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SCIENTIFIC COMMITTEE ON TOXICITY, ECOTOXICITY AND THE ENVIRONMENT (CSTEE)

Opinion on:

Draft CPMP Discussion Paper on

Environmental Risk Assessment of Medicinal Products for Human Use [Non-Genetically Modified Organism (Non-GMO) Containing]

expressed at the 24th CSTEE plenary meeting

Brussels, 12 June 2001

Terms of reference

A request for comments from the Committee for Proprietary Medicinal Products (CPMP) of the European Agency for the Evaluation of Medicinal Products (EMEA) was received by the CSTEE secretariat at 9-2-01. This CPMP draft on "environmental risk assessment of non-genetically modified organism (non-GMO) containing medicinal products for human use" (CPMP, 2001) was distributed at the same date. This request for comments was first discussed at the CSTEE plenary meeting at 6/7-3-01 and at a meeting of a working group of the CSTEE held on June 6th.

General comments on the CPMP discussion paper

1. The CSTEE would like to stress the relevance of evaluating the potential environmental risks of pharmaceuticals. It has been noted that some human pharmaceuticals are used in large volumes (> 100 tonnes/year in the EU), have a widespread use and may give rise to acute and chronic ecotoxicological effects in the aquatic environment. The CSTEE therefore welcomes the discussion paper by the CPMP. In order to provide comments on this CPMP draft the CSTEE decided, as an exception, to make a short literature review of the environmental risks of pharmaceuticals on the basis of a quick scan of easily obtainable literature (Annex 1). This quick scan was aimed at providing a context for the opinion of the CSTEE.

2. Drugs that are present in rivers and streams may have adverse effects on aquatic organisms. Currently, an in depth analysis of the environmental risks of pharmaceuticals is not possible. The risk assessment of human pharmaceuticals is hindered by the general lack of information on their use, fate and environmental effects. A proactive approach is needed to obtain these data. In case exposure of the environment is likely to occur, the CSTEE advises to use the base set for the assessment of their environmental risks. This base set is required for the notification of new industrial chemicals (Table 1). It is likely that this base set will suffice for most (≥ 90 %) of the pharmaceuticals and that further environmental data will not be required (Webb, 2000; see Annex 1).

3. As a result of the widespread dispersion and high use volumes of some drugs, they are likely to have a more or less constant presence in low concentrations in European rivers and other water bodies. Although the information is scarce, this is supported by measurements in surface waters. Chronic effects rather than acute toxic effects in these ecosystems are most likely. However, the CPMP paper focuses on acute effects.

4. Compared to other fields of environmental legislation, i.e. new industrial chemicals (Council Directive 67/548/EEC) and existing chemicals (Council Regulation No 793/93) the requirement to submit information on human pharmaceuticals in order to allow the assessment of their environmental risks is limited. This is unjustified from a scientific point of view as some human pharmaceuticals are: used in high volumes (some pharmaceuticals are used in quantities exceeding 100 tonnes in the EU on an annual basis), have a specific mode of therapeutic/toxic action likely to be relevant to other organisms, are

directly or indirectly discharged into the aquatic environment, and have been detected in surface waters at significant concentrations. They may pose a serious chronic risk to a variety of aquatic ecosystems. It should be noted that these observations are not restricted to endocrine disrupting compounds (eg. anticonceptives) only.

5. The scheme proposed by CPMP is not a complete coverage. Thus the scope of the CPMP paper is only relevant for a part of the substance life cycle: i.e. the use and disposal phase of pharmaceuticals. Risk assessment for the production and formulation phases is excluded from the CPMP proposal. The CSTEE acknowledges the practical value of this approach and recommends for pharmaceuticals that the same risk assessment methodologies are employed for the production and formulation phases as used for industrial chemicals.

6. For existing pharmaceuticals, it is recognised that a prioritisation procedure needs to be developed for their environmental risk assessment. To ensure further harmonisation, this procedure should be in line with the general scheme for chemicals as described in the White Paper, i.e. the strategy for a future chemicals policy of the Commission (2001). Additionally, the specific environmental concern of certain groups of pharmaceuticals must be taken into account when setting these priorities. In particular, pharmaceuticals with endocrine disruptive activity; reprotoxic, mutagenic, immunotoxic chemicals and antimicrobials, require special attention. Furthermore, in order to assess the exposure not only on the basis of production volumes, but also on expected environmental emissions the available pharmacokinetic information must be used to quantify emissions to the environment of parent compounds and metabolites.

7. The CSTEE recognