp. 7-21.

ATTACHMENT A: NO INCREASED USE

The following are types of actions that are not considered to result in increased use of an active moiety if approved by the Agency:

- Chemistry, manufacturing and control supplements (§§ 314.70, 601.12).
- Abbreviated applications.
- Lower doses than previously approved for the same indication (i.e., total daily dose).
- Shorter duration of use than previously approved for the same indication (e.g., number of days).
- Exclusion of a patient population in the labeling (e.g., by age, gender, complicating medical conditions).
- A prodrug for which the active metabolite is an approved product in the United States and which is intended to substitute directly[4] for that approved product. An active moiety which is the active metabolite of an approved prodrug in the United States would be considered similarly.
- New dosage forms that substitute directly for an approved product.
- Product reformulations in which the labeled amount of active moiety/biologic substance remains constant.
- Packaging changes/dosage form product line extensions that substitute directly for an approved product (e.g., new delivery system, addition of a different vial fill size).
- Combination drugs in which the single product substitutes directly for two approved products that would be administered separately.

[4] In context of Attachments A and B, substitute directly means that the drug or biologic product (i.e., active moiety or biologic substance) will be used for the same indication, at the same or lower dosage levels (i.e., total daily dose), and for the same or shorter duration of use (e.g., number of days) as previously approved by the Agency for the same active moiety or biologic substance.

ATTACHMENT B: INCREASED USE

The following are types of actions that are considered to result in increased use of an active moiety if approved by the Agency:

- New molecular entities.
- A new indication for a drug that was previously approved. This includes those actions requesting approval of off-label uses and switches from a second-line to first-line indication.
- ℞ to OTC switches.
- Higher doses than were previously approved (i.e., total daily dose).
- Longer duration of use than previously approved (e.g., number of days).
- Inclusion of a patient population in the labeling that had previously been ***specifically excluded*** (e.g., by age, gender, complicating medical conditions).
- New dosage forms/routes of administration that increase the amount of active ingredient/biologic substance used. For example, the use of the active moiety or biologic substance for the same indication will normally increase if a switch is made from an injectable dosage form to an oral dosage form.

ATTACHMENT C: 40 CFR 1508.27

§ 1508.27 Significantly.

"Significantly" as used in NEPA requires considerations of both context and intensity:

(a) *Context.* This means that the significance of an action must be analyzed in several contexts such as society as a whole (human, national), the affected region, the affected interests, and the locality. Significance varies with the setting of the proposed action. For instance, in the case of a site-specific action, significance would usually depend upon the effects in the locale rather than in the world as a whole. Both short- and long-term effects are relevant.

(b) *Intensity.* This refers to the severity of impact. Responsible officials must bear in mind that more than one agency may make decisions about partial aspects of a major action. The following should be considered in evaluating intensity:

(1) Impacts that may be both beneficial and adverse. A significant effect may exist even if the Federal agency believes that on balance the effect will be beneficial.

(2) The degree to which the proposed action affects public health or safety.

(3) Unique characteristics of the geographic area such as proximity to historic or cultural resources, park lands, prime farmlands, wetlands, wild and scenic rivers, or ecologically critical areas.

(4) The degree to which the effects on the quality of the human environment are likely to be highly controversial.

(5) The degree to which the possible effects on the quality of the human environment are highly uncertain or involve unique or unknown risks.

(6) The degree to which the action may establish a precedent for future actions with significant effects or represents a decision in principle about a future consideration.

(7) Whether the action is related to other actions with individually insignificant but cumulatively significant impacts. Significance exists if it is reasonable to anticipate a cumulatively significant impact on the environment. Significance cannot be avoided by terming an action temporary or by breaking it down into small component parts.

(8) The degree to which the action may adversely affect districts, sites, highways, structures, or objects listed in or eligible for listing in the National Register of Historic Places or may cause loss or destruction of significant scientific, cultural, or historical resources.

(9) The degree to which the action may adversely affect an endangered or threatened species or its habitat that has been determined to be critical under the Endangered Species Act of 1973.

(10) Whether the action threatens a violation of Federal, State, or local law or requirements imposed for the protection of the environment.

ATTACHMENT D: EA FORMAT

1. Date
2. Name of Applicant/Petitioner
3. Address
4. Description of Proposed Action
   a. Requested Approval
   b. Need for Action
   c. Locations of Use
   d. Disposal Sites
5. Identification of Substances that are the Subject of the Proposed Action
   a. Nomenclature
      i. Established Name (U.S. Adopted Name - USAN)
      ii. Brand/Proprietary Name/Tradename
      iii. Chemical Names or Genus/Species of Biologic Product (e.g., virus)
         - Chemical Abstracts (CA) Index Name
         - Systematic Chemical Name
   b. Chemical Abstracts Service (CAS) Registration Number
   c. Molecular Formula
   d. Molecular Weight
   e. Structural (graphic) Formula/Amino Acid Sequence
6. Environmental Issues
7. Mitigation Measures
8. Alternatives to the Proposed Action
9. List of Preparers
10. References
11. Appendices

ATTACHMENT E: SAMPLE DATA SUMMARY TABLE

SAMPLE DATA SUMMARY TABLE	
PHYSICAL/CHEMICAL CHARACTERIZATION	
Water Solubility[1]	
Dissociation Constant(s)	
Log Octanol/Water Partition Coefficient (Log K_{ow})[1]	
Vapor Pressure or Henry's Law Constant	
Sorption/Desorption (K_{oc})[1]	
DEPLETION MECHANISMS	
Hydrolysis	
Aerobic Biodegradation	
Soil Biodegradation	
Photolysis	
Metabolism	
ENVIRONMENTAL EFFECTS[2]	
Microbial Inhibition	
Acute Toxicity	
Chronic Toxicity	

[1]Depending on dissociations constant(s), water solubility and octanol/water partition coefficient may have to be determined at pH 5 and 9, in addition to pH 7 or K_{oc} may have to be determined in acidic and/or alkaline soil in addition to neutral soil. See section IV.B.1.a.ii for guidance.

[2]Identify organism(s) and report results, e.g., NOEC, MIC, EC_{50}, LC_{50} in ppm of active moiety.

ATTACHMENT F: CONFIDENTIAL/NONCONFIDENTIAL

EA FORMAT ITEM	SUBSECTION	NONCONFIDENTIAL	CONFIDENTIAL
1.Date	***	X	
2. Name of Applicant/Petitioner	***	X	
3. Address	***	X	
4. Description of Proposed Action	a. Requested Approval	X	
	b. Need for Action	X	
	c. Locations of Use	X	
	d. Disposal Sites	X	
5. Identification of Substances that are the Subject of the Proposed Action	a. Nomenclature	X	
	b. CAS Number	X	
	c. Molecular Formula	X	
	d. Molecular Weight	X	
	e. Structural Formula	X	

EA FORMAT ITEM	SUBSECTION	NONCONFIDENTIAL	CONFIDENTIAL
6. Environmental Issue (Specific environmental issues identified in section IV.B)	a. Assessing Toxicity to Environmental Organisms	For example: * Substances expected to enter or exist in the environment. * Summary discussion of toxicity/activity of predominant SRSs relative to the parent (active) compound * Test results physical/chemical characterization * Method of calculating estimates of environmental concentration * Supporting information for spatial/temporal depletion factors. * Environmental effects test results	For example: * Specific toxicology/ pharmacological activity data for SRSs * Test reports * Environmental concentration estimates
	b. Use of Fauna or Flora	For example: * Biological identification and other information relating to species used (e.g., plant growth rate) * Geographic region of the source * Government oversight * Method of harvesting	For example: * Bulk weight of biomass needed to produce a kg of active moiety * Amount harvested * The expected patient population and kg of active moiety expected to be used per year
7. Mitigation Measures	***	X	
8. Alternatives to the Proposed Action	***	X	
9. List of Preparers	***	X	

EA FORMAT ITEM	SUBSECTION	NONCONFIDENTIAL	CONFIDENTIAL
10. References	***	X	
11. Appendices	***	For example: * Referenced articles not generally available or which are used to support specific claims in the EA document * Data summary table	For example: * Estimates of the kg of active moiety to be used/year * Test reports * Letters of authorization to DMFs

ATTACHMENT G: GLOSSARY OF TERMS

Active Moiety: The molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance (21 CFR 314.108(a)). The active moiety is the entire molecule or ion, not the "active site."

Bioaccumulation: The process by which industrial waste, chemicals, and other substances gradually accumulate in living tissue.

Bioconcentration: The process by which industrial waste, chemicals, and other substances accumulate directly from water into and onto aquatic organisms.

Biological (biologic) product: Any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component, derivative, allergenic product, or analogous product applicable to the prevention, treatment, or cure of a disease or condition of human beings (section 351 of the Public Health Service Act).

Biomass: The plant, plant part (e.g., bark, leaves, flower, seed), animal, or animal part (e.g., skin, liver, stomach) that is collected for processing into a drug or biologic.

Drug product: A finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more ingredients (21 CFR 314.3(b)).

Drug substance: An active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates used in the synthesis of such ingredient (21 CFR 314.3(b)).

Expected environmental concentration (EEC): The expected concentration of the active moiety or other structurally related substance of interest that organisms would be exposed to in the environment (e.g., surface water) after consideration of spatial or temporal concentration or depletion factors such as dilution, degradation, sorption, bioaccumulation. This is sometimes referred to as the predicted environmental concentration (PEC).

Expected introduction concentration (EIC) for disposal: The expected introduction concentration of the active moiety that may enter the environment due to disposal. Depletion mechanisms that occur prior to introduction into the environment may be considered in the calculation as indicated in the text.

Expected introduction concentration (EIC) for use: The expected introduction concentration, based on fifth-year marketing estimates, of the active moiety that can enter the environment due to use. Depletion mechanisms that occur prior to introduction into the environment and human metabolism may be considered in the calculation as indicated in the text.

Half-life ($t_{1/2}$): Time required to reduce by one-half the concentration of a material.

Lowest observed effect concentration (LOEC): The lowest concentration of a material used in a toxicity test that has a statistically significant adverse effect on the exposed population of the test organisms as compared with the controls.

Master file: A submission of information to the FDA by a person who intends it to be referenced during the review of an application. See 21 CFR 314.420 for specific information on drug master files.

Maximum expected environmental concentration (MEEC): The expected introduction concentration (EIC) or expected environmental concentration (EEC), whichever is greater.

Median effective concentration (EC_{50}): The concentration of material to which organisms are exposed that is estimated to be effective in producing some sublethal response in 50 percent of the test organisms. The EC_{50} is usually expressed as a time-dependent variable (e.g., 24 hour EC_{50}).

Median lethal concentration (LC_{50}): The concentration of material to which organisms are exposed that is estimated to be lethal to 50 percent of the test organisms. The LC_{50} is usually expressed as a time-dependent variable (e.g., 24 hour LC_{50}).

Minimum inhibitory concentration (MIC): The lowest concentration of a chemical that inhibits the visible growth of the test organisms.

New molecular entity: An active moiety (present as the unmodified base [parent] compound, or an ester or a salt, clathrate, or other noncovalent derivative of the base [parent] compound) that has not been previously approved or marketed as the active moiety in the United States for use in a drug product, either as a single ingredient or as part of a combination product, or as part of a mixture of stereoisomers.

No observed effect concentration (NOEC): The highest concentration of a material used in a toxicity test that has no statistically significant adverse effect on the exposed population of test organisms as compared with the controls.

Octanol/water partition coefficient (K_{ow}): The ratio of a chemical's solubility in n-octanol and water at equilibrium; also expressed as P. A measurement of a drug's or biologic's lipophilicity and an indication of its ability to cross cell membranes. The logarithm of P or K_{ow} is used as an estimate of the tendency of the chemical to bioaccumulate or adsorb to soil or sediments.

Parts per billion (ppb): One unit of chemical (usually expressed as mass) per 1,000,000,000 (10^9) units of medium (e.g., water) or organism (e.g., tissue) in which it is contained. For water 1 µg/L = 1 ppb; for tissue 1 µg/kg = 1 ng/g = 1 ppb.

Parts per million (ppm): One unit of chemical (usually expressed as mass) per 1,000,000 (10^6) units of medium (e.g., water) or organism (e.g., tissue) in which it is contained. For water 1 mg/L = 1 ppm; for tissue 1 mg/kg = 1 µg/g = 1 ppm.

Parts per trillion (pptr): One unit of chemical (usually expressed as mass) per 1,000,000,000,000 (10^{12}) units of medium (e.g., water) or organism (e.g., tissue) in which it is contained. For water 1 ng/L = 1 pptr; for tissue 1 ng/kg = 1 pptr.

Soil or sediment/water partition coefficient (K_{oc}): The ratio of chemical adsorbed per unit weight of organic carbon in soil or sediment to the concentration of the chemical in solution at equilibrium.

Toxicity: The inherent potential or capacity of a material to cause adverse effects in a living organism.

Supplement 4
Summary of measurement data of human pharmaceuticals in the aquatic environment

Pharmaceutical or metabolite	Therapeutic use	Concentration in matrix in ng/l	n	Median ng/l	90-perc. ng/l	Matrix	Country	Reference
Hospital or industrial effluent								
Antiepileptics (pharmaceuticals for treatment of epilepsy)								
Carbamazepine	antiepileptic	2500000				pharmaceutical industry effluent	GER	Sacher et al. (1997)
Cytostatics (pharmaceuticals for treatment of cancer)								
Bleomycin	cytostatic (antibiotic drug)	20	estimated			hospital effluent	CH	Hartmann et al. (1998)
Mitomycin C	cytostatic (antibiotic drug)	20	estimated			hospital effluent	CH	Hartmann et al. (1998)
Cisplatin	cytostatic (alkylating drug)	90	estimated			hospital effluent	CH	Hartmann et al. (1998)
Cyclophosphamide	cytostatic (alkylating drug)	19 - 4486	7			hospital effluent		Steger-Hartmann et al. (1996)
Dacarbazin	cytostatic (alkylating drug)	190	estimated			hospital effluent	CH	Hartmann et al. (1998)
Etoposide	cytostatic (natural substance)	490	estimated			hospital effluent	CH	Hartmann et al. (1998)
Ifosfamide	cytostatic (alkylating drug)	24				hospital effluent	GER	Steger-Hartmann et al. (1996)
Ifosfamide	cytostatic (alkylating drug)	50 - 8500	estimated			hospital effluent	GER	Kümmerer et al. (1997)
Ifosfamide	cytostatic (alkylating drug)	<6 - 1914		109		hospital effluent	GER	Kümmerer et al. (1997)
Fluorouracil	cytostatic (antimetabolic drug)	2030	estimated			hospital effluent	CH	Hartmann et al. (1998)
Antibiotics and pharmaceuticals for treatment of infections with protozoa and parasites								
Amoxicillin	antibiotic (penicillins)	201000	estimated			hospital effluent	CH	Hartmann et al. (1998)
Penicillin G	antibiotic (penicillins)	4000 - 140000	estimated			hospital effluent	GER	Al-Ahmad et al. (1999)
Ciprofloxacin	antibiotic (fluoroquinolones)	3000 - 87000	16			hospital effluent	CH	Hartmann et al. (1998)
Ciprofloxacin	antibiotic (fluoroquinolones)	14500	estimated			hospital effluent	CH	Hartmann et al. (1998)
Ciprofloxacin	antibiotic (fluoroquinolones)	2000 - 30000	estimated			hospital effluent	GER	Al-Ahmad et al. (1999)
Norfloxacin	antibiotic (fluoroquinolones)	6200	estimated			hospital effluent	CH	Hartmann et al. (1998)
Sulfamethoxazole	antibiotic (sulfonamides)	1000 - 140000	estimated			hospital effluent	GER	Al-Ahmad et al. (1999)
Metronidazol	antibiotic, for treatment against protozoa (imidazoles)	6200	estimated			hospital effluent	CH	Hartmann et al. (1998)
Ornidazol	for treatment against protozoa (imidazoles)	8300	estimated			hospital effluent	CH	Hartmann et al. (1998)
Meropenem	antibiotic (other categories)	1000 - 3000	estimated			hospital effluent	GER	Al-Ahmad et al. (1999)
Other pharmaceuticals								
Methaqualone	sedative	~ 1000				hospital effluent		Richardson & Bowron (1985)

Pharmaceutical or metabolite	Therapeutic use	Concentration in matrix in ng/l	n	Median ng/l	90-perc. ng/l	Matrix	Country	Reference
Influent of sewage treatment plant								
Pharmaceuticals for treatment of cardiovascular diseases								
Bezafibrate	lipid regulator (fibrate)	up to 4400	11			stp influent	GER	Stumph et al. (1996)
Bezafibrate	lipid regulator (fibrate)	~1200	1			stp influent	BRAZ	Stumph et al. (1999)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etophyllinclofibrate	5.3 - 14	11			stp influent	GER	Stumph et al. (1996)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etophyllinclofibrate	1000	1			stp influent	BRAZ	Stumph et al. (1999)
Fenofibric acid	metabolite of Fenofibrate	up to 3000	11			stp influent	GER	Stumph et al. (1996)
Fenofibric acid	metabolite of Fenofibrate	~450	1			stp influent	BRAZ	Stumph et al. (1999)
Gemfibrozil	lipid regulator (fibrate)	up to 5500	11			stp influent	GER	Stumph et al. (1996)
Gemfibrozil	lipid regulator (fibrate)	~300	1			stp influent	BRAZ	Stumph et al. (1999)
Pentoxifylline	vasodilator (blood diluent)	<210 - 230	8			stp influent	GER	Möhle et al. (1999).
Antiepileptics (pharmaceuticals for treatment of epilepsy)								
Carbamazepine	antiepileptic	150 - 1760	8	1310		stp influent	GER	Möhle et al. (1999).
Primidon	antiepileptic	<250 - 670	8	560		stp influent	GER	Möhle et al. (1999).
Analgesics (pain relievers)								
Acetylsalicylic acid	analgesic	3200	6			stp influent	GER	Ternes et al. (1998b)
Diclofenac	analgesic, antirheumatic	up to 2000	11			stp influent	GER	Stumph et al. (1996)
Diclofenac	analgesic, antirheumatic	470 - 1920	5			stp influent	CH	Buser et al. (1998)
Diclofenac	analgesic, antirheumatic	up to 6220	9	1040		stp influent	GER	Möhle et al. (1999).
Diclofenac	analgesic, antirheumatic	~800	1			stp influent	BRAZ	Stumph et al. (1999)
Dihydrocodeine	analgesic, antitussive (cough suppressant)	1060 - 5040	5			stp influent	GER	Möhle et al. (1999).
Dihydrocodeine	analgesic, antitussive (cough suppressant)	up to 4060	8	1470		stp influent	GER	Möhle et al. (1999).
Gentisic acid	metabolite of acetylsalicylic acid	4600	6			stp influent	GER	Ternes et al. (1998b)
Ibuprofen	analgesic, antirheumatic	up to 12000	11			stp influent	GER	Stumph et al. (1996)
Ibuprofen	analgesic, antirheumatic	~350	1			stp influent	BRAZ	Stumph et al. (1999)
Indometacine	analgesic, antirheumatic	below detection limit	11			stp influent	GER	Stumph et al. (1996)
Indometacine	analgesic, antirheumatic	~950	1			stp influent	BRAZ	Stumph et al. (1999)
Ketoprofen	analgesic, antirheumatic	up to 800	11			stp influent	GER	Stumph et al. (1996)
Ketoprofen	analgesic, antirheumatic	~550	1			stp influent	BRAZ	Stumph et al. (1999)
Naproxen	analgesic	~650	1			stp influent	BRAZ	Stumph et al. (1999)
o-hydroxyhippuric acid	metabolite of acetylsalicylic acid	6800	6			stp influent	GER	Ternes et al. (1998b)
Paracetamol	analgesic	26000	6			stp influent	GER	Ternes et al. (1998b)
Propyphenazone	anti-inflammatory, antipyretic and analgesic	up to 420	4	420		stp influent	GER	Möhle et al. (1999).
Salicylic acid	metabolite of acetylsalicylic acid	54000	6			stp influent	GER	Ternes et al. (1998b)

Pharmaceutical or metabolite	Therapeutic use	Concentration in matrix in ng/l	n	Median ng/l	90-perc. ng/l	Matrix	Country	Reference
Cytostatics (pharmaceuticals for treatment of cancer)								
Cyclophosphamide	cytostatic (alkylating drug)	<6 - 143	21			stp influent near hospitals		Steger-Hartmann et al. (1996)
Ifosfamide	cytostatic (alkylating drug)	35 - 360	estimated			stp influent	GER	Kümmerer et al. (1997)
Ifosfamide	cytostatic (alkylating drug)	7 - 29	6	8.5		stp influent	GER	Kümmerer et al. (1997)
Ifosfamide	cytostatic (alkylating drug)	<6 - 29	6	6.2		stp influent	GER	Kümmerer et al. (1997)
Methotrexate	cytostatic (antimetabolic drug)	~ 1000				sewer effluent		Aherne et al. (1985)
Antibiotics and pharmaceuticals for treatment of infections with protozoa and parasites								
Penicillin G	antibiotic (penicillins)	6000	estimated (worst case)			stp influent	GER	Al-Ahmad et al. (1999)
Ciprofloxacin	antibiotic (fluorochinolones)	600	estimated (worst case)			stp influent	GER	Al-Ahmad et al. (1999)
Sulfamethoxazole	antibiotic (sulfonamides)	12000	estimated (worst case)			stp influent	GER	Al-Ahmad et al. (1999)
Meropenem	antibiotic (other categories)	<100	estimated (worst case)			stp influent	GER	Al-Ahmad et al. (1999)
Other pharmaceuticals								
Crotamiton	pharmaceutical for treatment of headlice and scabies	<120 - 130	3			stp influent	GER	Möhle et al. (1999).
Fenoprofen	antirheumatic	up to 300	11			stp influent	GER	Stumph et al. (1996)
Hydrocodone	antitussive (cough suppressant)	<100 - 450	5			stp influent	GER	Möhle et al. (1999).
Hydrocodone	antitussive (cough suppressant)	<300 - 1940	8	720		stp influent	GER	Möhle et al. (1999).

Pharmaceutical or metabolite	Therapeutic use	Concentration in matrix in ng/l	n	Median ng/l	90-perc. ng/l	Matrix	Country	Reference
Effluent of sewage treatment plant								
Pharmaceuticals for treatment of cardiovascular diseases								
Betaxolol	beta-blocker (antihypertensive)	<25 - 188	25	63	103	stp effluent	GER	Hirsch et al. (1996)
Betaxolol	beta-blocker (antihypertensive)	<25 - 190	29	57	100	stp effluent	GER	Ternes (1998b)
Bisoprolol	beta-blocker (antihypertensive)	<25 - 370	25	57	176	stp effluent	GER	Hirsch et al. (1996)
Bisoprolol	beta-blocker (antihypertensive)	<25 - 370	29	57	130	stp effluent	GER	Ternes (1998b)
Carazolol	beta-blocker (antihypertensive)	<25 - 117	25	<25	88	stp effluent	GER	Hirsch et al. (1996)
Carazolol	beta-blocker (antihypertensive)	<25 - 120	29	<25	70	stp effluent	GER	Ternes (1998b)
Metoprolol	beta-blocker (antihypertensive)	220 - 530	2			stp effluent	NL, B	Mons et al. (2000)
Metoprolol	beta-blocker (antihypertensive)	up to 2200	25	732	1320	stp effluent	GER	Hirsch et al. (1996)
Metoprolol	beta-blocker (antihypertensive)	up to 2200	29	730	1300	stp effluent	GER	Ternes (1998b)
Nadolol	beta-blocker (antihypertensive)	<25 - 57	25	26	45	stp effluent	GER	Hirsch et al. (1996)
Nadolol	beta-blocker (antihypertensive)	<25 - 60	29	25	42	stp effluent	GER	Ternes (1998b)
Propranolol	beta-blocker (antihypertensive)	<25 - 286	25	166	228	stp effluent	GER	Hirsch et al. (1996)
Propranolol	beta-blocker (antihypertensive)	<25 - 290	29	170	230	stp effluent	GER	Ternes (1998b)
Timolol	beta-blocker (antihypertensive)	<25 - 69	25	<25	38	stp effluent	GER	Hirsch et al. (1996)
Timolol	beta-blocker (antihypertensive)	<25 - 70	29	<25	<25	stp effluent	GER	Ternes (1998b)
Bezafibrate	lipid regulator (fibrate)	<250 - 4560	39	2610	3490	stp effluent	GER	Stumph et al.(1996)
Bezafibrate	lipid regulator (fibrate)	<250 - 4600	49	2200	3400	stp effluent	GER	Ternes (1998b)
Bezafibrate	lipid regulator (fibrate)	3320	1			stp effluent	GER	AWWR (1996)
Bezafibrate	lipid regulator (fibrate)	~850	1			stp effluent (biological filter)	BRAZ	Stumph et al. (1999)
Bezafibrate	lipid regulator (fibrate)	~600	1			stp effluent (active sludge)	BRAZ	Stumph et al. (1999)
Bezafibrate	lipid regulator (fibrate)	<10 - 20	4			stp effluent	NL, B	Mons et al. (2000)
Clofibrate	lipid regulator (fibrate)	<100	20	<100	<100	stp effluent	GER	Ternes (1998b)
Fenofibrate	lipid regulator (fibrate)	<50	20	<50	<50	stp effluent	GER	Ternes (1998b)
Fenofibrate	lipid regulator (fibrate)	15 - 75	5			stp effluent	GER	Kalbfus (1997)
Fenofibrate	lipid regulator (fibrate)	<100	2			stp effluent	NL, B	Mons et al. (2000)
Etofibrate	lipid regulator (fibrate)	<100	20	<100	<100	stp effluent	GER	Ternes (1998b)
Gemfibrozil	lipid regulator (fibrate)	<50 - 1460	39	300	870	stp effluent	GER	Stumph et al. (1996)
Gemfibrozil	lipid regulator (fibrate)	<50 - 1500	49	400	840	stp effluent	GER	Ternes (1998b)
Gemfibrozil	lipid regulator (fibrate)	1320	1			stp effluent	GER	AWWR (1996)
Gemfibrozil	lipid regulator (fibrate)	~250	1			stp effluent (biological filter)	BRAZ	Stumph et al. (1999)
Gemfibrozil	lipid regulator (fibrate)	~100	1			stp effluent (active sludge)	BRAZ	Stumph et al. (1999)

Pharmaceutical or metabolite	Therapeutic use	Concentration in matrix in ng/l	n	Median ng/l	90-perc. ng/l	Matrix	Country	Reference
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etophyllinclofibrate	<50 - 1560				stp effluent	GER	Stumph et al. (1996)?
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etophyllinclofibrate	2540 - 9710	7			stp effluent	USA	Hignite & Azarnoff (1977)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etophyllinclofibrate	<20 - 1600	49	360	720	stp effluent	GER	Ternes (1998b)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etophyllinclofibrate	450-680	2			stp effluent	GER	Heberer et al. (1998)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etophyllinclofibrate	50 -1056				stp effluent		In: Römbke et al. (1996)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etophyllinclofibrate	60 - 420				stp effluent	GER	Kalbfus (1997)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etophyllinclofibrate	460 - 1030				stp effluent	GER	AWWR (1996)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etophyllinclofibrate	<10 - 70	2			stp effluent	NL, B	Mons et al. (2000)
Fenofibric acid	metabolite of Fenofibrate	<50 - 1190	39	270	700	stp effluent	GER	Stumph et al. (1996)
Fenofibric acid	metabolite of Fenofibrate	<50 - 1200	49	380	680	stp effluent	GER	Ternes (1998b)
Fenofibric acid	metabolite of Fenofibrate	680	1			stp effluent	GER	AWWR (1996)
Fenofibric acid	metabolite of Fenofibrate	~450	1			stp effluent (biological filter)	BRAZ	Stumph et al. (1999)
Fenofibric acid	metabolite of Fenofibrate	~200	1			stp effluent (active sludge)	BRAZ	Stumph et al. (1999)
Antiepileptics (pharmaceuticals for treatment of epilepsy)								
Carbamazepine	antiepileptic	580 - 870	2			stp effluent	NL, B	Mons et al. (2000)
Carbamazepine	antiepileptic	up to 6300	30	2100	3700	stp effluent	GER	Ternes (1998b)
Analgesics (pain relievers)								
Acetylsalicylic acid	analgesic	<100 - 1500	49	220	320	stp effluent	GER	Ternes (1998b)
Acetylsalicylic acid	analgesic	<50 - 1051				stp effluent		In: Römbke et al. (1996)
Acetylsalicylic acid	analgesic	290				stp effluent	GER	AWWR (1996)
Acetylsalicylic acid	analgesic	~1000				stp effluent		Richardson & Bowron (1985)
Acetylsalicylic acid	analgesic	<50 - 1510	39	130	460	stp effluent	GER	Stumph et al.(1996)
Acetylsalicylic acid	analgesic	500	6			stp effluent	GER	Ternes et al. (1998b)
Diclofenac	analgesic, antirheumatic	100 - 280	2			stp effluent	NL, B	Mons et al. (2000)
Diclofenac	analgesic, antirheumatic	up to 1590	39	750	1050	stp effluent	GER	Stumph et al. (1996)
Diclofenac	analgesic, antirheumatic	310 - 930	4			stp effluent	CH	Buser et al. (1998)
Diclofenac	analgesic, antirheumatic	up to 2100	49	810	1600	stp effluent	GER	Ternes (1998b)
Diclofenac	analgesic, antirheumatic	135 - 760	2			stp effluent	GER	Heberer et al. (1998)
Diclofenac	analgesic, antirheumatic	50 - 1590				stp effluent		In: Römbke et al. (1996)
Diclofenac	analgesic, antirheumatic	1000	1			stp effluent	GER	AWWR (1996)
Diclofenac	analgesic, antirheumatic	~700	1			stp effluent (biological filter)	BRAZ	Stumph et al. (1999)
Diclofenac	analgesic, antirheumatic	~200	1			stp effluent (active sludge)	BRAZ	Stumph et al. (1999)
Dihydrocodeine	analgesic, antitussive (cough suppressant)	<1000 - 3590	5			stp effluent	GER	Möhle et al. (1999).
Dimethylaminophenazone	metabolite of Phenazone?	<100 - 1000	16	<100	150	stp effluent	GER	Ternes (1998b)
Gentisic acid	metabolite of acetylsalicylic acid	<100	6			stp effluent	GER	Ternes et al. (1998b)
Gentisic acid	metabolite of acetylsalicylic acid	<200 - 590	36	<200	200	stp effluent	GER	Ternes (1998b)

Pharmaceutical or metabolite	Therapeutic use	Concentration in matrix in ng/l	n	Median ng/l	90-perc. ng/l	Matrix	Country	Reference
Ibuprofen	analgesic, antirheumatic	<50 - 3350	39	260	1200	stp effluent	GER	Stumph et al. (1996)
Ibuprofen	analgesic, antirheumatic	<50 - 3400	49	370	1200	stp effluent	GER	Ternes (1998b)
Ibuprofen	analgesic, antirheumatic	<detection limit - 10	2			stp effluent	GER	Heberer et al. (1998)
Ibuprofen	analgesic, antirheumatic	<50 - 3350				stp effluent		In: Römbke et al. (1996)
Ibuprofen	analgesic, antirheumatic	<10	2			stp effluent	NL, B	Mons et al. (2000)
Ibuprofen	analgesic, antirheumatic	3350				stp effluent	GER	AWWR (1996)
Ibuprofen	analgesic, antirheumatic	up to 1900	10	340	1040	stp effluent	GER	Stumpf et al. (1998)
Ibuprofen	analgesic, antirheumatic	~850	1			stp effluent (biological filter)	BRAZ	Stumph et al. (1999)
Ibuprofen	analgesic, antirheumatic	~650	1			stp effluent (active sludge)	BRAZ	Stumph et al. (1999)
Ibuprofen-COOH	metabolite of Ibuprofen	up to 260	10	140	240	stp effluent	GER	Stumpf et al. (1998)
Ibuprofen-OH	metabolite of Ibuprofen	up to 5960	10	920	5360	stp effluent	GER	Stumpf et al. (1998)
Indometacine	analgesic, antirheumatic	up to 520	39	270	390	stp effluent	GER	Stumph et al. (1996)
Indometacine	analgesic, antirheumatic	up to 520	49	270	400	stp effluent	GER	Ternes (1998b)
Indometacine	analgesic, antirheumatic	290	1			stp effluent	GER	AWWR (1996)
Indometacine	analgesic, antirheumatic	~300	1			stp effluent (biological filter)	BRAZ	Stumph et al. (1999)
Indometacine	analgesic, antirheumatic	~150	1			stp effluent (active sludge)	BRAZ	Stumph et al. (1999)
Ketoprofen	analgesic, antirheumatic	<50 - 380	39	180	260	stp effluent	GER	Stumph et al. (1996)
Ketbprofen	analgesic, antirheumatic	<50 - 380	49	200	250	stp effluent	GER	Ternes (1998b)
Ketoprofen	analgesic, antirheumatic	<50	1			stp effluent	GER	AWWR (1996)
Ketoprofen	analgesic, antirheumatic	~250	1			stp effluent (biological filter)	BRAZ	Stumph et al. (1999)
Ketoprofen	analgesic, antirheumatic	~200	1			stp effluent (active sludge)	BRAZ	Stumph et al. (1999)
Meclofenamic acid	anti-inflammatory, antipyretic and analgesic	<50	10	<50	<50	stp effluent	GER	Ternes (1998b)
Naproxen	analgesic	<50 - 520	10	300	420	stp effluent	GER	Ternes (1998b)
Naproxen	analgesic	~550	1			stp effluent (biological filter)	BRAZ	Stumph et al. (1999)
Naproxen	analgesic	~100	1			stp effluent (active sludge)	BRAZ	Stumph et al. (1999)
o-hydroxyhippuric acid	metabolite of acetylsalicylic acid	<200	36	<200	<200	stp effluent	GER	Ternes (1998b)
o-hydroxyhippuric acid	metabolite of acetylsalicylic acid	<100	6			stp effluent	GER	Ternes et al. (1998b)
Paracetamol	analgesic	<100	4			stp effluent	NL, B	Mons et al. (2000)
Paracetamol	analgesic	<200	6			stp effluent	GER	Ternes et al. (1998b)
Phenazone	anti-inflammatory, antipyretic and analgesic	<100 - 410	30	160	300	stp effluent	GER	Ternes (1998b)
Salicylic acid	metabolite of acetylsalicylic acid	<20	6			stp effluent	GER	Ternes et al. (1998b)
Salicylic acid	metabolite of acetylsalicylic acid	1830 - 95620	5			stp effluent	USA	Hignite & Azarnoff (1977)
Salicylic acid	metabolite of acetylsalicylic acid	<50 - 140	36	<50	63	stp effluent	GER	Ternes (1998b)

Pharmaceutical or metabolite	Therapeutic use	Concentration in matrix in ng/l	n	Median ng/l	90-perc. ng/l	Matrix	Country	Reference
Cytostatics (pharmaceuticals for treatment of cancer)								
Bleomycin	cytostatic (antibiotic drug)	11 - 19 (radioimmuno assay)				stp effluent		Aherne et al. (1990)
Cyclophosphamide	cytostatic (alkylating drug)	6 - 17	21			stp effluent near hospitals		Steger-Hartmann et al. (1996)
Cyclophosphamide	cytostatic (alkylating drug)	<10 - 20	16	<10	18	stp effluent	GER	Ternes (1998b)
Cyclophosphamide	cytostatic (alkylating drug)	up to 60				stp effluent		In: Römbke et al. (1996)
Ifosfamide	cytostatic (alkylating drug)	<10	2			stp effluent	NL, B	Mons et al. (2000)
Ifosfamide	cytostatic (alkylating drug)	24				treated hospital effluent	GER	Steger-Hartmann et al. (1996)
Ifosfamide	cytostatic (alkylating drug)	8 - 29	estimated			stp effluent	GER	Kümmerer et al. (1997)
Ifosfamide	cytostatic (alkylating drug)	<6 - 43	6	6.5		stp effluent	GER	Kümmerer et al. (1997)
Ifosfamide	cytostatic (alkylating drug)	10 - 40	6	9.3		stp effluent	GER	Kümmerer et al. (1997)
Antibiotics and pharmaceuticals for treatment of infections with protozoa and parasites								
Doxycycline	antibiotic (tetracyclines)	< 50	5			stp effluent	GER	Hirsch et al. (1999)
Oxytetracycline	antibiotic (tetracyclines)	< 50	5			stp effluent	GER	Hirsch et al. (1999)
Tetracycline	antibiotic (tetracyclines)	< 50	5			stp effluent	GER	Hirsch et al. (1999)
Clarithromycin	antibiotic (macrolides)	up to 240	1			stp effluent	GER	Hirsch et al. (1999)
Erythromycin	antibiotic (macrolides)	120 - 900	2			stp effluent	NL, B	Mons et al. (2000)
Erythromycin-H2O	antibiotic (macrolides)	up to 6000	10	2500	5100	stp effluent	GER	Hirsch et al. (1999)
Roxithromycin	antibiotic (macrolides)	up to 1000	10	680	800	stp effluent	GER	Hirsch et al. (1999)
Cloxacillin	antibiotic (penicillins)	< 20	4			stp effluent	GER	Hirsch et al. (1999)
Dicloxacillin	antibiotic (penicillins)	< 20	4			stp effluent	GER	Hirsch et al. (1999)
Methicillin	antibiotic (penicillins)	< 20	4			stp effluent	GER	Hirsch et al. (1999)
Nafcillin	antibiotic (penicillins)	< 20	4			stp effluent	GER	Hirsch et al. (1999)
Oxacillin	antibiotic (penicillins)	< 20	4			stp effluent	GER	Hirsch et al. (1999)
Penicillin G	antibiotic (penicillins)	< 20	4			stp effluent	GER	Hirsch et al. (1999)
Penicillin V	antibiotic (penicillins)	< 20	4			stp effluent	GER	Hirsch et al. (1999)
Sulfamethazine	antibiotic (sulfonamides)	< 20	10			stp effluent	GER	Hirsch et al. (1999)
Sulfamethoxazole	antibiotic (sulfonamides)	<10 - 70	4			stp effluent	NL, B	Mons et al. (2000)
Sulfamethoxazole	antibiotic (sulfonamides)	up to 2000	10	400	900	stp effluent	GER	Hirsch et al. (1999)
Chloramphenicol	antibiotic (other categories)	up to 560	10			stp effluent	GER	Hirsch et al. (1999)
Trimethoprim	antibiotic (other categories)	up to 660	10	320	620	stp effluent	GER	Hirsch et al. (1999)
Antidepressants and other psychiatric pharmaceuticals								
Diazepam	psychiatric drug	<1000				stp effluent		Richardson & Bowron (1985)
Diazepam	psychiatric drug	<30 - 40	20	<30	30	stp effluent	GER	Ternes (1998b)
Diazepam	psychiatric drug	<1000				stp effluent		In: Römbke et al. (1996)

Pharmaceutical or metabolite	Therapeutic use	Concentration in matrix in ng/l	n	Median ng/l	90-perc. ng/l	Matrix	Country	Reference
Iodinated X-ray contrasting agents								
Diatrizoate	iodinated X-ray contrasting agent	up to 8700				stp effluent	GER	Ternes & Hirsch (2000)
Diatrizoate	iodinated X-ray contrasting agent	1140	1			stp effluent	GER	Hirsch et al. (2000)
Iopamidol	iodinated X-ray contrasting agent	up to 1500		490		stp effluent	GER	Ternes & Hirsch (2000)
Iopamidol	iodinated X-ray contrasting agent	590	1			stp effluent	GER	Hirsch et al. (2000)
Iomeprol	iodinated X-ray contrasting agent	up to 8700				stp effluent	GER	Ternes & Hirsch (2000)
Iomeprol	iodinated X-ray contrasting agent	2060	1			stp effluent	GER	Hirsch et al. (2000)
Iopromide	iodinated X-ray contrasting agent	3070	1			stp effluent	GER	Hirsch et al. (2000)
Iopromide	iodinated X-ray contrasting agent	up to 9000		5000		stp effluent	GER	Rosenberg et al. (1994)
Iopromide	iodinated X-ray contrasting agent	up to 11000				stp effluent	GER	Ternes & Hirsch (2000)
Iothalamic acid	iodinated X-ray contrasting agent	range ng/l				stp effluent	GER	Ternes & Hirsch (2000)
Iothalamic acid	iodinated X-ray contrasting agent	90	1			stp effluent	GER	Hirsch et al. (2000)
Ioxithalamic acid	iodinated X-ray contrasting agent	range ng/l				stp effluent	GER	Ternes & Hirsch (2000)
Ioxithalamic acid	iodinated X-ray contrasting agent	undetectable	1			stp effluent	GER	Hirsch et al. (2000)
Other pharmaceuticals								
Clenbuterol	bronchospasmolytic	<25 - 181	25	<25	72	stp effluent	GER	Hirsch et al. (1996)
Clenbuterol	bronchospasmolytic	<50 - 80	29	<50	<50	stp effluent	GER	Ternes (1998b)
Fenoterol	bronchospasmolytic	<25 - 67	25	<25	29	stp effluent	GER	Hirsch et al. (1996)
Fenoterol	bronchospasmolytic	<50 - 60	29	<50	<50	stp effluent	GER	Ternes (1998b)
Salbutamol	bronchospasmolytic	<25 - 174	25	48	74	stp effluent	GER	Hirsch et al. (1996)
Salbutamol	bronchospasmolytic	<50 - 170	29	<50	72	stp effluent	GER	Ternes (1998b)
Terbutalin	bronchospasmolytic	<25 - 115	25	65	89	stp effluent	GER	Hirsch et al. (1996)
Terbutalin	bronchospasmolytic	<50 - 120	29	<50	87	stp effluent	GER	Ternes (1998b)
Fenoprofen	antirheumatic	<50	39	<50	<50	stp effluent	GER	Stumph et al. (1996)
Fenoprofen	antirheumatic	<50	49	<50	<50	stp effluent	GER	Ternes (1998b)
Fenoprofen	antirheumatic	<50	1			stp effluent	GER	AWWR (1996)
Tolfenamic acid	antirheumatic	<50	10	<50	<50	stp effluent	GER	Ternes (1998b)
Hydrocodone	antitussive (cough suppressant)	<100 - 1940	5			stp effluent	GER	Möhle et al. (1999)
Acetaminophen		<500 - 6000	49	<500	<500	stp effluent	GER	Ternes (1998b)

Pharmaceutical or metabolite	Therapeutic use	Concentration in matrix in ng/l	n	Median ng/l	90-perc. ng/l	Matrix	Country	Reference
Waste water (influent or effluent)								
Pharmaceuticals for treatment of cardiovascular diseases								
Bezafibrate	lipid regulator (fibrate)	3320				waste water	GER	AWWR (1996)
Gemfibrozil	lipid regulator (fibrate)	1320				waste water	GER	AWWR (1996)
Pentoxifylline	vasodilator (blood diluent)	<380				waste water	GER	Möhle et al. (1997)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etophyllinclofibrate	460-1030				waste water	GER	AWWR (1996)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etophyllinclofibrate	<50-1560				waste water	GER	Sacher et al. (1997)
Fenofibric acid	metabolite of Fenofibrate	680				waste water	GER	AWWR (1996)
Antiepileptics (pharmaceuticals for treatment of epilepsy)								
Carbamazepine	antiepileptic	5000-46000				waste water	GER	Sacher et al. (1997)
Carbamazepine	antiepileptic	500-2000				waste water	GER	Möhle et al. (1997)
Pheneturide	antiepileptic	detected				waste water	GER	Möhle et al. (1997)
Primidon	antiepileptic	detected				waste water	GER	Möhle et al. (1997)
Analgesics (pain relievers)								
Acetylsalicylic acid	analgesic	290				waste water	GER	AWWR (1996)
Diclofenac	analgesic, antirheumatic	1000				waste water	GER	AWWR (1996)
Diclofenac	analgesic, antirheumatic	6590-11920				waste water		Möhle et al. (1997)
Dihydrocodeine	analgesic, antitussive (cough suppressant)	detected				waste water	GER	Möhle et al. (1997)
Ibuprofen	analgesic, antirheumatic	3350				waste water	GER	AWWR (1996)
Indometacine	analgesic, antirheumatic	290				waste water	GER	AWWR (1996)
Ketoprofen	analgesic, antirheumatic	<50				waste water	GER	AWWR (1996)
Propyphenazone	analgesic	detected				waste water	GER	Möhle et al. (1997)
4-Acetylaminoantipyrin	metabolite of Metamizol (analgesic)	detected				waste water	GER	Möhle et al. (1997)
Other pharmaceuticals								
Fenoprofen	antirheumatic	<50				waste water	GER	AWWR (1996)
Hydrocodone	antitussive (cough suppressant)	detected				waste water	GER	Möhle et al. (1997)

Pharmaceutical or metabolite	Therapeutic use	Concentration in matrix in ng/l	n	Median ng/l	90-perc. ng/l	Matrix	Country	Reference
Receiving surface water								
Pharmaceuticals for treatment of cardiovascular diseases								
Betaxolol	beta-blocker (antihypertensive)	<3 - 28	24	6	9	various rivers	GER	Hirsch et al. (1996)
Betaxolol	beta-blocker (antihypertensive)	<10 - 28	45	<10	<10	various rivers	GER	Ternes (1998b)
Bisoprolol	beta-blocker (antihypertensive)	<3 - 124	24	6	36	various rivers	GER	Hirsch et al. (1996)
Bisoprolol	beta-blocker (antihypertensive)	<10 - 2900	45	<10	<10	various rivers	GER	Ternes (1998b)
Carazolol	beta-blocker (antihypertensive)	<3 - 124	24	<3	8	various rivers	GER	Hirsch et al. (1996)
Carazolol	beta-blocker (antihypertensive)	<10 - 110	45	<10	100	various rivers	GER	Ternes (1998b)
Metoprolol	beta-blocker (antihypertensive)	<10 - 30	11			surface water	NL, B	Mons et al. (2000)
Metoprolol	beta-blocker (antihypertensive)	<3 - 1540	24	31	114	various rivers	GER	Hirsch et al. (1996)
Metoprolol	beta-blocker (antihypertensive)	up to 2200	45	45	1200	various rivers	GER	Ternes (1998b)
Nadolol	beta-blocker (antihypertensive)	<5 - 9	24	<5	9	various rivers	GER	Hirsch et al. (1996)
Nadolol	beta-blocker (antihypertensive)	<10	45	<10	<10	various rivers	GER	Ternes (1998b)
Propranolol	beta-blocker (antihypertensive)	<3 - 98	24	7	27	various rivers	GER	Hirsch et al. (1996)
Propranolol	beta-blocker (antihypertensive)	<10 - 590	45	12	440	various rivers	GER	Ternes (1998b)
Timolol	beta-blocker (antihypertensive)	<3 - 10	24	6	9	various rivers	GER	Hirsch et al. (1996)
Timolol	beta-blocker (antihypertensive)	<10 - 10	45	<10	<10	various rivers	GER	Ternes (1998b)
Pentoxifilline	vasodilator (blood diluent)	<60				surface water	GER	Sacher et al. (1997)
Pentoxifilline	vasodilator (blood diluent)	<25 - 190	50		<25	river (Rhine)	GER	Sacher et al. (1998)
Pentoxifilline	vasodilator (blood diluent)	<25 - 260	35		150	river (Elbe)	GER	Sacher et al. (1998)
Bezafibrate	lipid regulator (fibrate)	<10 - 40	22			surface water	NL, B	Mons et al. (2000)
Bezafibrate	lipid regulator (fibrate)	<25 - 295	8			river (Rhine)	GER	Stumph et al. (1996)
Bezafibrate	lipid regulator (fibrate)	156 - 380	11			various rivers	GER	Stumph et al. (1996)
Bezafibrate	lipid regulator (fibrate)	<25 - 3100	43	350	1200	various rivers	GER	Ternes (1998b)
Bezafibrate	lipid regulator (fibrate)	<100 - 200	7			river (Main)	GER	Ternes (1998b)
Bezafibrate	lipid regulator (fibrate)	up to 315	14			river (Rhine)	GER	Ternes (1998b)
Bezafibrate	lipid regulator (fibrate)	<150				surface water	GER	Sacher et al. (1997)
Bezafibrate	lipid regulator (fibrate)	<10 -210			49	river (Rhine)	GER	Sacher et al. (1998).
Bezafibrate	lipid regulator (fibrate)	<10 - 75	35		59	river (Elbe)	GER	Sacher et al. (1998).
Bezafibrate	lipid regulator (fibrate)	380	1			river (Ruhr)	GER	AWWR (1996)
Bezafibrate	lipid regulator (fibrate)	<25	8			river (Paraíba do Sul)	BRAZ	Stumpf et al. (1999)
Clofibrate	lipid regulator (fibrate)	~ 40				river		Richardson & Bowron (1985)
Clofibrate	lipid regulator (fibrate)	<30	36			various rivers	GER	Ternes (1998b)
Clofibrate	lipid regulator (fibrate)	<0.5	10			river (Lech)	GER	Kalbfus (1997)
Etofibrate	lipid regulator (fibrate)	<30	36			various rivers	GER	Ternes (1998b)
Fenofibrate	lipid regulator (fibrate)	<10	11			surface water	NL, B	Mons et al. (2000)
Fenofibrate	lipid regulator (fibrate)	<1 - 100				surface water	GER	Kalbfus (1997)

Pharmaceutical or metabolite	Therapeutic use	Concentration in matrix in ng/l	n	Median ng/l	90-perc. ng/l	Matrix	Country	Reference
Fenofibrate	lipid regulator (fibrate)	<10	36			various rivers	GER	Ternes (1998b)
Fenofibrate	lipid regulator (fibrate)	<25	50			river (Rhine)	GER	Sacher et al. (1998)
Fenofibrate	lipid regulator (fibrate)	<25	35			river (Elbe)	GER	Sacher et al. (1998)
Fenofibrate	lipid regulator (fibrate)	7 - 87	10			river (Lech)	GER	Kalbfus (1997)
Gemfibrozil	lipid regulator (fibrate)	<20	?			surface water	GER	Sacher et al. (1997)
Gemfibrozil	lipid regulator (fibrate)	<5	8			river (Rhine)	GER	Stumph et al. (1996)
Gemfibrozil	lipid regulator (fibrate)	<5 - 190	11			various rivers	GER	Stumph et al. (1996)
Gemfibrozil	lipid regulator (fibrate)	<10 - 510	43	52	190	various rivers	GER	Ternes (1998b)
Gemfibrozil	lipid regulator (fibrate)	<20 - 30	7			river (Main)	GER	Ternes (1998b)
Gemfibrozil	lipid regulator (fibrate)	<5 - 110	50		<5	river (Rhine)	GER	Sacher et al. (1998)
Gemfibrozil	lipid regulator (fibrate)	<5 - 220	35		18	river (Elbe)	GER	Sacher et al. (1998)
Gemfibrozil	lipid regulator (fibrate)	120	1			river (Ruhr)	GER	AWWR (1996)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etophyllinclofibrate	<10 - 30	11			surface water	NL, B	Mons et al. (2000)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etophyllinclofibrate	1.0 - 9.0	>4			various lakes	CH	Buser & Müller (1998)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etophyllinclofibrate	0.5 - 7.8	6			North Sea		Buser & Müller (1998)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etophyllinclofibrate	27 - 157	?			river (Elbe)	GER	Heberer et al. (1995)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etophyllinclofibrate	<5 - 51	8			river (Rhine)	GER	Stumph et al. (1996)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etophyllinclofibrate	<0.5 - 1750				river in Berlin	GER	Heberer (1995)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etophyllinclofibrate	<0.5 - 220				river in Europe		Heberer (1995)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etophyllinclofibrate	<5 - 180	11			various rivers	GER	Stumph et al. (1996)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etophyllinclofibrate	<10 - 550	43	66	210	various rivers	GER	Ternes (1998b)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etophyllinclofibrate	<5 - 51	8			river (Rhine)	GER	Stumph et al. (1996)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etophyllinclofibrate	up to 220				various rivers	GER	Stan et al. (1993); Heberer (1995)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etophyllinclofibrate	30	1			river (Po)	I	Heberer & Stan (1997)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etophyllinclofibrate	<20 - 30	7			river (Main)	GER	Ternes (1998b)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etophyllinclofibrate	up to 120	14			river (Rhine)	GER	Ternes (1998b)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etophyllinclofibrate	<detection limit - 875	27			rivers & canals in Berlin	GER	Heberer et al. (1998)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etophyllinclofibrate	<detection limit - 222	17			various rivers	GER	Stan et al. (1993); Heberer (1995)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etophyllinclofibrate	1 - 300				surface water	GER	Kalbfus (1997)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etophyllinclofibrate	140 - 180				surface water	GER	AWWR (1996)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etophyllinclofibrate	up to 120				surface water	GER	Sacher et al. (1997)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etophyllinclofibrate	1 - 1750				from various references		In: Römbke et al. (1996)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etophyllinclofibrate	<detection limit - 460				canal (Teltow)	GER	Heberer et al. (1998)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etophyllinclofibrate	<10 - 200	50		43	river (Rhine)	GER	Sacher et al. (1998)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etophyllinclofibrate	<10 - 140	35		36	river (Elbe)	GER	Sacher et al. (1998)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etophyllinclofibrate	<1	10			river (Lech)	GER	Kalbfus (1997)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etophyllinclofibrate	<10 - 30	8			river (Paraíba do Sul)	BRAZ	Stumph et al. (1999)

Pharmaceutical or metabolite	Therapeutic use	Concentration in matrix in ng/l	n	Median ng/l	90-perc. ng/l	Matrix	Country	Reference
Fenofibric acid	metabolite of Fenofibrate	<5	8			river (Rhine)	GER	Stumph et al. (1996)
Fenofibric acid	metabolite of Fenofibrate	<5 - 172	11			various rivers	GER	Stumph et al. (1996)
Fenofibric acid	metabolite of Fenofibrate	<10 - 280	43	45	170	various rivers	GER	Ternes (1998b)
Fenofibric acid	metabolite of Fenofibrate	<20 - 30	7			river (Main)	GER	Ternes (1998b)
Fenofibric acid	metabolite of Fenofibrate	50	1			river (Ruhr)	GER	AWWR (1996)
Antiepileptics (pharmaceuticals for treatment of epilepsy)								
Carbamazepine	antiepileptic	<10 - 230	11			surface water	NL, B	Mons et al. (2000)
Carbamazepine	antiepileptic	<30 - 1100	26	250	820	various rivers	GER	Ternes (1998b)
Carbamazepine	antiepileptic	detected but not quantified				river (Mulde)	GER	Franke et al. (1995)
Carbamazepine	antiepileptic	< 800				surface water	GER	Sacher et al. (1997)
Carbamazepine	antiepileptic	<20 -2100	161		690	river (Rhine)	GER	Sacher et al. (1998)
Carbamazepine	antiepileptic	<20 - 170	35		42	river (Elbe)	GER	Sacher et al. (1998)
Analgesics (pain relievers)								
Acetylsalicylic acid	analgesic	<20 - 340	43	<20	160	various rivers	GER	Ternes (1998b)
Acetylsalicylic acid	analgesic	<20	7			river (Main)	GER	Ternes (1998b)
Acetylsalicylic acid	analgesic	<10				from various references		In: Römbke et al. (1996)
Acetylsalicylic acid	analgesic	<50	1			river (Ruhr)	GER	AWWR (1996)
Acetylsalicylic acid	analgesic	<10	11			various rivers	GER	Stumph et al. (1996)
Acetylsalicylic acid	analgesic	<10	8			river (Rhine)	GER	Stumph et al. (1996)
Detropropoxyphene	analgesic	~ 1000				river		Richardson & Bowron (1985)
Diclofenac	analgesic, antirheumatic	<10 - 20	11			surface water	NL, B	Mons et al. (2000)
Diclofenac	analgesic, antirheumatic	15 - 304	8			river (Rhine)	GER	Stumph et al. (1996)
Diclofenac	analgesic, antirheumatic	38 - 489	11			various rivers	GER	Stumph et al. (1996)
Diclofenac	analgesic, antirheumatic	<1 - 12	24			various rivers and lakes	CH	Buser et al. (1998)
Diclofenac	analgesic, antirheumatic	11 - 310	10			river (Aabach)	CH	Buser et al. (1998)
Diclofenac	analgesic, antirheumatic	~5 - 370	3			river (Aabach)	CH	Buser et al. (1998)
Diclofenac	analgesic, antirheumatic	up to 1200	43	150	800	various rivers	GER	Ternes (1998b)
Diclofenac	analgesic, antirheumatic	70 - 140	7			river (Main)	GER	Ternes (1998b)
Diclofenac	analgesic, antirheumatic	up to 570	14			river (Rhine)	GER	Ternes (1998b)
Diclofenac	analgesic, antirheumatic	<detection limit - 960	27			rivers & canals in Berlin	GER	Heberer et al. (1998)
Diclofenac	analgesic, antirheumatic	14				surface water	GER	AWWR (1996)
Diclofenac	analgesic, antirheumatic	15 - 489				from various references		In: Römbke et al. (1996)
Diclofenac	analgesic, antirheumatic	<20 - 300	49		190	river (Rhine)	GER	Sacher et al. (1998)
Diclofenac	analgesic, antirheumatic	<20 - 420	35		270	river (Elbe)	GER	Sacher et al. (1998)
Diclofenac	analgesic, antirheumatic	90	1			river (Ruhr)	GER	AWWR (1996)
Diclofenac	analgesic, antirheumatic	20 - 60	8			river (Paraíba do Sul)	BRAZ	Stumph et al. (1999)
Dimethylaminophenazone	metabolite of Phenazone?	<30 - 340	26	<30	<30	various rivers	GER	Ternes (1998b)
Gentisic acid	metabolite of acetylsalicylic acid	<75 - 1200	35	<75	110	various rivers	GER	Ternes (1998b)

Pharmaceutical or metabolite	Therapeutic use	Concentration in matrix in ng/l	n	Median ng/l	90-perc. ng/l	Matrix	Country	Reference
Ibuprofen-COOH	metabolite of Ibuprofen	up to ~25	12			various rivers	GER	Stumpf et al. (1998)
Ibuprofen-OH	metabolite of Ibuprofen	up to ~1000	12			various rivers	GER	Stumpf et al. (1998)
Ibuprofen	analgesic, antirheumatic	< 5 - 41	8			river (Rhine)	GER	Stumph et al. (1996)
Ibuprofen	analgesic, antirheumatic	17 - 139	11			various rivers	GER	Stumph et al. (1996)
Ibuprofen	analgesic, antirheumatic	<10 - 530	43	70	280	various rivers	GER	Ternes (1998b)
Ibuprofen	analgesic, antirheumatic	<20 - 20	7			river (Main)	GER	Ternes (1998b)
Ibuprofen	analgesic, antirheumatic	up to 120	14			river (Rhine)	GER	Ternes (1998b)
Ibuprofen	analgesic, antirheumatic	<detection limit - 280	27			rivers & canals in Berlin	GER	Heberer et al. (1998)
Ibuprofen	analgesic, antirheumatic	<50				surface water	GER	Sacher et al. (1997)
Ibuprofen	analgesic, antirheumatic	<5 - 139				from various references		In: Römbke et al. (1996)
Ibuprofen	analgesic, antirheumatic	<5 - 12	49		<5	river (Rhine)	GER	Sacher et al. (1998)
Ibuprofen	analgesic, antirheumatic	<5 - 450	35		77	river (Elbe)	GER	Sacher et al. (1998)
Ibuprofen	analgesic, antirheumatic	140	1			river (Ruhr)	GER	AWWR (1996)
Ibuprofen	analgesic, antirheumatic	<10	8			river (Paraíba do Sul)	BRAZ	Stumpf et al. (1999)
Ibuprofen	analgesic, antirheumatic	up to ~150	12			various rivers	GER	Stumpf et al. (1998)
Indometacine	analgesic, antirheumatic	<10				surface water	GER	Sacher et al. (1997)
Indometacine	analgesic, antirheumatic	<5 - 26				river (Rhine)	GER	Stumph et al. (1996)
Indometacine	analgesic, antirheumatic	17 - 121				various rivers	GER	Stumph et al. (1996)
Indometacine	analgesic, antirheumatic	<5 - 26	8			river (Rhine)	GER	Stumph et al. (1996)
Indometacine	analgesic, antirheumatic	17 - 121	11			various rivers	GER	Stumph et al. (1996)
Indometacine	analgesic, antirheumatic	<10 - 200	43	40	170	various rivers	GER	Ternes (1998b)
Indometacine	analgesic, antirheumatic	<20 - 30	7			river (Main)	GER	Ternes (1998b)
Indometacine	analgesic, antirheumatic	<5 -30	50		<5	river (Rhine)	GER	Sacher et al. (1998)
Indometacine	analgesic, antirheumatic	<5	35			river (Elbe)	GER	Sacher et al. (1998)
Indometacine	analgesic, antirheumatic	50	1			river (Ruhr)	GER	AWWR (1996)
Morfine-like structure	(analgesic)	< 1000				river		Richardson & Bowron (1985)
Naproxen	analgesic	up to 390	20	70	150	various rivers	GER	Ternes (1998b)
Naproxen	analgesic	up to 260	14			river (Rhine)	GER	Ternes (1998b)
Naproxen	analgesic	<10 - 50	8			river (Paraíba do Sul)	BRAZ	Stumpf et al. (1999)
Naproxen	analgesic	<5 - 400	22			various rivers	GER	Ternes et al. (1998b)
o-hydroxyhippuric acid	metabolite of acetylsalicylic acid	<75	35	<75	<75	various rivers	GER	Ternes (1998b)
Paracetamol	analgesic	<100	22			surface water	NL, B	Mons et al. (2000)

Pharmaceutical or metabolite	Therapeutic use	Concentration in matrix in ng/l	n	Median ng/l	90-perc. ng/l	Matrix	Country	Reference
Phenazone	anti-inflammatory, antipyretic and analgesic	<20 - 950	26	24	150	various rivers	GER	Ternes (1998b)
Phenazone	anti-inflammatory, antipyretic and analgesic	<280				surface water	GER	Sacher et al. (1997)
Phenazone	anti-inflammatory, antipyretic and analgesic	<25 - 370	50		290	river (Rhine)	GER	Sacher et al. (1998)
Phenazone	anti-inflammatory, antipyretic and analgesic	<25	35			river (Elbe)	GER	Sacher et al. (1998)
Propyphenazone	anti-inflammatory, antipyretic and analgesic	<detection limit - 1900				rivers and canals in Berlin	GER	Heberer et al. (1998)
Salicylic acid	metabolite of acetylsalicylic acid	<10 - 4100	35	25	130	various rivers	GER	Ternes (1998b)
Salicylic acid	metabolite of acetylsalicylic acid	up to 140	6			river (Rhine)	GER	Ternes et al. (1998b)
Cytostatics (pharmaceuticals for treatment of cancer)		1200						
Bleomycin	cytostatic (antibiotic drug)	< 5 - 17				river		Aherne et al. (1990)
Cyclophosphamide	cytostatic (alkylating drug)	<10	26	<10	<10	various rivers	GER	Ternes (1998b)
Ifosfamide	cytostatic (alkylating drug)	<10	11			surface water	NL, B	Mons et al. (2000)
Ifosfamide	cytostatic (alkylating drug)	<10	26	<10	<10	various rivers	GER	Ternes (1998b)
Ifosfamide	cytostatic (alkylating drug)	0.8	estimated			surface water	GER	Kümmerer et al. (1997)
Methotrexate	cytostatic (antimetabolic drug)	<6.25				river		Aherne & English (1985)
Antibiotics and pharmaceuticals for treatment of infections with protozoa and parasites								
Doxycycline	antibiotic (tetracyclines)	<50	14			various rivers	GER	Hirsch et al. (1999)
Oxytetracycline	antibiotic (tetracyclines)	<50	14			various rivers	GER	Hirsch et al. (1999)
Tetracycline	antibiotic (tetracyclines)	~ 1000				river		Watts et al. (1983)
Tetracycline	antibiotic (tetracyclines)	~ 1000				from various references		In: Römbke et al. (1996)
Tetracycline	antibiotic (tetracyclines)	<50	14			various rivers	GER	Hirsch et al. (1999)
Clarithromycin	antibiotic (macrolides)	up to 260	33		150	various rivers	GER	Hirsch et al. (1999)
Erythromycin	antibiotic (macrolides)	<10 - 30	11			surface water	NL, B	Mons et al. (2000)
Erythromycin	antibiotic (macrolides)	~ 1000				river		Watts et al. (1983)
Erythromycin	antibiotic (macrolides)	~ 1000				from various references		In: Römbke et al. (1996)
Erythromycin-H2O	antibiotic (macrolides)	up to 1700	52	150	630	various rivers	GER	Hirsch et al. (1999)
Roxithromycin	antibiotic (macrolides)	up to 560	52		200	various rivers	GER	Hirsch et al. (1999)
Cloxacillin	antibiotic (penicillins)	<50	14			various rivers	GER	Hirsch et al. (1999)
Dicloxacillin	antibiotic (penicillins)	<50	14			various rivers	GER	Hirsch et al. (1999)
Methicillin	antibiotic (penicillins)	<50	14			various rivers	GER	Hirsch et al. (1999)
Nafcillin	antibiotic (penicillins)	<50	14			various rivers	GER	Hirsch et al. (1999)
Oxacillin	antibiotic (penicillins)	<50	14			various rivers	GER	Hirsch et al. (1999)
Penicillin G	antibiotic (penicillins)	600	estimated (worst case)			surface water	GER	Al-Ahmad et al. (1999)
Penicillin G	antibiotic (penicillins)	<50	14			various rivers	GER	Hirsch et al. (1999)
Penicillin V	antibiotic (penicillins)	<50	14			various rivers	GER	Hirsch et al. (1999)
Ciprofloxacin	antibiotic (fluoroquinolones)	60	estimated (worst case)			surface water	GER	Al-Ahmad et al. (1999)

Pharmaceutical or metabolite	Therapeutic use	Concentration in matrix in ng/l	n	Median ng/l	90-perc. ng/l	Matrix	Country	Reference
Sulfamethazine	antibiotic (sulfonamides)	<20	52			various rivers	GER	Hirsch et al. (1999)
Sulfamethoxazole	antibiotic (sulfonamides)	<10 - 70	22			surface water	NL, B	Mons et al. (2000)
Sulfamethoxazole	antibiotic (sulfonamides)		estimated (worst case)			surface water	GER	Al-Ahmad et al. (1999)
Sulfamethoxazole	antibiotic (sulfonamides)	up to 480	52	30	140	various rivers	GER	Hirsch et al. (1999)
Sulfamethoxazole	antibiotic (sulfonamides)	~ 1000				river		Watts et al. (1983)
Chloramphenicol	antibiotic (other categories)	up to 60	52			various rivers	GER	Hirsch et al. (1999)
Meropenem	antibiotic (other categories)	<10	estimated (worst case)			surface water	GER	Al-Ahmad et al. (1999)
Trimethoprim	antibiotic (other categories)	up to 200	52		90	various rivers	GER	Hirsch et al. (1999)
Penicillinic group	metabolite of a penicillin metabolite	not above 25				river (immunoassay)		Wal et al. (1975)
Antidepressants and other psychiatric pharmaceuticals								
Diazepam	psychiatric drug	~ 10				river		Waggott (1981)
Diazepam	psychiatric drug	< 30	30	<30	<30	various rivers	GER	Ternes (1998b)
Diazepam	psychiatric drug	~ 0.01				from various references		In: Römbke et al. (1996)
Medazepam	tranquilizer	detected, not quantified				river (Elbe)	GER	Franke et al. (1995).
Iodinated X-ray contrasting agents								
Diatrizoate	iodinated X-ray contrasting agent	detected		up to 230		rivers and streams	GER	Ternes & Hirsch (2000)
Diatrizoate	iodinated X-ray contrasting agent	110 -140	2			surface water	GER	Hirsch et al. (2000)
Iomeprol	iodinated X-ray contrasting agent	40	1			surface water	GER	Hirsch et al. (2000)
Iopamidol	iodinated X-ray contrasting agent	detected		up to 490		rivers and streams	GER	Ternes & Hirsch (2000)
Iopamidol	iodinated X-ray contrasting agent	up to 100000				surface water	GER	Ternes & Hirsch (2000)
Iopamidol	iodinated X-ray contrasting agent	180 - 300	2			surface water	GER	Hirsch et al. (2000)
Iopromide	iodinated X-ray contrasting agent	detected				surface water	GER	Ternes & Hirsch (2000)
Iopromide	iodinated X-ray contrasting agent	150	2			surface water	GER	Hirsch et al. (2000)
Ioxithalamic acid	iodinated X-ray contrasting agent	40	2			surface water	GER	Hirsch et al. (2000)
Iothalamic acid	iodinated X-ray contrasting agent	10	2			surface water	GER	Hirsch et al. (2000)
Other pharmaceuticals								
Clenbuterol	bronchospasmolytic	<5	24	<5	<5	various rivers	GER	Hirsch et al. (1996)
Clenbuterol	bronchospasmolytic	<10 - 50	45	<10	<10	various rivers	GER	Ternes (1998b)
Fenoterol	bronchospasmolytic	<3 - 8	24	<3	8	various rivers	GER	Hirsch et al. (1996)
Fenoterol	bronchospasmolytic	<10 - 61	45	<10	<10	various rivers	GER	Ternes (1998b)
Salbutamol	bronchospasmolytic	<5	24	<5	<5	various rivers	GER	Hirsch et al. (1996)
Salbutamol	bronchospasmolytic	<10 - 35	45	<10	<10	various rivers	GER	Ternes (1998b)
Terbutalin	bronchospasmolytic	<3 - 9	24	<3	9	various rivers	GER	Hirsch et al. (1996)
Terbutalin	bronchospasmolytic	<10	45	<10	<10	various rivers	GER	Ternes (1998b)

Pharmaceutical or metabolite	Therapeutic use	Concentration in matrix in ng/l	n	Median ng/l	90-perc. ng/l	Matrix	Country	Reference
Fenoprofen	antirheumatic	<50	1			river (Ruhr)	GER	AWWR (1996)
Fenoprofen	antirheumatic	<5	8			river (Rhine)	GER	Stumph et al. (1996)
Fenoprofen	antirheumatic	<5	11			various rivers	GER	Stumph et al. (1996)
Fenoprofen	antirheumatic	<10	43	<10	<10	various rivers	GER	Ternes (1998b)
Fenoprofen	antirheumatic	<20	7			river (Main)	GER	Ternes (1998b)
Fenoprofen	antirheumatic	not detected	?			surface water	GER	Sacher et al. (1997)
Fenoprofen	antirheumatic	<5	36			river (Rhine)	GER	Sacher et al. (1998)
Fenoprofen	antirheumatic	<5 - 42	35			river (Elbe)	GER	Sacher et al. (1998)
Fenoprofen	antirheumatic	<50	1			river (Ruhr)	GER	AWWR (1996)
Tolfenamic acid	antirheumatic	<10	30	<10	<10	various rivers	GER	Ternes (1998b)
Ketoprofen	anti-inflammatory, antirheumatic	<5	8			river (Rhine)	GER	Stumph et al. (1996)
Ketoprofen	anti-inflammatory, antirheumatic	<5	11			various rivers	GER	Stumph et al. (1996)
Ketoprofen	anti-inflammatory, antirheumatic	<10 - 12	43	<10	12	various rivers	GER	Ternes (1998b)
Ketoprofen	anti-inflammatory, antirheumatic	<detection limit	?			surface water	GER	Sacher et al. (1997)
Ketoprofen	anti-inflammatory, antirheumatic	<20	7			river (Main)	GER	Ternes (1998b)
Ketoprofen	anti-inflammatory, antirheumatic	<10	36			river (Rhine)	GER	Sacher et al. (1998)
Ketoprofen	anti-inflammatory, antirheumatic	<10	35			river (Elbe)	GER	Franke et al. (1995).
Ketoprofen	anti-inflammatory, antirheumatic	<50	1			river (Ruhr)	GER	AWWR (1996)
Theophylline	pharmaceutical to treat asthma and bronchitis	~ 1000				river		Watts et al. (1983)

Pharmaceutical or metabolite	Therapeutic use	Concentration in matrix in ng/l	n	Median ng/l	90-perc. ng/l	Matrix	Country	Reference
Receiving sediment								
Pharmaceuticals for treatment of cardiovascular diseases								
Clofibrate	lipid regulator (fibrate)	<100 ng/kg	10			sediment	GER	Kalbfus (1997)
Fenofibrate	lipid regulator (fibrate)	1000 -180000 ng/kg	10			sediment	GER	Kalbfus (1997)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etofyllinclofibrate	<100 ng/kg	10			sediment	GER	Kalbfus (1997)
Groundwater								
Pharmaceuticals for treatment of cardiovascular diseases								
Clofibrate	lipid regulator (fibrate)	<0.5	3			groundwater	GER	Kalbfus (1997)
Fenofibrate	lipid regulator (fibrate)	<detection limit - 45	17			groundwater (at pumping station)	GER	Heberer et al. (1997)
Fenofibrate	lipid regulator (fibrate)	5.3 - 45	3			groundwater	GER	Kalbfus (1997)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etofyllinclofibrate	1 - 4000				groundwater	GER	Heberer (1995)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etofyllinclofibrate	70 - 7300	17			groundwater (at pumping station)	GER	Heberer et al. (1997)
Clofibric acid derivate	metabolite of Clofibric acid	50 - 2900 (estimated)	17			groundwater (at pumping station)	GER	Heberer et al. (1997)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etofyllinclofibrate	<0.5	3			groundwater	GER	Kalbfus (1997)
Analgesics (pain relievers)								
Ibuprofen	analgesic, antirheumatic	<detection limit - 200	17			groundwater (at pumping station)	GER	Heberer et al. (1997)
Phenazone	anti-inflammatory, antipyretic and analgesic	<10 - 1250	17			groundwater (at pumping station)	GER	Heberer et al. (1997)
Propyphenazone	anti-inflammatory, antipyretic and analgesic	<detection limit - 1465	17			groundwater (at pumping station)	GER	Heberer et al. (1997)
Iodinated X-ray contrasting agents								
various	iodinated X-ray contrasting agent	up to 2400				groundwater	GER	Ternes & Hirsch (2000)
Other pharmaceuticals								
Diclofenac	antirheumatic	<detection limit - 380	17			groundwater (at pumping station)	GER	Heberer et al. (1997)

Pharmaceutical or metabolite	Therapeutic use	Concentration in matrix in ng/l	n	Median ng/l	90-perc. ng/l	Matrix	Country	Reference
Surface water during the treatment process for drinking water production								
Pharmaceuticals for treatment of cardiovascular diseases								
Metoprolol	beta-blocker (antihypertensive)	<10	4			treated surface water	NL, B	Mons et al. (2000)
Bezafibrate	lipid regulator (fibrate)	<10	8			treated surface water	NL, B	Mons et al. (2000)
Fenofibrate	lipid regulator (fibrate)	<100	4			treated surface water	NL, B	Mons et al. (2000)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etofyllinclofibrate	<10 - 10	4			treated surface water	NL, B	Mons et al. (2000)
Antiepileptics (pharmaceuticals for treatment of epilepsy)								
Carbamazepine	antiepileptic	<10 - 190	4			treated surface water	NL, B	Mons et al. (2000)
Analgesics (pain relievers)								
Ibuprofen	analgesic, antirheumatic	<10	4			treated surface water	NL, B	Mons et al. (2000)
Paracetamol	analgesic	<100	8			treated surface water	NL, B	Mons et al. (2000)
Cytostatics (pharmaceuticals for treatment of cancer)								
Ifosfamide	cytostatic (alkylating drug)	<10	4			treated surface water	NL, B	Mons et al. (2000)
Antibiotics and pharmaceuticals for treatment of infections with protozoa and parasites								
Erythromycin	antibiotic (macrolides)	<10	4			treated surface water	NL, B	Mons et al. (2000)
Sulfamethoxazole	antibiotic (sulfonamides)	<10 - 100	8			treated surface water	NL, B	Mons et al. (2000)
Other pharmaceuticals								
Diclofenac	antirheumatic	<10	4			treated surface water	NL, B	Mons et al. (2000)

Pharmaceutical or metabolite	Therapeutic use	Concentration in matrix in ng/l	n	Median ng/l	90-perc. ng/l	Matrix	Country	Reference
Drinking water								
Pharmaceuticals for treatment of cardiovascular diseases								
Betaxolol	beta-blocker (antihypertensive)	<3	16			drinking water	GER	Hirsch et al. (1996)
Betaxolol	beta-blocker (antihypertensive)	<10	1			bank filtrate	GER	Hirsch et al. (1996)
Bisoprolol	beta-blocker (antihypertensive)	<3	16			drinking water	GER	Hirsch et al. (1996)
Carazolol	beta-blocker (antihypertensive)	<3	16			drinking water	GER	Hirsch et al. (1996)
Metoprolol	beta-blocker (antihypertensive)	<3	16			drinking water	GER	Hirsch et al. (1996)
Metoprolol	beta-blocker (antihypertensive)	<10	1			bank filtrate	GER	Hirsch et al. (1996)
Metoprolol	beta-blocker (antihypertensive)	<10	6			drinking water	NL, B	Mons et al. (2000)
Nadolol	beta-blocker (antihypertensive)	<5	16			drinking water	GER	Hirsch et al. (1996)
Propranolol	beta-blocker (antihypertensive)	<3	16			drinking water	GER	Hirsch et al. (1996)
Timolol	beta-blocker (antihypertensive)	<3	16			drinking water	GER	Hirsch et al. (1996)
Bezafibrate	lipid regulator (fibrate)	<10	12			drinking water	NL, B	Mons et al. (2000)
Clofibrate	lipid regulator (fibrate)	<0.5	3			drinking water	GER	Kalbfus (1997)
Fenofibrate	lipid regulator (fibrate)	<100	6			drinking water	NL, B	Mons et al. (2000)
Fenofibrate	lipid regulator (fibrate)	91 - 210	3			drinking water	GER	Kalbfus (1997)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etofyllinclofibrate	undetectable	>2			drinking water	USA	Hignite & Azarnoff (1977)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etofyllinclofibrate	<1 - 170	14			drinking water (around Berlin)	GER	Heberer & Stan (1997)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etofyllinclofibrate	up to 165	64			drinking water (around Berlin)	GER	Stan et al. (1994)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etofyllinclofibrate	<0.5	3			drinking water	GER	Kalbfus (1997)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etofyllinclofibrate	up to 270	48			drinking water	GER	Heberer & Stan (1996b)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etofyllinclofibrate	<10	6			drinking water	NL, B	Mons et al. (2000)
Antiepileptics (pharmaceuticals for treatment of epilepsy)								
Carbamazepine	antiepileptic	<10	6			drinking water	NL, B	Mons et al. (2000)
Analgesics (pain relievers)								
Acetylsalicylic acid	analgesic	290				drinking water	GER	AWWR (1996)
Diclofenac	analgesic, antirheumatic	<10	6			drinking water	NL, B	Mons et al. (2000)
Ibuprofen	analgesic, antirheumatic	<10	6			drinking water	NL, B	Mons et al. (2000)
Paracetamol	analgesic	<100	12			drinking water	NL, B	Mons et al. (2000)
Salicylic acid	metabolite of acetylsalicylic acid	undetectable	>2			drinking water	USA	Hignite & Azarnoff (1977)
Cytostatics (pharmaceuticals for treatment of cancer)								
Bleomycin	cytostatic (antibiotic drug)	5.0 -13.0	9			drinking water	GB	Aherne et al. (1990)
Ifosfamide	cytostatic (alkylating drug)	<10	6			drinking water	NL, B	Mons et al. (2000)
Methotrexate	cytostatic (antimetabolic drug)	<6.25				drinking water		Aherne & English (1985)

Pharmaceutical or metabolite	Therapeutic use	Concentration in matrix in ng/l	n	Median ng/l	90-perc. ng/l	Matrix	Country	Reference
Antibiotics and pharmaceuticals for treatment of infections with protozoa and parasites								
Erythromycin	antibiotic (macrolides)	<10	6			drinking water	NL, B	Mons et al. (2000)
Sulfamethoxazole	antibiotic (sulfonamides)	<10	12			drinking water	NL, B	Mons et al. (2000)
Penicillin-like group	metabolite of a penicillin metabolite	up to 10				drinking water (immunoassay)		Wal et al. (1975)
Antidepressants and other psychiatric pharmaceuticals								
Diazepam	psychiatric drug	~ 10				drinking water		Waggott (1981)
Iodinated X-ray contrasting agents								
Diatrizoate	iodinated X-ray contrasting agent	60	1			drinking water	GER	Hirsch et al. (2000)
Iopamidol	iodinated X-ray contrasting agent	70	1			drinking water	GER	Hirsch et al. (2000)
Iopromide	iodinated X-ray contrasting agent	40	1			drinking water	GER	Hirsch et al. (2000)
Iothalamic acid	iodinated X-ray contrasting agent	10	1			drinking water	GER	Hirsch et al. (2000)
Ioxithalamic acid	iodinated X-ray contrasting agent	undetectable	1			drinking water	GER	Hirsch et al. (2000)
Other pharmaceuticals								
Clenbuterol	bronchospasmolytic	<5	16			drinking water	GER	Hirsch et al. (1996)
Fenoterol	bronchospasmolytic	<3	16			drinking water	GER	Hirsch et al. (1996)
Salbutamol	bronchospasmolytic	<5	16			drinking water	GER	Hirsch et al. (1996)
Salbutamol	bronchospasmolytic	<10	1			bank filtrate	GER	Hirsch et al. (1996)
Terbutalin	bronchospasmolytic	<3	16			drinking water	GER	Hirsch et al. (1996)

Supplement 5
Summary of analysis methods for human pharmaceuticals in the environment

	Monster volume	Extraction	Pretreatment	Analysis/Detection	Detection limit	Recovery	References
Fibrates							
Bezafibrate	1L	SPE (C18), pH 2	filtr. 0.45 µm, derivatization	GC-MS(-MS)	25 ng/L	80%	Stumpf et al., 1996
	1L	SPE (C18), pH 3	derivatization	GC-MS-MS	10 ng/L	96%	Sacher et al., 1998
Gemfibrozil	1L	SPE (C18), pH 2	filtr. 0.45 µm, derivatization	GC-MS(-MS)	5 ng/L	85%	Stumpf et al., 1996
	1L	SPE (C18), pH 3	derivatization	GC-MS-MS	5 ng/L	48%	Sacher et al., 1998
Clofibrate	1L	SPE (C18), pH 7.5	filtr. 0.45 µm, derivatization	GC-MS	20-100 ng/L	71%	Ternes et al., 1998a
Beta-blockers							
Metoprolol	1.4L?	SPE (C18), pH 7.5	derivatization	GC-MS	n.k.	n.k.	Hirsch et al., 1996
	1L	SPE (C18), pH 7.5	filtr. 0.45 µm, derivatization	GC-MS	5-25 ng/L	93-98%	Ternes et al., 1998a
Antiepileptics							
Carbamazepine	1-2L	wet, with hexane	-	GC-MS	- (only screening)	-	Franke et al., 1995
	1L	SPE (C18), pH 7.5	filtr. 0.45 µm, derivatization	GC-MS	20-100 ng/L	99%	Ternes et al., 1998a
	1L	SPE (C18), pH 7.5	filtr. 0.45 µm, derivatization	LC-ESMS-MS	10 ng/L	92%	Ternes et al., 1998a
	1L	SPE (C18), pH 3	-	GC-MS-MS	20 ng/L	86%	Sacher et al., 1998
Valproic acid	n.k.	n.k.	n.k.	n.k.	n.k.	n.k.	
Sodium valproate	n.k.	n.k.	n.k.	n.k.	n.k.	n.k.	
Analgesics							
Acetylsalicylic acid	1L	SPE (C18), pH 2	filtr. 0.45 µm, derivatization	GC-MS(-MS)	10 ng/L	90%	Stumpf et al., 1996
Naproxen	?	SPE (C18), pH 2	filtr. 0.45 µm, derivatization	GC-MS (SIM)	10-50 ng/L	91%	Ternes et al., 1998b; Ternes 1998b
Ibuprofen	0.5L	SPE (C18) at pH < 2	derivatization	GC-MS(-MS) (SIM)	n.k.	n.k.	Heberer et al., 1997, 1998
	1L	SPE (C18), pH 2	filtr. 0.45 µm, derivatization	GC-MS(-MS)	5 ng/L	71%	Stumpf et al., 1996
	1L	SPE (C18), pH 3	derivatization	GC-MS-MS	5 ng/L	73%	Sacher et al., 1998
Diclofenac	1L	SPE at pH 2	methylated	GC-MS	<1 ng/L	50-90%	Buser et al. 1998b
	0.5L	SPE (C18) at pH < 2	derivatization	GC-MS(-MS) (SIM)	n.k.	n.k.	Heberer et al., 1997, 1998
	1L	SPE (C18), pH 2	filtr. 0.45 µm, derivatization	GC-MS(-MS)	5 ng/L	75%	Stumpf et al., 1996
	1L	SPE (C18), pH 3	derivatization	GC-MS-MS	20 ng/L	100%	Sacher et al., 1998
Cytostatics							
Cyclofosfamide	0.5L	SPE (C18)	filtr. 0.45 µm, derivatization	GC-MS (SIM)	6 ng/L	72-86%	Steger-Hartmann et al., 1996
	1L	SPE (C18), pH 7.5	filtr. 0.45 µm, derivatization	GC-MS	50-250 ng/L	57%	Ternes et al., 1998a
	1L	SPE (C18), pH 7.5	filtr. 0.45 µm, derivatization	LC-ESMS-MS	10 ng/L	47%	Ternes et al., 1998a
Bleomycin	25mL	lyophilize	-	radioimmunoassay	60 ng/L	85%	Aherne et al., 1990
Cisplatin							
Antibiotics							
Doxycycline	100mL	lyophilize (or SPE)	filtr. 0.45µm, EDTA	HPLC-ESMS-MS	50 ng/L	68-80%	Hirsch et al. ,1998
Erytromycin	100mL	lyophilize (or SPE)	filtr. 0.45µm, EDTA	HPLC-ESMS-MS	20 ng/L	54-106%	Hirsch et al. ,1998
Amoxicillin	n.k.	n.k.	n.k.	n.k.	n.k.	n.k.	
Ciprofloxacin	2L	none	filtr. 0.45 µm	HPLC (fluorescence)	500 ng/L	102-104%	Hartmann et al. 1998
Nitrofurantoin	n.k.	n.k.	n.k.	n.k.	n.k.	n.k.	
Cefalexin	n.k.	n.k.	n.k.	n.k.	n.k.	n.k.	
Iodinated X-ray contrast agents							
divers	n.k.	SPE, pH 2.8	filtr. glass fibre (<1µm)	LC-MS-MS	10 ng/L	>70%	Hirsch et al. 2000
Metabolites							
Clofibric acid	0.5-1L	SPE at pH 2	methylated	HRGC-MS(-MS) (SIM)	0.2-1.0 ng/L	>50%	Buser et al., 1998a
	1L	SPE (C18) at pH < 2	derivatization	GC-MS-MS (SIM)	~1 ng/L	90-100%	Stan et al., 1994
	1L	SPE (C18), pH 2	filtr. 0.45 µm, derivatization	GC-MS(-MS)	5 ng/L	58%	Stumpf et al., 1996
	1L	SPE (C18), pH 3	derivatization	GC-MS-MS	10 ng/L	63%	Sacher et al., 1998

n.k. = not known
- = not applicable
SPE = Solid Phase Extraction
GC = Gas Chromatography
HRGC = High Resolution GC
LC = Liquid Chromatography
HPLC = High Performance Liquid Chromatography
MS = Mass Spectrometry
ESMS = Electrospray Tandem MS
SIM = Selective Ion Monitoring

Supplement 6
Summary of ecotoxicological data for human pharmaceuticals

Pharmaceutical or metabolite	Therapeutic use	Test organism	Species	Toxicity (mg/l)	Effect, Time	Parameter	Reference
Pharmaceuticals for treatment of cardiovascular diseases							
Propanolol	beta-blocker (antihypertensive)	crustacean (freshwater)	*Daphnia magna*	3.1	EC50 (acute)	immobility	In: Römbke et al. (1996)
Propanolol	beta-blocker (antihypertensive)	crustacean (freshwater)	*Daphnia magna*	17.7	EC50 (acute)	immobility	In: Römbke et al. (1996)
Propanolol HCl	beta-blocker (antihypertensive)	bacterium	*Vibrio fischeri*	*184*	EC50, 15 min	bioluminescence	Calleja et al. (1993)
Propanolol HCl	beta-blocker (antihypertensive)	crustacean (freshwater)	*Daphnia magna*	*15.6*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Propanolol HCl	beta-blocker (antihypertensive)	crustacean (freshwater)	*Daphnia magna*	*17.7*	EC50, acute	immobility	Lilius et al. (1995)
Propanolol HCl	beta-blocker (antihypertensive)	crustacean (freshwater)	*Streptocepahalus proboscideus*	*1.84*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Propanolol HCl	beta-blocker (antihypertensive)	crustacean (freshwater)	*Brachionus calyciflorus*	*2.59*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Propanolol HCl	beta-blocker (antihypertensive)	crustacean (salt water)	*Artemia salina*	*402*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Propanolol HCl	beta-blocker (antihypertensive)	fish, liver cells	*Oncorhynchus mykiss*	*482*	EC50, 3 hrs	toxicity (86Rb+ leakage)	Lilius et al. (1994)
Verapamil	beta-blocker (antihypertensive)	crustacean (freshwater)	*Daphnia magna*	50.9	EC50 (acute)	immobility	In: Römbke et al. (1996)
Verapamil	beta-blocker (antihypertensive)	crustacean (freshwater)	*Daphnia magna*	302.3	EC50 (acute)	immobility	In: Römbke et al. (1996)
Verapamil	beta-blocker (antihypertensive)	crustacean (freshwater)	*Daphnia magna*	*53.9 - 328*	EC50 (acute?)	immobility	Lilius et al. (1995)
Verapamil HCl	beta-blocker (antihypertensive)	bacterium	*Vibrio fischeri*	*438*	EC50, 15 min	bioluminescence	Calleja et al. (1993)
Verapamil HCl	beta-blocker (antihypertensive)	crustacean (freshwater)	*Daphnia magna*	*55.1*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Verapamil HCl	beta-blocker (antihypertensive)	crustacean (freshwater)	*Streptocepahalus proboscideus*	*6.18*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Verapamil HCl	beta-blocker (antihypertensive)	crustacean (freshwater)	*Brachionus calyciflorus*	*10.7*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Verapamil HCl	beta-blocker (antihypertensive)	crustacean (salt water)	*Artemia salina*	*356*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Verapamil HCl	beta-blocker (antihypertensive)	fish, liver cells	*Oncorhynchus mykiss*	*1841*	EC50, 3 hrs	toxicity (86Rb+ leakage)	Lilius et al. (1994)
Diltiazem	calcium antagonist	bacterium	*Vibrio fischeri*	35.3	EC10, 24 hrs	bioluminescence	Backhaus & Grimme (1999)
Diltiazem	calcium antagonist	bacterium	*Vibrio fischeri*	152	EC50, 24 hrs	bioluminescence	Backhaus & Grimme (1999)
Diltiazem	calcium antagonist	bacterium	*Vibrio fischeri*	388	EC90, 24 hrs	bioluminescence	Backhaus & Grimme (1999)
Nifedipine	calcium antagonist	bacterium	*Vibrio fischeri*	35	EC60, 24 hrs	bioluminescence	Backhaus & Grimme (1999)
Digoxin	cardiac glycoside	crustacean (freshwater)	*Daphnia magna*	24.2	EC50 (acute)	immobility	In: Römbke et al. (1996)
Digoxin	cardiac glycoside	crustacean (freshwater)	*Daphnia magna*	780.8	EC50 (acute)	immobility	In: Römbke et al. (1996)
Digoxin	cardiac glycoside	crustacean (freshwater)	*Daphnia magna*	21.2	EC50, 24 hrs	immobility	US EPA (1999)
Clofibrate	lipid regulator (fibrate)	algae & bacterium	not further specified	0.005 - 0.040	NOEC	not further specified	Kalbfus & Kopf (1997)
Clofibrate	lipid regulator (fibrate)	crustacean (freshwater)	*Daphnia*	0.010	NOEC, chronic?	reproduction?	Kalbfus & Kopf (1997)
Clofibrate	lipid regulator (fibrate)	crustacean (freshwater)	*Daphnia*	0.106	EC50, 24 hrs	immobility	Kalbfus & Kopf (1997)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etofyllinclofibrate	algae (freshwater)	*Scenedesmus subspicatus*	89	EC50, 72 hrs	number of cells	Henschel et al. (1997)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etofyllinclofibrate	bacterium	*Vibrio fischeri*	100	EC50, 30 min	bioluminescence	Henschel et al. (1997)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etofyllinclofibrate	crustacean (freshwater)	*Daphnia magna*	106	EC50, 48 hrs	immobility	Henschel et al. (1997)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etofyllinclofibrate	protozoan (ciliate)	*Tetrahymena pyriformis*	175	EC50, 48 hrs	number of cells	Henschel et al. (1997)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etofyllinclofibrate	fish	*Brachydanio rerio*	126	EC50, 48 hrs	mortality	Henschel et al. (1997)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etofyllinclofibrate	fish	*Brachydanio rerio*	175	EC50, 48 hrs	heart beat of embryos	Henschel et al. (1997)
Clofibric acid	metabolite of Clofibrate, Etofibrate & Etofyllinclofibrate	fish cells in vitro	*Bluegill sunfish*	14	EC50, 48 hrs	cell density	Henschel et al. (1997)
Clofibric acid ethyl ester	metabolite of Clofibric acid?	algae (freshwater)	*Scenedesmus subspicatus*	5.4	EC10, 72 hrs	biomass on base of chlorofyl	Kopf (1997)
Clofibric acid ethyl ester	metabolite of Clofibric acid?	algae (freshwater)	*Scenedesmus subspicatus*	12	EC50, 72 hrs	biomass on base of chlorofyl	Kopf (1997)
Clofibric acid ethyl ester	metabolite of Clofibric acid?	bacterium	*Vibrio fischeri*	14.2	EC10, 30 min	bioluminescence	Kopf (1997)
Clofibric acid ethyl ester	metabolite of Clofibric acid?	bacterium	*Vibrio fischeri*	40.3	EC50, 30 min	bioluminescence	Kopf (1997)
Clofibric acid ethyl ester	metabolite of Clofibric acid?	crustacean (freshwater)	*Daphnia magna*	0.0084	EC10, 21 days	reproduction	Kopf (1997)
Clofibric acid ethyl ester	metabolite of Clofibric acid?	crustacean (freshwater)	*Daphnia magna*	0.01	NOEC, 21 days	reproduction	Kopf (1997)
Clofibric acid ethyl ester	metabolite of Clofibric acid?	crustacean (freshwater)	*Daphnia magna*	0.106	EC50, 21 days	reproduction	Kopf (1997)
Clofibric acid ethyl ester	metabolite of Clofibric acid?	crustacean (freshwater)	*Daphnia magna*	17.7	EC10, 24 hrs	immobility	Kopf (1997)
Clofibric acid ethyl ester	metabolite of Clofibric acid?	crustacean (freshwater)	*Daphnia magna*	28.2	EC50, 24 hrs	immobility	Kopf (1997)
Isosorbide dinitrate	vasodilatator (against agina pectoris)	bacterium	*Salmonella* (TA1535, 1537, 98 & 100)	no effect		genotoxicity (Ames-test)	Stoyanov et al. (1987)
Isosorbide mononitrate	vasodilatator (against agina pectoris)	bacterium	*Salmonella* (TA1535, 1537, 98 & 100)	no effect		genotoxicity (Ames-test)	Stoyanov et al. (1987)

Pharmaceutical or metabolite	Therapeutic use	Test organism	Species	Toxicity (mg/l)	Effect, Time	Parameter	Reference
Antiepileptics (pharmaceuticals for treatment of epilepsy)							
Phenobarbital	antiepileptic	bacterium	*Vibrio fischeri*	*2992*	EC50, 5 min	bioluminescence	Calleja et al. (1993)
Phenobarbital	antiepileptic	crustacean (freshwater)	*Daphnia magna*	*1399*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Phenobarbital	antiepileptic	crustacean (freshwater)	*Daphnia magna*	232.2	EC50 (acute)	immobility	In: Römbke et al. (1996)
Phenobarbital	antiepileptic	crustacean (freshwater)	*Daphnia magna*	1400.3	EC50 (acute)	immobility	In: Römbke et al. (1996)
Phenobarbital	antiepileptic	crustacean (freshwater)	*Streptocepahalus proboscideus*	*1191*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Phenobarbital	antiepileptic	crustacean (freshwater)	*Brachionus calyciflorus*	*5199*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Phenobarbital	antiepileptic	fish, liver cells	*Oncorhynchus mykiss*	*6781*	EC50, 3 hrs	toxicity ($^{86}Rb^+$ leakage)	Lilius et al. (1994)
Valproic acid	antiepileptic	hydroid (salt water)	*Hydractinia echinata*	*128.7*	EC50 malformations, 48 hrs	embryogenesis	Berking (1991)
Valproic acid	antiepileptic	hydroid (salt water)	*Hydractinia echinata*	*715*	EC50, 24 hrs	delayed metamorphosis	Berking (1991)
Valproic acid	antiepileptic	hydroid (salt water)	*Hydractinia echinata*	*1430*	strong effect, 3 hrs	stimulated metamorphosis	Berking (1991)
Valproic acid	antiepileptic	polyp (freshwater)	*Hydra attenuata*	*5.72*	EC50, 24 hrs	head regeneration	Berking (1991)
Valproic acid	antiepileptic	fish	*Brachydanio rerio*	*4.29*	LOEC delayed development	early life stage test	Herrmann (1993)
Valproic acid	antiepileptic	fish	*Brachydanio rerio*	*14.3*	LOEC malformations	early life stage test	Herrmann (1993)
Valproic acid	antiepileptic	fish	*Brachydanio rerio*	*429*	LOEC death embryos	early life stage test	Herrmann (1993)
2-en-valproic acid	active analogue of Valproic acid	hydroid (salt water)	*Hydractinia echinata*	*84.6*	EC50 malformations, 48 hrs	embryogenesis	Berking (1991)
2-en-valproic acid	active analogue of Valproic acid	hydroid (salt water)	*Hydractinia echinata*	*846*	EC50, 24 hrs	delayed metamorphosis	Berking (1991)
2-en-valproic acid	active analogue of Valproic acid	polyp (freshwater)	*Hydra attenuata*	*42.3*	EC50, 24 hrs	head regeneration	Berking (1991)
2-en-valproic acid	active analogue of Valproic acid	fish	*Brachydanio rerio*	*42.3*	LOEC delayed development	early life stage test	Herrmann (1993)
2-en-valproic acid	active analogue of Valproic acid	fish	*Brachydanio rerio*	*423*	LOEC death embryos	early life stage test	Herrmann (1993)
4-en-valproic acid	active analogue of Valproic acid	hydroid (salt water)	*Hydractinia echinata*	*705*	EC50, 24 hrs	delayed metamorphosis	Berking (1991)
4-en-valproic acid	active analogue of Valproic acid	hydroid (salt water)	*Hydractinia echinata*	*155.1*	EC50 malformations, 48 hrs	embryogenesis	Berking (1991)
4-en-valproic acid	active analogue of Valproic acid	polyp (freshwater)	*Hydra attenuata*	*5.64*	EC50, 24 hrs	head regeneration	Berking (1991)
4-en-valproic acid	active analogue of Valproic acid	fish	*Brachydanio rerio*	*>423*	NOEC death embryos	early life stage test	Herrmann (1993)
4-en-valproic acid	active analogue of Valproic acid	fish	*Brachydanio rerio*	*42.3*	LOEC delayed development	early life stage test	Herrmann (1993)

Pharmaceutical or metabolite	Therapeutic use	Test organism	Species	Toxicity (mg/l)	Effect, Time	Parameter	Reference
Analgetics (pain relievers)							
Acetylsalicylic acid	analgetic	crustacean (freshwater)	*Daphnia magna*	167.5	EC50 (acute)	immobility	In: Römbke et al. (1996)
Acetylsalicylic acid	analgetic	crustacean (freshwater)	*Daphnia magna*	167.5	LC50 (acute)	death	In: Römbke et al. (1996)
Acetylsalicylic acid	analgetic	crustacean (freshwater)	*Daphnia magna*	1468.2	EC50 (acute)	immobility	In: Römbke et al. (1996)
Acetylsalicylic acid	analgetic	crustacean (freshwater)	*Daphnia magna*	61-68	EC50, 21 days	reproduction	US EPA (1999)
Acetylsalicylic acid	analgetic	crustacean (freshwater)	*Daphnia magna*	*154 - 1492*	EC50 (acute)	immobility	Lilius et al. (1995)
Acetylsalicylic acid (ortho-)	analgetic	crustacean (freshwater)	*Daphnia magna*	>1000	EC50	immobility	Safety Data Sheet, Chem. Fabrik Anbirg GmbH, Mannheim
Acetylsalicylic acid (ortho-)	analgetic	crustacean (freshwater)	*Daphnia magna*	1000	EC50, 24 hrs	immobility	Safety Data Sheet, Rhône-Poulenc NL B.V., Amstelveen
Salicylic acid	metabolite of acetylsalicylic acid (analgetic)	algae & bacterium	not further specified	15 - 60	NOEC	not further specified	Kalbfus & Kopf (1997)
Salicylic acid	metabolite of acetylsalicylic acid (analgetic)	algae (freshwater)	*Scenedesmus subspicatus*	> 100	EC50, 72 hrs	number of cells	Henschel et al. (1997)
Salicylic acid	metabolite of acetylsalicylic acid (analgetic)	bacterium	*Vibrio fischeri*	90	EC50, 30 min	bioluminescence	Henschel et al. (1997)
Salicylic acid	metabolite of acetylsalicylic acid (analgetic)	bacterium	*Vibrio fischeri*	213.9	EC50, 5 min	bioluminescence	Somasundaram et al. (1990)
Salicylic acid	metabolite of acetylsalicylic acid (analgetic)	crustacean (freshwater)	*Daphnia*	10	NOEC	not further specified	Kalbfus & Kopf (1997)
Salicylic acid	metabolite of acetylsalicylic acid (analgetic)	crustacean (freshwater)	*Daphnia magna*	118	EC50, 48 hrs	immobility	Henschel et al. (1997)
Salicylic acid	metabolite of acetylsalicylic acid (analgetic)	enchytraeid	*Enchytraeus albidus*	18	LC50 (acute)	death	In: Römbke et al. (1996)
Salicylic acid	metabolite of acetylsalicylic acid (analgetic)	protozoan (ciliate)	*Tetrahymena pyriformis*	>100	EC50, 48 hrs	number of cells	Henschel et al. (1997)
Salicylic acid	metabolite of acetylsalicylic acid (analgetic)	fish	*Brachydanio rerio*	37	EC50, 48 hrs	mortality	Henschel et al. (1997)
Salicylic acid	metabolite of acetylsalicylic acid (analgetic)	fish	*Brachydanio rerio*	50	EC50, 48 hrs	heart beat of embryos	Henschel et al. (1997)
Salicylic acid	metabolite of acetylsalicylic acid (analgetic)	fish cells in vitro	*Bluegill sunfish*	>500	EC50, 48 hrs	cell density	Henschel et al. (1997)
Diclofenac	analgetic, antirheumatic	bacterium	*Salmonella* (TA1535, 1537, 98 & 100)	no effect		genotoxicity (Ames-test)	Stoyanov et al. (1987)
Ibuprofen	analgetic, antirheumatic	algae (salt water)	*Skeletonema costatum*	7.1	EC50, 96 hrs	growth inhibition	Knoll (1995)
Ibuprofen	analgetic, antirheumatic	bacterium	*Mucor sp.*	120 - 140	MIC, pH = 5	not further specified	Sanyal et al. (1993)
Ibuprofen	analgetic, antirheumatic	bacterium	*Staphylococus aureus*	50	MIC, pH = 6	not further specified	Elvers & Wright (1995)
Ibuprofen	analgetic, antirheumatic	bacterium	*Staphylococus aureus*	150	MIC, pH = 7	not further specified	Elvers & Wright (1995)
Ibuprofen	analgetic, antirheumatic	bacterium	*Staphylococus aureus*	40 - 80	MIC, pH = 5	not further specified	Sanyal et al. (1993)
Ibuprofen	analgetic, antirheumatic	bacterium	*Vibrio fischeri*	12.30	EC50, 5 min	bioluminescence	Knoll (1995)
Ibuprofen	analgetic, antirheumatic	bacterium	*Epidermophytes floccosum*	20 - 40	MIC, pH = 5	not further specified	Sanyal et al. (1993)
Ibuprofen	analgetic, antirheumatic	bacterium	*Mycrosporum fulva*	10 - 40	MIC, pH = 5	not further specified	Sanyal et al. (1993)
Ibuprofen	analgetic, antirheumatic	bacterium	*Trichphyton mentagrophytes*	5 - 20	MIC, pH = 5	not further specified	Sanyal et al. (1993)
Ibuprofen	analgetic, antirheumatic	bacterium	*Trichphyton rubrum*	5	MIC	not further specified	Sanyal et al. (1993)
Ibuprofen	analgetic, antirheumatic	bacterium	*Trichphyton rubrum*	5 - 10	MIC, pH = 5	not further specified	Sanyal et al. (1993)
Ibuprofen	analgetic, antirheumatic	bacterium	*Trichphyton tonsurans*	20 - 40	MIC, pH = 5	not further specified	Sanyal et al. (1993)
Ibuprofen	analgetic, antirheumatic	crustacean (freshwater)	*Daphnia magna*	9.06 - 11.5	EC50, 48 hrs	immobility	Knoll (1995)
Ibuprofen	analgetic, antirheumatic	crustacean (freshwater)	*Daphnia magna*	approx. 3	NOEC, 48 hrs	immobility	Knoll (1995)
Ibuprofen	analgetic, antirheumatic	crustacean (salt water)	*Mysodopsis bahia*	30	NOEC, 96 hrs	immobility	Knoll (1995)
Ibuprofen	analgetic, antirheumatic	crustacean (salt water)	*Mysodopsis bahia*	>100	NEL, 96 hrs	immobility	Knoll (1995)
Ibuprofen	analgetic, antirheumatic	pathogen yeast	*Candida albicans*	140 - 160	MIC, pH = 5	not further specified	Sanyal et al. (1993).
Ibuprofen	analgetic, antirheumatic	fish	*Cyprinodon variegatus*	>300	NEL, 96 hrs	death	Knoll (1995)
Ibuprofen	analgetic, antirheumatic	fish	*Lepomis machrochirus*	10	NOEC, 96 hrs	death	Knoll (1995)
Ibuprofen	analgetic, antirheumatic	fish	*Lepomis machrochirus*	173	LC50, 96 hrs	death	Knoll (1995)
Paracetamol	analgetic	algae (freshwater)	*Scenedesmus subspicatus*	134	EC50, 72 hrs	number of cells	Henschel et al. (1997)
Paracetamol	analgetic	bacterium	*Vibrio fischeri*	650	EC50, 30 min	bioluminescence	Henschel et al. (1997)
Paracetamol	analgetic	crustacean (freshwater)	*Daphnia magna*	50	EC50, 48 hrs	immobility	Henschel et al. (1997)
Paracetamol	analgetic	crustacean (freshwater)	*Daphnia magna*	9.2	EC50, 48 hrs	immobility	US EPA (1999)
Paracetamol	analgetic	crustacean (freshwater)	*Daphnia magna*	136	EC50, 24 hrs	immobility	US EPA (1999)
Paracetamol	analgetic	crustacean (freshwater)	*Daphnia magna*	136	EC50, 24 hrs	immobility	US EPA (1998)
Paracetamol	analgetic	crustacean (freshwater)	*Daphnia magna*	*40.9 - 135*	EC50 (acute)	immobility	Lilius et al. (1995)
Paracetamol	analgetic	crustacean (freshwater)	*Streptocepahalus probosciceus*	29.6	LC50, 24 hrs	death	US EPA (1999)
Paracetamol	analgetic	protozoan (ciliate)	*Tetrahymena pyriformis*	112	EC50, 48 hrs	number of cells	Henschel et al. (1997)
Paracetamol	analgetic	fish	*Brachydanio rerio*	378	EC50, 48 hrs	mortality	Henschel et al. (1997)
Paracetamol	analgetic	fish	*Brachydanio rerio*	920	EC50, 48 hrs	heart beat of embryos	Henschel et al. (1997)
Paracetamol	analgetic	fish cells in vitro	*Bluegill sunfish*	19	EC50, 48 hrs	cell density	Henschel et al. (1997)

Pharmaceutical or metabolite	Therapeutic use	Test organism	Species	Toxicity (mg/l)	Effect, Time	Parameter	Reference
Cytostatics (pharmaceuticals for treatment of cancer)							
Cisplatin	cytostatic (alkylating drug)	bacterium	*Salmonella typhimurium*	1.25	LOEC (*umuC* IF = 2), 30 min	genotoxicity (umuC-test)	Hartmann et al. (1998)
Cyclofosfamide	cytostatic (alkylating drug)	bacterium	not further specified	from 770	effect concentration	toxicity	Krämer & Wendel (1968)
Cyclofosfamide	cytostatic (alkylating drug)	bacterium	from stp effluent close to hospitals	at 2.5 no effect	toxicity control	in Closed Bottle Test	Kümmerer et al. (1996)
Cyclofosfamide	cytostatic (alkylating drug)	bacterium	from stp effluent close to hospitals	no effect	Colony Forming Units	in Closed Bottle Test	Kümmerer et al. (1996)
Dacarbazin	cytostatic (alkylating drug)	bacterium	*Salmonella typhimurium*	>1	LOEC (*umuC* IF = 2), 30 min	genotoxicity (umuC-test)	Hartmann et al. (1998)
Ifosfamide	cytostatic (alkylating drug)	bacterium	*Pseudomonas putida*	>25	NOEC	growth inhibition	Kümmerer et al. (1996)
Ifosfamide	cytostatic (alkylating drug)	bacterium	from stp effluent close to hospitals	at 2.5 no effect	toxicity control	in Closed Bottle Test	Kümmerer et al. (1996)
Ifosfamide	cytostatic (alkylating drug)	bacterium	from stp effluent close to hospitals	no effect	Colony Forming Units	in Closed Bottle Test	Kümmerer et al. (1996)
Bleomycin	cytostatic (antibiotic drug)	bacterium	*Salmonella typhimurium*	0.05	LOEC (*umuC* IF = 2), 30 min	genotoxicity (umuC-test)	Hartmann et al. (1998)
Mitomycin C	cytostatic (antibiotic drug)	bacterium	*Salmonella typhimurium*	0.02	LOEC (*umuC* IF = 2), 30 min	genotoxicity (umuC-test)	Hartmann et al. (1998)
Flourouracil	cytostatic (antimetabolic drug)	bacterium	*Vibrio fischeri*	0.014	EC10, 24 hrs	bioluminescence	Backhaus & Grimme (1999)
Flourouracil	cytostatic (antimetabolic drug)	bacterium	*Vibrio fischeri*	0.122	EC50, 24 hrs	bioluminescence	Backhaus & Grimme (1999)
Flourouracil	cytostatic (antimetabolic drug)	bacterium	*Vibrio fischeri*	1.25	EC90, 24 hrs	bioluminescence	Backhaus & Grimme (1999)
Fluorouracil	cytostatic (antimetabolic drug)	bacterium	*Salmonella typhimurium*	>26	LOEC (*umuC* IF = 2), 30 min	genotoxicity (umuC-test)	Hartmann et al. (1998)
Methotrexate	cytostatic (antimetabolic drug)	algae (freshwater)	*Scenedesmus subspicatus*	260	EC50, 72 hrs	number of cells	Henschel et al. (1997)
Methotrexate	cytostatic (antimetabolic drug)	bacterium	*Vibrio fischeri*	1220	EC50, 30 min	bioluminescence	Henschel et al. (1997)
Methotrexate	cytostatic (antimetabolic drug)	crustacean (freshwater)	*Daphnia magna*	>1000	EC50, 48 hrs	immobility	Henschel et al. (1997)
Methotrexate	cytostatic (antimetabolic drug)	protozoan (ciliate)	*Tetrahymena pyriformis*	45	EC50, 48 hrs	number of cells	Henschel et al. (1997)
Methotrexate	cytostatic (antimetabolic drug)	fish	*Brachydanio rerio*	85	EC50, 48 hrs	mortality	Henschel et al. (1997)
Methotrexate	cytostatic (antimetabolic drug)	fish	*Brachydanio rerio*	142	EC50, 48 hrs	heart beat of embryos	Henschel et al. (1997)
Methotrexate	cytostatic (antimetabolic drug)	fish cells in vitro	*Bluegill sunfish*	3	EC50, 48 hrs	cell density	Henschel et al. (1997)
Etoposide	cytostatic (natural substance)	bacterium	*Salmonella typhimurium*	25	LOEC (*umuC* IF = 2), 30 min	genotoxicity (umuC-test)	Hartmann et al. (1998)

Pharmaceutical or metabolite	Therapeutic use	Test organism	Species	Toxicity (mg/l)	Effect, Time	Parameter	Reference
Antibiotics and pharmaceuticals for treatment of infections with protozoa and parasites							
Chloortetracycline	antibiotic (tetracyclines)	algae (freshwater)	*Selenastrum capricornutum*	3.1	EC50, 3 days	growth inhibition (chlorofyl)	Halling-Sørensen (2000)
Chloortetracycline	antibiotic (tetracyclines)	cyanobacterium	*Mycrocystis aeruginosa*	0.05	EC50, 7 days	growth inhibition (chlorofyl)	Halling-Sørensen (2000)
Oxytetracycline	antibiotic (tetracyclines)	algae (freshwater)	*Selenastrum capricornutum*	4.5	EC50, 72 hrs	growth inhibition (chlorofyl)	Holten Lützhøft et al. (1999)
Oxytetracycline	antibiotic (tetracyclines)	algae (salt water)	*Rhodomonas salina*	1.6	EC50, 72 hrs	growth inhibition (chlorofyl)	Holten Lützhøft et al. (1999)
Oxytetracycline	antibiotic (tetracyclines)	cyanobacterium	*Mycrocystis aeruginosa*	0.207	EC50, 7 days	growth inhibition (chlorofyl)	Holten Lützhøft et al. (1999)
Oxytetracycline	antibiotic (tetracyclines)	crustacean (freshwater)	*Daphnia magna*	7.4	EC10, 21 days	reproduction	Wollenberger et al. (2000)
Oxytetracycline	antibiotic (tetracyclines)	crustacean (freshwater)	*Daphnia magna*	46.2	EC50, 21 days	reproduction	Wollenberger et al. (2000)
Oxytetracycline	antibiotic (tetracyclines)	crustacean (freshwater)	*Daphnia magna*	100	LOEC, 48 hrs	immobility	Wollenberger et al. (2000)
Oxytetracycline	antibiotic (tetracyclines)	water plant	*Lemna minor*	>10	inhibition	growth	Nickell & Finley (1954)
Oxytetracycline	antibiotic (tetracyclines)	water plant	*Lemna minor*	at 5 and 10	stimulation	growth	Nickell & Finley (1954)
Tetracycline	antibiotic (tetracyclines)	algae (freshwater)	*Selenastrum capricornutum*	2.2	EC50, 3 days	growth inhibition (chlorofyl)	Halling-Sørensen (2000)
Tetracycline	antibiotic (tetracyclines)	bacterium	*Vibrio fischeri*	0.0046	EC10, 24 hrs	bioluminescence	Backhaus & Grimme (1999)
Tetracycline	antibiotic (tetracyclines)	bacterium	*Vibrio fischeri*	0.0251	EC50, 24 hrs	bioluminescence	Backhaus & Grimme (1999)
Tetracycline	antibiotic (tetracyclines)	bacterium	*Vibrio fischeri*	0.0738	EC90, 24 hrs	bioluminescence	Backhaus & Grimme (1999)
Tetracycline	antibiotic (tetracyclines)	cyanobacterium	*Mycrocystis aeruginosa*	0.09	EC50, 7 days	growth inhibition (chlorofyl)	Halling-Sørensen (2000)
Tetracycline	antibiotic (tetracyclines)	crustacean (freshwater)	*Daphnia magna*	29.4	EC10, 21 days	reproduction	Wollenberger et al. (2000)
Tetracycline	antibiotic (tetracyclines)	crustacean (freshwater)	*Daphnia magna*	44.8	EC50, 21 days	reproduction	Wollenberger et al. (2000)
Tetracycline	antibiotic (tetracyclines)	crustacean (freshwater)	*Daphnia magna*	340	NOEC, 48 hrs	immobility	Wollenberger et al. (2000)
Tetracycline	antibiotic (tetracyclines)	fish	not further specified	1818	LC50	death	In: v.d. Heide & Hueck v.d. Plass (1984)
Erythromycin	antibiotic (macrolides)	crustacean (freshwater)	*Daphnia magna*	387.7	EC50, 24 hrs	immobility	di Delupis et al. (1992)
Erythromycin	antibiotic (macrolides)	crustacean (freshwater)	*Daphnia magna*	211	LC50 (acute)	death	In: Römbke et al. (1996)
Erythromycin	antibiotic (macrolides)	crustacean (freshwater)	*Daphnia magna*	no effect	decrease or increase	phototactic behaviour	Macri et al. (1998)
Erythromycin	antibiotic (macrolides)	crustacean (freshwater)	*Daphnia magna*	210.6	EC50, 48 hrs	immobility	Macri et al. (1998); di Delupis et al. (1992)
Spiramycin	antibiotic (macrolides)	algae (freshwater)	*Selenastrum capricornutum*	2.3	EC50, 3 days	growth inhibition (chlorofyl)	Halling-Sørensen (2000)
Spiramycin	antibiotic (macrolides)	cyanobacterium	*Mycrocystis aeruginosa*	0.005	EC50, 7 days	growth inhibition (chlorofyl)	Halling-Sørensen (2000)
Amoxicillin	antibiotic (penicillins)	algae (freshwater)	*Selenastrum capricornutum*	250	NOEC, 72 hrs	growth inhibition (chlorofyl)	Holten Lützhøft et al. (1999)
Amoxicillin	antibiotic (penicillins)	algae (salt water)	*Rhodomonas salina*	3108 (extrapolated)	EC50, 72 hrs	growth inhibition (chlorofyl)	Holten Lützhøft et al. (1999)
Amoxicillin	antibiotic (penicillins)	bacterium	*Salmonella typhimurium*	20	LOEC (*umuC* IF = 2), 30 min	genotoxicity (umuC-test)	Hartmann et al. (1998)
Amoxicillin	antibiotic (penicillins)	cyanobacterium	*Mycrocystis aeruginosa*	0.0037	EC50, 7 days	growth inhibition (chlorofyl)	Holten Lützhøft et al. (1999)
Ampicillin	antibiotic (penicillins)	bacterium	*Vibrio fischeri*	90.1	EC10, 24 hrs	bioluminescence	Backhaus & Grimme (1999)
Ampicillin	antibiotic (penicillins)	bacterium	*Vibrio fischeri*	163	EC50, 24 hrs	bioluminescence	Backhaus & Grimme (1999)
Ampicillin	antibiotic (penicillins)	bacterium	*Vibrio fischeri*	238	EC90, 24 hrs	bioluminescence	Backhaus & Grimme (1999)
Ampicillin	antibiotic (penicillins)	bacterium	*Vibrio harveyi*	>100	?	growth rate	Thomulka et al. (1993)
Benzylpenicillin (Penicillin G)	antibiotic (penicillins)	algae (freshwater)	*Selenastrum capricornutum*	100	NOEC, 3 days	growth inhibition (chlorofyl)	Halling-Sørensen (2000)
Benzylpenicillin (Penicillin G)	antibiotic (penicillins)	cyanobacterium	*Mycrocystis aeruginosa*	0.006	EC50, 7 days	growth inhibition (chlorofyl)	Halling-Sørensen (2000)
Penicillin G	antibiotic (penicillins)	bacterium	*Pseudomonas putida*	>256	IC50, 16 hrs	growth inhibition	Al-Ahmad et al. (1999)
Penicillin G	antibiotic (penicillins)	bacteria	sensitive pathogens	0.004 - 16.0	MIC50	growth inhibition	Al-Ahmad et al. (1999)
Penicillin G	antibiotic (penicillins)	bacteria	from stp effluent close to hospitals	no effect	Colony Forming Units	in Closed Bottle Test	Al-Ahmad et al. (1999)
Penicillin G	antibiotic (penicillins)	bacteria	from stp effluent close to hospitals	no effect	toxicity control	in Closed Bottle Test	Al-Ahmad et al. (1999)
Penicillenic acid	metabolite of penicillin (antibiotic)	bacterium	*Vibrio fischeri*	7.44	EC50, 20 min	bioluminescence	Yates & Porter (1982)
Penicillenic acid	metabolite of penicillin (antibiotic)	bacterium	*Vibrio fischeri*	8.72	EC50, 15 min	bioluminescence	Yates & Porter (1982)
Penicillenic acid	metabolite of penicillin (antibiotic)	bacterium	*Vibrio fischeri*	10.65	EC50, 10 min	bioluminescence	Yates & Porter (1982)
Penicillenic acid	metabolite of penicillin (antibiotic)	bacterium	*Vibrio fischeri*	15.95	EC50, 5 min	bioluminescence	Yates & Porter (1982)
Cinoxacin	antibiotic (fluoroquinolones)	bacterium	*Escherichia coli* mutant	0.5	SOSIP (delta IF/nmol)	genotoxicity (SOS-chromotest)	Mersch-Sundermann et al. (1994)
Ciprofloxacin	antibiotic (fluoroquinolones)	algae (freshwater)	*Scenedesmus capricornutum*	2.97	EC50, 72 hrs	growth inhibition (chlorofyl)	Holten Lützhøft et al. (1999)
Ciprofloxacin	antibiotic (fluoroquinolones)	bacterium	*Escherichia coli* mutant	0.0002 - 0.0004	LOEC, 2 hrs	genotoxicity (SOS-chromotest)	Kümmerer et al. (2000)
Ciprofloxacin	antibiotic (fluoroquinolones)	bacterium	*Escherichia coli* mutant	184	SOSIP (delta IF/nmol)	genotoxicity (SOS-chromotest)	Mersch-Sundermann et al. (1994)
Ciprofloxacin	antibiotic (fluoroquinolones)	bacterium	*Pseudomonas putida*	0.08	IC50, 16 hrs	growth inhibition	Al-Ahmad et al. (1999)
Ciprofloxacin	antibiotic (fluoroquinolones)	bacterium	*Pseudomonas putida*	0.010	NOEC, 16 hrs; average (n=2)	growth inhibition	Kümmerer et al. (2000)
Ciprofloxacin	antibiotic (fluoroquinolones)	bacterium	*Pseudomonas putida*	0.080	EC50, 16 hrs; average (n=2)	growth inhibition	Kümmerer et al. (2000)
Ciprofloxacin	antibiotic (fluoroquinolones)	bacterium	*Pseudomonas putida*	0.320	EC100, 16 hrs; average (n=2)	growth inhibition	Kümmerer et al. (2000)
Ciprofloxacin	antibiotic (fluoroquinolones)	bacterium	*Salmonella typhimurium*	0.025	LOEC (*umuC* IF = 2), 30 min	genotoxicity (umuC-test)	Hartmann et al. (1998)
Ciprofloxacin	antibiotic (fluoroquinolones)	bacterium	*Salmonella typhimurium*	0.0052	LOEC (*umuC* IF = 2), 30 min	genotoxicity (umu-C test) +S9	Hartmann et al. (1999)
Ciprofloxacin	antibiotic (fluoroquinolones)	bacterium	*Salmonella typhimurium*	0.0059	LOEC (*umuC* IF = 2), 30 min	genotoxicity (umu-C test) -S9	Hartmann et al. (1999)
Ciprofloxacin	antibiotic (fluoroquinolones)	bacteria	sensitive pathogens	0.002 - 8.0	MIC50	growth inhibition	Al-Ahmad et al. (1999)
Ciprofloxacin	antibiotic (fluoroquinolones)	bacteria	sensitive pathogens	0.002 - 8.000	MIC50	growth inhibition	Kümmerer et al. (2000)
Ciprofloxacin	antibiotic (fluoroquinolones)	bacteria	from stp effluent close to hospitals	no effect	toxicity control	in Closed Bottle Test	Al-Ahmad et al. (1999)
Ciprofloxacin	antibiotic (fluoroquinolones)	bacteria	from stp effluent close to hospitals	weak, sign. effect	Colony Forming Units	in Closed Bottle Test	Al-Ahmad et al. (1999)
Ciprofloxacin	antibiotic (fluoroquinolones)	bacteria	from stp effluent close to hospitals	no effect	toxicity control (n=2)	in Closed Bottle Test	Kümmerer et al. (2000)
Ciprofloxacin	antibiotic (fluoroquinolones)	bacteria	from stp effluent close to hospitals	weak, sign. effect	Colony Forming Units (n=2)	in Closed Bottle Test	Kümmerer et al. (2000)
Ciprofloxacin	antibiotic (fluoroquinolones)	cyanobacterium	*Mycrocystis aeruginosa*	0.005	EC50, 7 days	growth inhibition (chlorofyl)	Holten Lützhøft & Halling-Sørensen (ongepubl.), geciteerd in H

Pharmaceutical or metabolite	Therapeutic use	Test organism	Species	Toxicity (mg/l)	Effect, Time	Parameter	Reference
Enoxacin	antibiotic (fluoroquinolones)	bacterium	*Escherichia coli* mutant	18	SOSIP (delta IF/nmol)	genotoxicity (SOS-chromotest)	Mersch-Sundermann et al. (1994)
Fleroxacin	antibiotic (fluoroquinolones)	bacterium	*Escherichia coli* mutant	25	SOSIP (delta IF/nmol)	genotoxicity (SOS-chromotest)	Mersch-Sundermann et al. (1994)
Flumequine	antibiotic (fluoroquinolones)	algae (freshwater)	*Selenastrum capricornutum*	5	EC50, 72 hrs	growth inhibition (chlorofyl)	Holten Lützhøft et al. (1999)
Flumequine	antibiotic (fluoroquinolones)	algae (salt water)	*Rhodomonas salina*	18	EC50, 72 hrs	growth inhibition (chlorofyl)	Holten Lützhøft et al. (1999)
Flumequine	antibiotic (fluoroquinolones)	bacterium	*Aeromonas salmonicida*	4	MIC, 24 hrs; trypton soya broth	growth inhibition	Pursell et al. (1995)
Flumequine	antibiotic (fluoroquinolones)	bacterium	*Aeromonas salmonicida*	16	MIC, 72 hrs; trypton soya broth	growth inhibition	Pursell et al. (1995)
Flumequine	antibiotic (fluoroquinolones)	bacterium	*Aeromonas salmonicida*	16	MBC, 24 hrs; trypton soya broth	100% bacterial death	Pursell et al. (1995)
Flumequine	antibiotic (fluoroquinolones)	bacterium	*Aeromonas salmonicida*	32	MBC, 72 hrs; trypton soya broth	100% bacterial death	Pursell et al. (1995)
Flumequine	antibiotic (fluoroquinolones)	bacterium	*Aeromonas salmonicida*	128	MIC, 24 hrs; trypton + Mg & Ca ions	growth inhibition	Pursell et al. (1995)
Flumequine	antibiotic (fluoroquinolones)	bacterium	*Aeromonas salmonicida*	256	MIC, 72 hrs; trypton + Mg & Ca ions	growth inhibition	Pursell et al. (1995)
Flumequine	antibiotic (fluoroquinolones)	bacterium	*Aeromonas salmonicida*	256	MBC, 72 hrs; trypton + Mg & Ca ions	100% bacterial death	Pursell et al. (1995)
Flumequine	antibiotic (fluoroquinolones)	bacterium	*Aeromonas salmonicida*	2048	MBC, 24 hrs; trypton + Mg & Ca ions	100% bacterial death	Pursell et al. (1995)
Flumequine	antibiotic (fluoroquinolones)	cyanobacterium	*Mycrocystis aeruginosa*	0.159	EC50, 7 days	growth inhibition (chlorofyl)	Holten Lützhøft et al. (1999)
Flumequine	antibiotic (fluoroquinolones)	crustacean (salt water)	*Artemia salina*	477	LC50, 24 hrs	death	Brambilla et al. (1994)
Flumequine	antibiotic (fluoroquinolones)	crustacean (salt water)	*Artemia salina*	96	LC50, 72 hrs	death	Migliore et al. (1997)
Flumequine	antibiotic (fluoroquinolones)	crustacean (salt water)	*Artemia salina*	308	LC50, 48 hrs	death	Migliore et al. (1997)
Flumequine	antibiotic (fluoroquinolones)	crustacean (salt water)	*Artemia salina* nauplii	6.3	LC22	death	Migliore et al. (1997)
Flumequine	antibiotic (fluoroquinolones)	water plant	*Lythrum salicaria*	0.05	sign. reduction, 35 days	length hypocotyl	Migliore et al. (2000)
Flumequine	antibiotic (fluoroquinolones)	water plant	*Lythrum salicaria*	0.050	sign. stimulation, 35 days	length third leaf	Migliore et al. (2000)
Flumequine	antibiotic (fluoroquinolones)	water plant	*Lythrum salicaria*	100	sign. reduction, 20 & 30 days	length primary root	Migliore et al. (2000)
Flumequine	antibiotic (fluoroquinolones)	water plant	*Lythrum salicaria*	100	sign. reduction, 30 days	number of secundary roots	Migliore et al. (2000)
Flumequine	antibiotic (fluoroquinolones)	water plant	*Lythrum salicaria*	100	sign. reduction, 10, 20 & 30 days	length hypocotyl	Migliore et al. (2000)
Flumequine	antibiotic (fluoroquinolones)	water plant	*Lythrum salicaria*	100	sign. reduction, 10, 20 & 30 days	length cotyledon	Migliore et al. (2000)
Flumequine	antibiotic (fluoroquinolones)	water plant	*Lythrum salicaria*	100	sign. reduction, 10, 20 & 30 days	number of leaves per plant	Migliore et al. (2000)
Flumequine	antibiotic (fluoroquinolones)	water plant	*Lythrum salicaria*	100	sign. reduction, 10, 20 & 30 days	length first leaf	Migliore et al. (2000)
Flumequine	antibiotic (fluoroquinolones)	water plant	*Lythrum salicaria*	100	sign. reduction, 10, 20 & 30 days	length second leaf	Migliore et al. (2000)
Flumequine	antibiotic (fluoroquinolones)	water plant	*Lythrum salicaria*	100	sign. reduction, 30 days	length third leaf	Migliore et al. (2000)
Flumequine	antibiotic (fluoroquinolones)	water plant	*Lythrum salicaria*	>5.000	LOEC, 35 days	length primary root	Migliore et al. (2000)
Flumequine	antibiotic (fluoroquinolones)	water plant	*Lythrum salicaria*	>5.000	LOEC, 35 days	length cotyledon	Migliore et al. (2000)
Flumequine	antibiotic (fluoroquinolones)	water plant	*Lythrum salicaria*	>5.000	LOEC, 35 days	length fourth leaf	Migliore et al. (2000)
Flumequine	antibiotic (fluoroquinolones)	water plant	*Lythrum salicaria*	0.050 - 5.000	sign. stimulation, 35 days	number of leaves per plant	Migliore et al. (2000)
Flumequine	antibiotic (fluoroquinolones)	water plant	*Lythrum salicaria*	0.050 - 0.500	sign. stimulation, 35 days	number of secundary roots	Migliore et al. (2000)
Flumequine	antibiotic (fluoroquinolones)	water plant	*Lythrum salicaria*	0.050 - 5.000	sign. stimulation, 35 days	length first leaf	Migliore et al. (2000)
Flumequine	antibiotic (fluoroquinolones)	water plant	*Lythrum salicaria*	0.050 - 5.000	(sign.) stimulation, 35 days	length second leaf	Migliore et al. (2000)
Flumequine	antibiotic (fluoroquinolones)	water plant	*Lythrum salicaria*	0.100 - 5.000	no effect, 35 days	length hypocotyl	Migliore et al. (2000)
Nalidixic acid	antibiotic (fluoroquinolones)	bacterium	*Escherichia coli* mutant	0.5	SOSIP (delta IF/nmol)	genotoxicity (SOS-chromotest)	Mersch-Sundermann et al. (1994)
Nalidixic acid	antibiotic (fluoroquinolones)	bacterium	*Vibrio fischeri*	0.1082	EC10, 24 hrs	bioluminescence	Backhaus & Grimme (1999)
Nalidixic acid	antibiotic (fluoroquinolones)	bacterium	*Vibrio fischeri*	0.206	EC50, 24 hrs	bioluminescence	Backhaus & Grimme (1999)
Nalidixic acid	antibiotic (fluoroquinolones)	bacterium	*Vibrio fischeri*	0.308	EC90, 24 hrs	bioluminescence	Backhaus & Grimme (1999)
Norfloxacin	antibiotic (fluoroquinolones)	bacterium	*Escherichia coli* mutant	120	SOSIP (delta IF/nmol)	genotoxicity (SOS-chromotest)	Mersch-Sundermann et al. (1994)
Norfloxacin	antibiotic (fluoroquinolones)	bacterium	*Salmonella typhimurium*	0.025	LOEC (*umuC* IF = 2), 30 min	genotoxicity (umuC-test)	Hartmann et al. (1998)
Norfloxacin	antibiotic (fluoroquinolones)	bacterium	*Vibrio fischeri*	0.0115	EC10, 24 hrs	bioluminescence	Backhaus & Grimme (1999)
Norfloxacin	antibiotic (fluoroquinolones)	bacterium	*Vibrio fischeri*	0.0223	EC50, 24 hrs	bioluminescence	Backhaus & Grimme (1999)
Norfloxacin	antibiotic (fluoroquinolones)	bacterium	*Vibrio fischeri*	0.0339	EC90, 24 hrs	bioluminescence	Backhaus & Grimme (1999)
Ofloxacin	antibiotic (fluoroquinolones)	bacterium	*Escherichia coli* mutant	0.001 - 0.002	LOEC, 2 hrs	genotoxicity (SOS-chromotest)	Kümmerer et al. (2000)
Ofloxacin	antibiotic (fluoroquinolones)	bacterium	*Escherichia coli* mutant	70	SOSIP (delta IF/nmol)	genotoxicity (SOS-chromotest)	Mersch-Sundermann et al. (1994)
Ofloxacin	antibiotic (fluoroquinolones)	bacterium	*Pseudomonas putida*	0.010	EC50, 16 hrs; gemiddeld (n=2)	growth inhibition	Kümmerer et al. (2000)
Ofloxacin	antibiotic (fluoroquinolones)	bacterium	*Pseudomonas putida*	0.040	EC100, 16 hrs; gemiddeld (n=2)	growth inhibition	Kümmerer et al. (2000)
Ofloxacin	antibiotic (fluoroquinolones)	bacterium	*Pseudomonas putida*	<0.010	NOEC, 16 hrs; gemiddeld (n=2)	growth inhibition	Kümmerer et al. (2000)
Ofloxacin	antibiotic (fluoroquinolones)	bacterium	*Vibrio fischeri*	0.0039	EC10, 24 hrs	bioluminescence	Backhaus & Grimme (1999)
Ofloxacin	antibiotic (fluoroquinolones)	bacterium	*Vibrio fischeri*	0.0135	EC50, 24 hrs	bioluminescence	Backhaus & Grimme (1999)
Ofloxacin	antibiotic (fluoroquinolones)	bacterium	*Vibrio fischeri*	0.0298	EC90, 24 hrs	bioluminescence	Backhaus & Grimme (1999)
Ofloxacin	antibiotic (fluoroquinolones)	bacteria	sensitive pathogens	0.0075	MIC50	growth inhibition	Kümmerer et al. (2000)
Ofloxacin	antibiotic (fluoroquinolones)	bacteria	from effluent of hospital stp	no effect	Colony Forming Units (n=2)	in Closed Bottle Test	Kümmerer et al. (2000)
Ofloxacin	antibiotic (fluoroquinolones)	bacteria	from effluent of hospital stp	weak, sign. effect	toxicity control (n=2)	in Closed Bottle Test	Kümmerer et al. (2000)
Pipemic acid	antibiotic (fluoroquinolones)	bacterium	*Escherichia coli* mutant	4.6	SOSIP (delta IF/nmol)	genotoxicity (SOS-chromotest)	Mersch-Sundermann et al. (1994)
Rosoxacin	antibiotic (fluoroquinolones)	bacterium	*Escherichia coli* mutant	85	SOSIP (delta IF/nmol)	genotoxicity (SOS-chromotest)	Mersch-Sundermann et al. (1994)
Sparfloxacin	antibiotic (fluoroquinolones)	bacterium	*Escherichia coli* mutant	2400	SOSIP (delta IF/nmol)	genotoxicity (SOS-chromotest)	Mersch-Sundermann et al. (1994)
Sulfadiazine	antibiotic (sulfonamides)	algae (freshwater)	*Selenastrum capricornutum*	7.8	EC50, 72 hrs	growth inhibition	Holten Lützhøft et al. (1999)
Sulfadiazine	antibiotic (sulfonamides)	algae (salt water)	*Rhodomonas salina*	403 (extrapolated)	EC50, 72 hrs	growth inhibition	Holten Lützhøft et al. (1999)
Sulfadiazine	antibiotic (sulfonamides)	cyanobacterium	*Mycrocystis aeruginosa*	0.135	EC50, 7 days	growth inhibition	Holten Lützhøft et al. (1999)
Sulfadiazine	antibiotic (sulfonamides)	crustacean (freshwater)	*Daphnia magna*	8.8	EC10, 21 days	reproduction	Wollenberger et al. (2000)

Pharmaceutical or metabolite	Therapeutic use	Test organism	Species	Toxicity (mg/l)	Effect, Time	Parameter	Reference
Sulfadiazine	antibiotic (sulfonamides)	crustacean (freshwater)	*Daphnia magna*	13.7	EC50, 21 days	reproduction	Wollenberger et al. (2000)
Sulfadiazine	antibiotic (sulfonamides)	crustacean (freshwater)	*Daphnia magna*	127	EC10, 48 hrs	immobility	Wollenberger et al. (2000)
Sulfadiazine	antibiotic (sulfonamides)	crustacean (freshwater)	*Daphnia magna*	150	LOEC, 24 hrs	immobility	Wollenberger et al. (2000)
Sulfadiazine	antibiotic (sulfonamides)	crustacean (freshwater)	*Daphnia magna*	221	EC50, 48 hrs	immobility	Wollenberger et al. (2000)
Sulfamethoxazole	antibiotic (sulfonamides)	bacterium	*Pseudomonas putida*	256	IC50, 16 hrs	growth inhibition	Al-Ahmad et al. (1999)
Sulfamethoxazole	antibiotic (sulfonamides)	bacteria	sensitive pathogens	0.002 - >256	MIC50	growth inhibition	Al-Ahmad et al. (1999)
Sulfamethoxazole	antibiotic (sulfonamides)	bacteria	from stp effluent close to hospitals	no effect	toxicity control	in Closed Bottle Test	Al-Ahmad et al. (1999)
Sulfamethoxazole	antibiotic (sulfonamides)	bacteria	from stp effluent close to hospitals	strong effect	Colony Forming Units	in Closed Bottle Test	Al-Ahmad et al. (1999)
Ornidazole	against protozoa (imidazoles)	bacterium	*Salmonella typhimurium*	5	LOEC (*umuC* IF = 2), 30 min	genotoxicity (umuC-test)	Hartmann et al. (1998)
Metronidazole	antibiotic, against protozoa (imidazoles)	algae (freshwater)	*Chlorella sp.*	12.5; 38.8; 45.1	EC50, 72 hrs (n=3)	growth inhibition (chlorofyl)	Lanzky & Halling-Sørensen (1997)
Metronidazole	antibiotic, against protozoa (imidazoles)	algae (freshwater)	*Chlorella sp.*	2.03; 4.41; 5.07	EC10, 72 hrs (n=3)	growth inhibition (chlorofyl)	Lanzky & Halling-Sørensen (1997)
Metronidazole	antibiotic, against protozoa (imidazoles)	algae (freshwater)	*Selenastrum capricornutum*	19.9; 21.7	EC10, 72 hrs (n=2)	growth inhibition (chlorofyl)	Lanzky & Halling-Sørensen (1997)
Metronidazole	antibiotic, against protozoa (imidazoles)	algae (freshwater)	*Selenastrum capricornutum*	39.1; 40.4	EC50, 72 hrs (n=2)	growth inhibition (chlorofyl)	Lanzky & Halling-Sørensen (1997)
Metronidazole	antibiotic, against protozoa (imidazoles)	bacterium	anaerob gram pos. cocci & *Clostridium sp.*	0.1 - 3.1	MIC	growth inhibition	Tally & Sullivan (1981)
Metronidazole	antibiotic, against protozoa (imidazoles)	bacterium	*Bacteroides fragilis*	0.2 - 3.1	MIC	growth inhibition	Tally & Sullivan (1981)
Metronidazole	antibiotic, against protozoa (imidazoles)	bacterium	*Bacteroides sp.*	1.0	MIC	growth inhibition	Pendland et al. (1994)
Metronidazole	antibiotic, against protozoa (imidazoles)	bacterium	*Escherichia coli* mutant	marginal (IF 1.8)	maximum effect after 2 hrs	genotoxicity (SOS-chromotest)	Kümmerer et al. (2000)
Metronidazole	antibiotic, against protozoa (imidazoles)	bacterium	gram neg. bacilli	0.1	MIC	growth inhibition	Tally & Sullivan (1981)
Metronidazole	antibiotic, against protozoa (imidazoles)	bacterium	*Pseudomonas putida*	64	NOEC, 16 hrs; average (n=2)	growth inhibition	Kümmerer et al. (2000)
Metronidazole	antibiotic, against protozoa (imidazoles)	bacterium	*Pseudomonas putida*	>64	EC50, 16 hrs; average (n=2)	growth inhibition	Kümmerer et al. (2000)
Metronidazole	antibiotic, against protozoa (imidazoles)	bacterium	*Pseudomonas putida*	>64	EC100, 16 hrs; average (n=2)	growth inhibition	Kümmerer et al. (2000)
Metronidazole	antibiotic, against protozoa (imidazoles)	bacterium	*Salmonella typhimurium*	50	LOEC (*umuC* IF = 2), 30 min	genotoxicity (umuC-test)	Hartmann et al. (1998)
Metronidazole	antibiotic, against protozoa (imidazoles)	bacteria	sensitive pathogens	0.060	MIC50	growth inhibition	Kümmerer et al. (2000)
Metronidazole	antibiotic, against protozoa (imidazoles)	bacteria	from effluent of hospital stp	no effect	Colony Forming Units (n=2)	in Closed Bottle Test	Kümmerer et al. (2000)
Metronidazole	antibiotic, against protozoa (imidazoles)	bacteria	from effluent of hospital stp	no effect	toxicity control (n=2)	in Closed Bottle Test	Kümmerer et al. (2000)
Metronidazole	antibiotic, against protozoa (imidazoles)	crustacean (freshwater)	*Daphnia magna*	250	NOEC, 21 days	reproduction	Wollenberger et al. (2000)
Metronidazole	antibiotic, against protozoa (imidazoles)	crustacean (freshwater)	*Daphnia magna*	1000	LOEC, 48 hrs	immobility	Wollenberger et al. (2000)
Metronidazole	antibiotic, against protozoa (imidazoles)	crustacean (salt water)	*Acartia tonsa*	100	NOEC	immobility	Lanzky & Halling-Sørensen (1997)
Metronidazole	antibiotic, against protozoa (imidazoles)	fish	*Brachydanio rerio*	500	NOEC, 96 hrs	death	Lanzky & Halling-Sørensen (1997)
1-(2-hydroxyethyl)-2-hydroxymethyl-	metabolite of Metronidazole (antibiotic)	bacterium	*Bacteroides sp.*	1.0 - 2.0	MIC	growth inhibition	Pendland et al. (1994)
2-methyl-5-nitroimidazole-1-acetic ac	metabolite of Metronidazole (antibiotic)	bacterium	not further specified	no effect	MIC	growth inhibition	Pendland et al. (1994)
Bacitracin	antibiotic (other categories)	crustacean (freshwater)	*Daphnia magna*	5	decrease	phototactic behaviour	di Delupis et al. (1992)
Bacitracin	antibiotic (other categories)	crustacean (freshwater)	*Daphnia magna*	126.4	EC50, 24 hrs	immobility	di Delupis et al. (1992)
Bacitracin	antibiotic (other categories)	crustacean (freshwater)	*Daphnia magna*	30.5	EC50, 48 hrs	immobility	Macri et al. (1998); di Delupis et al. (1992)
Chloramphenicol	antibiotic (other categories)	bacterium	*Vibrio fischeri*	0.0187	EC10, 24 hrs	bioluminescence	Backhaus & Grimme (1999)
Chloramphenicol	antibiotic (other categories)	bacterium	*Vibrio fischeri*	0.0643	EC50, 24 hrs	bioluminescence	Backhaus & Grimme (1999)
Chloramphenicol	antibiotic (other categories)	bacterium	*Vibrio fischeri*	0.129	EC90, 24 hrs	bioluminescence	Backhaus & Grimme (1999)
Chloramphenicol	antibiotic (other categories)	bacterium	*Vibrio fischeri*	*1696*	EC50, 5 min	bioluminescence	Calleja et al. (1993)
Chloramphenicol	antibiotic (other categories)	bacterium	*Vibrio harveyi*	0.16	EC50	bioluminescence	Thomulka et al. (1993)
Chloramphenicol	antibiotic (other categories)	crustacean (freshwater)	*Daphnia magna*	*1085*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Chloramphenicol	antibiotic (other categories)	crustacean (freshwater)	*Streptocephalus proboscideus*	*302*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Chloramphenicol	antibiotic (other categories)	crustacean (freshwater)	*Brachionus calyciflorus*	*2086*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Chloramphenicol	antibiotic (other categories)	crustacean (salt water)	*Artemia salina*	*2039*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Chloramphenicol	antibiotic (other categories)	fish, liver cells	*Oncorhynchus mykiss*	*3.55*	EC50, 3 hrs	toxicity (86Rb+ leakage)	Lilius et al. (1994)
Fosfomycin	antibiotic (other categories)	bacterium	*Vibrio fischeri*	5.32	EC10, 24 hrs	bioluminescence	Backhaus & Grimme (1999)
Fosfomycin	antibiotic (other categories)	bacterium	*Vibrio fischeri*	16.8	EC50, 24 hrs	bioluminescence	Backhaus & Grimme (1999)
Fosfomycin	antibiotic (other categories)	bacterium	*Vibrio fischeri*	35.3	EC90, 24 hrs	bioluminescence	Backhaus & Grimme (1999)
Fusidic acid	antibiotic (other categories)	bacterium	*Vibrio fischeri*	0.175	EC10, 24 hrs	bioluminescence	Backhaus & Grimme (1999)
Fusidic acid	antibiotic (other categories)	bacterium	*Vibrio fischeri*	1.68	EC50, 24 hrs	bioluminescence	Backhaus & Grimme (1999)
Fusidic acid	antibiotic (other categories)	bacterium	*Vibrio fischeri*	34.0	EC90, 24 hrs	bioluminescence	Backhaus & Grimme (1999)
Lincomycin	antibiotic (other categories)	crustacean (freshwater)	*Daphnia magna*	5	decrease	phototactic behaviour	Macri et al. (1998)
Lincomycin	antibiotic (other categories)	crustacean (freshwater)	*Daphnia magna*	379.4	EC50, 72 hrs	immobility	Macri et al. (1998); di Delupis et al. (1992)
Meropenem	antibiotic (other categories)	bacterium	*Pseudomonas putida*	<2	IC50, 16 hrs	growth inhibition	Al-Ahmad et al. (1999)
Meropenem	antibiotic (other categories)	bacteria	sensitive pathogens	0.008 - 16.0	MIC50	growth inhibition	Al-Ahmad et al. (1999)
Meropenem	antibiotic (other categories)	bacteria	from stp effluent close to hospitals	no effect	Colony Forming Units	in Closed Bottle Test	Al-Ahmad et al. (1999)
Meropenem	antibiotic (other categories)	bacteria	from stp effluent close to hospitals	weak, sign. effect	toxicity control	in Closed Bottle Test	Al-Ahmad et al. (1999)
Streptomycin	antibiotic (other categories)	algae (freshwater)	*Selenastrum capricornutum*	0.133	EC50, 3 days	growth inhibition (chlorofyl)	Halling-Sørensen (2000)
Streptomycin	antibiotic (other categories)	bacterium	*Vibrio fischeri*	2.25	EC10, 24 hrs	bioluminescence	Backhaus & Grimme (1999)
Streptomycin	antibiotic (other categories)	bacterium	*Vibrio fischeri*	8.21	EC50, 24 hrs	bioluminescence	Backhaus & Grimme (1999)
Streptomycin	antibiotic (other categories)	bacterium	*Vibrio fischeri*	18.8	EC90, 24 hrs	bioluminescence	Backhaus & Grimme (1999)
Streptomycin	antibiotic (other categories)	cyanobacterium	*Mycrocystis aeruginosa*	0.007	EC50, 7 days	growth inhibition (chlorofyl)	Halling-Sørensen (2000)
Streptomycin	antibiotic (other categories)	crustacean (freshwater)	*Daphnia magna*	32	NOEC, 21 days	reproduction	Wollenberger et al. (2000)

Pharmaceutical or metabolite	Therapeutic use	Test organism	Species	Toxicity (mg/l)	Effect, Time	Parameter	Reference
Streptomycin	antibiotic (other categories)	crustacean (freshwater)	*Daphnia magna*	64	EC100, 19 days	death	Wollenberger et al. (2000)
Streptomycin	antibiotic (other categories)	crustacean (freshwater)	*Daphnia magna*	120	EC10, 48 hrs	immobility	Wollenberger et al. (2000)
Streptomycin	antibiotic (other categories)	crustacean (freshwater)	*Daphnia magna*	408	EC10, 24 hrs	immobility	Wollenberger et al. (2000)
Streptomycin	antibiotic (other categories)	crustacean (freshwater)	*Daphnia magna*	487	EC50, 48 hrs	immobility	Wollenberger et al. (2000)
Streptomycin	antibiotic (other categories)	crustacean (freshwater)	*Daphnia magna*	947	EC50, 24 hrs	immobility	Wollenberger et al. (2000)
Streptomycin sulfate	antibiotic (other categories)	algae	*Ankistrodesmus sp.*	6.6	MIC	growth inhibition	Harrass et al. (1985)
Streptomycin sulfate	antibiotic (other categories)	algae	*Chlamydomonas reinhardtii*	0.66	MIC	growth inhibition	Harrass et al. (1985)
Streptomycin sulfate	antibiotic (other categories)	algae	*Pediastrum sp.*	2.1	MIC	growth inhibition	Harrass et al. (1985)
Streptomycin sulfate	antibiotic (other categories)	algae	*Stigeoclonium sp.*	6.6	MIC	growth inhibition	Harrass et al. (1985)
Streptomycin sulfate	antibiotic (other categories)	algae	*Ulothrix sp.*	21.0	MIC	growth inhibition	Harrass et al. (1985)
Streptomycin sulfate	antibiotic (other categories)	algae (freshwater)	*Chlorella vulgaris*	66	MIC	growth inhibition	Harrass et al. (1985)
Streptomycin sulfate	antibiotic (other categories)	algae (freshwater)	*Scenedesmus obliquus*	21.0	MIC	growth inhibition	Harrass et al. (1985)
Streptomycin sulfate	antibiotic (other categories)	algae (freshwater)	*Selenastrum capricornutum*	2.1	MIC	growth inhibition	Harrass et al. (1985)
Streptomycin sulfate	antibiotic (other categories)	cyanobacterium	*Anabaena cylindrica*	0.26	MIC	growth inhibition	Harrass et al. (1985)
Streptomycin sulfate	antibiotic (other categories)	cyanobacterium	*Anabaena flos-aquae*	0.26	MIC	growth inhibition	Harrass et al. (1985)
Streptomycin sulfate	antibiotic (other categories)	cyanobacterium	*Aphanizomenon flos-aquae*	0.86	MIC	growth inhibition	Harrass et al. (1985)
Streptomycin sulfate	antibiotic (other categories)	cyanobacterium	*Lyngbya sp.*	0.09	MIC	growth inhibition	Harrass et al. (1985)
Streptomycin sulfate	antibiotic (other categories)	cyanobacterium	*Mycrocystis aeruginosa*	0.26	MIC	growth inhibition	Harrass et al. (1985)
Streptomycin sulfate	antibiotic (other categories)	cyanobacterium	*Oscillatoria tenuis*	0.26	MIC	growth inhibition	Harrass et al. (1985)
Streptomycin sulfate	antibiotic (other categories)	diatom	*Navicula sp.*	6.6	MIC	growth inhibition	Harrass et al. (1985)
Trimetroprim	antibiotic (other categories)	algae (freshwater)	*Selenastrum capricornutum*	130	EC50, 72 hrs	growth inhibition (chlorofyl)	Holten Lützhøft et al. (1999)
Trimetroprim	antibiotic (other categories)	algae (salt water)	*Rhodomonas salina*	16	EC50, 72 hrs	growth inhibition (chlorofyl)	Holten Lützhøft et al. (1999)
Trimetroprim	antibiotic (other categories)	cyanobacterium	*Mycrocystis aeruginosa*	112	EC50, 7 days	growth inhibition (chlorofyl)	Holten Lützhøft et al. (1999)
Chloroquine phosphate	antiparasitic (against malaria)	bacterium	*Vibrio fischeri*	*856*	EC50, 5 min	bioluminescence	Calleja et al. (1993)
Chloroquine phosphate	antiparasitic (against malaria)	crustacean (freshwater)	*Daphnia magna*	*42.9*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Chloroquine phosphate	antiparasitic (against malaria)	crustacean (freshwater)	*Streptocepahalus proboscideus*	*11.3*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Chloroquine phosphate	antiparasitic (against malaria)	crustacean (freshwater)	*Brachionus calyciflorus*	*3.26*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Chloroquine phosphate	antiparasitic (against malaria)	crustacean (salt water)	*Artemia salina*	*2054*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Chloroquine phosphate	antiparasitic (against malaria)	fish, liver cells	*Oncorhynchus mykiss*	*20976*	EC50, 3 hrs	toxicity (86Rb+ leakage)	Lilius et al. (1994)
Pyrimethamine	antiparasitic (against malaria)	algae (freshwater)	*Chlorella pyrenoidosa*	20	EC50, 48 hrs	growth inhibition	Canton & van Esch (1976)
Pyrimethamine	antiparasitic (against malaria)	bacterium	*Vibrio fischeri*	25	EC50, 24 hrs	bioluminescence	Backhaus & Grimme (1999)
Pyrimethamine	antiparasitic (against malaria)	crustacean (freshwater)	*Daphnia magna*	4.8	EC50, 48 hrs	immobility	Canton & van Esch (1976)
Pyrimethamine	antiparasitic (against malaria)	crustacean (freshwater)	*Daphnia magna*	5.8	LC50, 48 hrs	death	Canton & van Esch (1976)
Pyrimethamine	antiparasitic (against malaria)	fish	*Lebistes reticulatus*	7.5	LC50, 48 hrs	death	Canton & van Esch (1976)
Pyrimethamine	antiparasitic (against malaria)	fish	*Salmo gairdneri*	5.9	LC50, 48 hrs	death	Canton & van Esch (1976)

Pharmaceutical or metabolite	Therapeutic use	Test organism	Species	Toxicity (mg/l)	Effect, Time	Parameter	Reference
Antidepressants and other psychiatric pharmaceuticals							
Amitriptyline	antidepressant	bacterium	*Vibrio fischeri*	*21.5*	EC50, 5 min	bioluminescence	Calleja et al. (1993)
Amitriptyline	antidepressant	crustacean (freshwater)	*Daphnia magna*	*4.93*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Amitriptyline	antidepressant	crustacean (freshwater)	*Daphnia magna*	1.1	EC50 (acute)	immobility	In: Römbke et al. (1996)
Amitriptyline	antidepressant	crustacean (freshwater)	*Daphnia magna*	5	EC50 (acute)	immobility	In: Römbke et al. (1996)
Amitriptyline	antidepressant	crustacean (freshwater)	*Daphnia magna*	5.0	EC50 (acute?)	immobility	Lilius et al. (1995)
Amitriptyline	antidepressant	crustacean (freshwater)	*Streptocepahalus proboscideus*	*0.76*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Amitriptyline	antidepressant	crustacean (freshwater)	*Brachionus calyciflorus*	*0.80*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Amitriptyline	antidepressant	crustacean (salt water)	*Artemia salina*	*36.6*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Amitriptyline	antidepressant	fish, liver cells	*Oncorhynchus mykiss*	*132*	EC50, 3 hrs	toxicity (86Rb+ leakage)	Lilius et al. (1994)
Fluoxetine (Prozac)	antidepressant	mussel	*Dreissena polymorpha*	~ 1.50 (10^{-6}M)	significant stimulation females	spawning	Fong (1998)
Fluoxetine (Prozac)	antidepressant	mussel	*Dreissena polymorpha*	~ 0.150 (10^{-7}M)	significant stimulation males	spawning	Fong (1998)
Fluoxetine (Prozac)	antidepressant	mussel	*Sphaerium striatinum*	>150 (>100 µM)	NOEC, 4 hrs	stim. reproduction ('parturation')	Fong et al. (1998)
Fluvoxamine (Luvox)	antidepressant	mussel	*Dreissena polymorpha*	~ 0.0318 (10^{-7}M)	significant stimulation females	spawning	Fong (1998)
Fluvoxamine (Luvox)	antidepressant	mussel	*Dreissena polymorpha*	~ 0.000318 (10^{-9}M)	significant stimulation males	spawning	Fong (1998)
Fluvoxamine (Luvox)	antidepressant	mussel	*Sphaerium striatinum*	~0.00318 (10 nM)	LOEC, 4 hrs	stim. reproduction ('parturation')	Fong et al. (1998)
Lithium sulfate	antidepressant	bacterium	*Vibrio fischeri*	*18660*	EC50, 5 min	bioluminescence	Calleja et al. (1993)
Lithium sulfate	antidepressant	crustacean (freshwater)	*Daphnia magna*	*33.2*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Lithium sulfate	antidepressant	crustacean (freshwater)	*Streptocepahalus proboscideus*	*112*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Lithium sulfate	antidepressant	crustacean (freshwater)	*Brachionus calyciflorus*	*709*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Lithium sulfate	antidepressant	crustacean (salt water)	*Artemia salina*	*4275*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Lithium sulfate	antidepressant	fish, liver cells	*Oncorhynchus mykiss*	*106803*	EC50, 3 hrs	toxicity (86Rb+ leakage)	Lilius et al. (1994)
Loxapine succinate	antidepressant	bacterium	*Salmonella* (TA1535, 1537, 98 & 100)	no effect		genotoxicity (Ames-test)	Stoyanov et al. (1987)
Paroxetine (Paxil)	antidepressant	mussel	*Dreissena polymorpha*	no effect	significant stimulation (M/V)	spawning	Fong (1998)
Paroxetine (Paxil)	antidepressant	mussel	*Sphaerium striatinum*	*only at 3.3 (10 µM)*	EC, 4 hrs (at 10nM - 100µM)	stim. reproduction ('parturation')	Fong et al. (1998)
Thioridazine HCl	antidepressant	bacterium	*Vibrio fischeri*	*0.63*	EC50, 5 min	bioluminescence	Calleja et al. (1993)
Thioridazine HCl	antidepressant	crustacean (freshwater)	*Daphnia magna*	*4.46*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Thioridazine HCl	antidepressant	crustacean (freshwater)	*Streptocepahalus proboscideus*	*0.33*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Thioridazine HCl	antidepressant	crustacean (freshwater)	*Brachionus calyciflorus*	*0.26*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Thioridazine HCl	antidepressant	crustacean (salt water)	*Artemia salina*	*14.4*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Thioridazine HCl	antidepressant	fish, liver cells	*Oncorhynchus mykiss*	*16.3*	EC50, 3 hrs	toxicity (86Rb+ leakage)	Lilius et al. (1994)
Viloxazine hydrocloride	antidepressant	bacterium	*Salmonella* (TA1535, 1537, 98 & 100)	no effect		genotoxicity (Ames-test)	Stoyanov et al. (1987)
Diazepam	psychiatric drug (benzodiapines)	crustacean (freshwater)	*Daphnia magna*	4.2	LC50 (active ingredient)	death	Calleja et al. (1993)
Diazepam	psychiatric drug (benzodiapines)	crustacean (freshwater)	*Daphnia magna*	4.3	EC50 (acute)	immobility	Calleja et al. (1993)
Diazepam	psychiatric drug (benzodiapines)	crustacean (freshwater)	*Daphnia magna*	*13.9*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Diazepam	psychiatric drug (benzodiapines)	crustacean (freshwater)	*Daphnia magna*	*14.1*	LC50 (formulation)	death	Calleja et al. (1993)
Diazepam	psychiatric drug (benzodiapines)	crustacean (freshwater)	*Daphnia magna*	*4.3 - 14.0*	EC50 (acute)	immobility	Lilius et al. (1995)
Diazepam	psychiatric drug (benzodiapines)	crustacean (freshwater)	*Streptocepahalus proboscideus*	*101*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Diazepam	psychiatric drug (benzodiapines)	crustacean (salt water)	*Artemia salina*	*53.7*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Diazepam	psychiatric drug (benzodiapines)	fish, liver cells	*Oncorhynchus mykiss*	*659*	EC50, 3 hrs	toxicity (86Rb+ leakage)	Lilius et al. (1994)

Pharmaceutical or metabolite	Therapeutic use	Test organism	Species	Toxicity (mg/l)	Effect, Time	Parameter	Reference
Iodinated X-ray contrasting agent							
Iohexol	Iodinated X-ray contrasting agent	bacterium	*Pseudomonas putida*	>1000	NOEC, 16 hrs	growth inhibition	Steger-Hartmann et al. (1996)
Iohexol	Iodinated X-ray contrasting agent	crustacean (freshwater)	*Daphnia magna*	>100	NOEC, 24 hrs	immobility	Steger-Hartmann et al. (1996)
Iohexol	Iodinated X-ray contrasting agent	crustacean (freshwater)	*Daphnia magna*	>100	NOEC, 48 hrs	immobility	Steger-Hartmann et al. (1996)
Iopromide	Iodinated X-ray contrasting agent	algae (freshwater)	*Scenedesmus subspicatus*	>10000	EC10, 72 hrs	biomass	Steger-Hartmann et al. (1996)
Iopromide	Iodinated X-ray contrasting agent	algae (freshwater)	*Scenedesmus subspicatus*	>10000	EC10, 72 hrs	growth rate	Steger-Hartmann et al. (1996)
Iopromide	Iodinated X-ray contrasting agent	bacterium	*Pseudomonas putida*	>10000	NOEC, 16 hrs	growth inhibition	Steger-Hartmann et al. (1996)
Iopromide	Iodinated X-ray contrasting agent	bacterium	*Vibrio fischeri*	>10000	NOEC, 30 min	bioluminescence	Steger-Hartmann et al. (1996)
Iopromide	Iodinated X-ray contrasting agent	crustacean (freshwater)	*Daphnia magna*	>1000	NOEC, 22 days	death	Steger-Hartmann et al. (1996)
Iopromide	Iodinated X-ray contrasting agent	crustacean (freshwater)	*Daphnia magna*	>1000	NOEC, 22 days	reproduction	Steger-Hartmann et al. (1996)
Iopromide	Iodinated X-ray contrasting agent	crustacean (freshwater)	*Daphnia magna*	>10000	NOEC, 24 hrs	immobility	Steger-Hartmann et al. (1996)
Iopromide	Iodinated X-ray contrasting agent	crustacean (freshwater)	*Daphnia magna*	>10000	NOEC, 48 hrs	immobility	Steger-Hartmann et al. (1996)
Iopromide	Iodinated X-ray contrasting agent	fish	*Danio rerio*	>10000	NOEC, 96 hrs	death	Steger-Hartmann et al. (1996)
Iopromide	Iodinated X-ray contrasting agent	fish	*Leuciscus idus melanotus*	>10000	NOEC, 48 hrs	death	Steger-Hartmann et al. (1996)
Iotrolan	Iodinated X-ray contrasting agent	algae (freshwater)	*Scenedesmus subspicatus*	>10000	EC10, 72 hrs	biomass	Steger-Hartmann et al. (1996)
Iotrolan	Iodinated X-ray contrasting agent	algae (freshwater)	*Scenedesmus subspicatus*	>10000	EC10, 72 hrs	growth rate	Steger-Hartmann et al. (1996)
Iotrolan	Iodinated X-ray contrasting agent	bacterium	*Pseudomonas putida*	>10000	NOEC, 16 hrs	growth inhibition	Steger-Hartmann et al. (1996)
Iotrolan	Iodinated X-ray contrasting agent	bacterium	*Vibrio fischeri*	>10000	NOEC, 30 min	bioluminescence	Steger-Hartmann et al. (1996)
Iotrolan	Iodinated X-ray contrasting agent	crustacean (freshwater)	*Daphnia magna*	>1000	NOEC, 22 days	death	Steger-Hartmann et al. (1996)
Iotrolan	Iodinated X-ray contrasting agent	crustacean (freshwater)	*Daphnia magna*	>1000	NOEC, 22 days	reproduction	Steger-Hartmann et al. (1996)
Iotrolan	Iodinated X-ray contrasting agent	crustacean (freshwater)	*Daphnia magna*	>10000	NOEC, 24 hrs	immobility	Steger-Hartmann et al. (1996)
Iotrolan	Iodinated X-ray contrasting agent	crustacean (freshwater)	*Daphnia magna*	>10000	NOEC, 48 hrs	immobility	Steger-Hartmann et al. (1996)
Iotrolan	Iodinated X-ray contrasting agent	fish	*Danio rerio*	>10000	NOEC, 96 hrs	death	Steger-Hartmann et al. (1996)
Iotrolan	Iodinated X-ray contrasting agent	fish	*Leuciscus idus melanotus*	>10000	NOEC, 48 hrs	death	Steger-Hartmann et al. (1996)
Meglumin amidotrizoate	Iodinated X-ray contrasting agent	bacterium	*Pseudomonas putida*	>1000	NOEC, 16 hrs	growth inhibition	Steger-Hartmann et al. (1996)
Meglumin amidotrizoate	Iodinated X-ray contrasting agent	crustacean (freshwater)	*Daphnia magna*	>100	NOEC, 24 hrs	immobility	Steger-Hartmann et al. (1996)
Meglumin amidotrizoate	Iodinated X-ray contrasting agent	crustacean (freshwater)	*Daphnia magna*	>100	NOEC, 48 hrs	immobility	Steger-Hartmann et al. (1996)

Pharmaceutical or metabolite	Therapeutic use	Test organism	Species	Toxicity (mg/l)	Effect, Time	Parameter	Reference
Other pharmaceuticals							
Atropine sulfate	spasmolytic (dilates the eye pupil)	bacterium	*Vibrio fischeri*	*5519*	EC50, 15 min	bioluminescence	Calleja et al. (1993)
Atropine sulfate	spasmolytic (dilates the eye pupil)	crustacean (freshwater)	*Daphnia magna*	*356*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Atropine sulfate	spasmolytic (dilates the eye pupil)	crustacean (freshwater)	*Daphnia magna*	258.5	EC50 (acute)	immobility	In: Römbke et al. (1996)
Atropine sulfate	spasmolytic (dilates the eye pupil)	crustacean (freshwater)	*Daphnia magna*	354.4	EC50 (acute)	immobility	In: Römbke et al. (1996)
Atropine sulfate	spasmolytic (dilates the eye pupil)	crustacean (freshwater)	*Streptocepahalus proboscideus*	*864*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Atropine sulfate	spasmolytic (dilates the eye pupil)	crustacean (freshwater)	*Brachionus calyciflorus*	*325*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Atropine sulfate	spasmolytic (dilates the eye pupil)	crustacean (salt water)	*Artemia salina*	*15556*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Atropine sulfate	spasmolytic (dilates the eye pupil)	fish, liver cells	*Oncorhynchus mykiss*	*11694*	EC50, 3 hrs	toxicity (86Rb+ leakage)	Lilius et al. (1994)
Cetrimonium bromide	desinfectant	bacterium	*Vibrio fischeri*	1.62	EC10, 24 hrs	bioluminescence	Backhaus & Grimme (1999)
Cetrimonium bromide	desinfectant	bacterium	*Vibrio fischeri*	2.21	EC50, 24 hrs	bioluminescence	Backhaus & Grimme (1999)
Cetrimonium bromide	desinfectant	bacterium	*Vibrio fischeri*	2.51	EC90, 24 hrs	bioluminescence	Backhaus & Grimme (1999)
Theophylline	pharmaceutical to treat asthma and bronchitis	bacterium	*Vibrio fischeri*	*2486*	EC50, 5 min	bioluminescence	Calleja et al. (1993)
Theophylline	pharmaceutical to treat asthma and bronchitis	crustacean (freshwater)	*Daphnia magna*	*474*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Theophylline	pharmaceutical to treat asthma and bronchitis	crustacean (freshwater)	*Daphnia magna*	155.1	EC50 (acute)	immobility	In: Römbke et al. (1996)
Theophylline	pharmaceutical to treat asthma and bronchitis	crustacean (freshwater)	*Daphnia magna*	473.6	EC50 (acute)	immobility	In: Römbke et al. (1996)
Theophylline	pharmaceutical to treat asthma and bronchitis	crustacean (freshwater)	*Streptocepahalus proboscideus*	*422*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Theophylline	pharmaceutical to treat asthma and bronchitis	crustacean (freshwater)	*Brachionus calyciflorus*	*2854*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Theophylline	pharmaceutical to treat asthma and bronchitis	crustacean (salt water)	*Artemia salina*	*8043*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Theophylline	pharmaceutical to treat asthma and bronchitis	fish, liver cells	*Oncorhynchus mykiss*	*<solubility*	EC50, 3 hrs	toxicity (86Rb+ leakage)	Lilius et al. (1994)
Orphenadrine	tranquilizer (used for Parkinson disease)	bacterium	*Vibrio fischeri*	*368*	EC50, 5 min	bioluminescence	Calleja et al. (1993)
Orphenadrine	tranquilizer (used for Parkinson disease)	crustacean (freshwster)	*Daphnia magna*	*10.4*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Orphenadrine	tranquilizer (used for Parkinson disease)	crustacean (freshwater)	*Daphnia magna*	8.9	EC50 (acute)	immobility	In: Römbke et al. (1996)
Orphenadrine	tranquilizer (used for Parkinson disease)	crustacean (freshwater)	*Daphnia magna*	10.4	EC50 (acute)	immobility	In: Römbke et al. (1996)
Orphenadrine	tranquilizer (used for Parkinson disease)	crustacean (freshwater)	*Streptocepahalus proboscideus*	*4.32*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Orphenadrine	tranquilizer (used for Parkinson disease)	crustacean (freshwater)	*Brachionus calyciflorus*	*5.31*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Orphenadrine	tranquilizer (used for Parkinson disease)	crustacean (salt water)	*Artemia salina*	*44.2*	EC50, 24 hrs	immobility	Calleja et al. (1993)
Orphenadrine	tranquilizer (used for Parkinson disease)	fish, liver cells	*Oncorhynchus mykiss*	*287*	EC50, 3 hrs	toxicity (86Rb+ leakage)	Lilius et al. (1994)

Colophon

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RIWA

Groenendael 6
NL - 3439 LV Nieuwegein
t + 31 30 600 90 30
f + 31 30 600 90 39
e riwa@riwa.org
w www.riwa.org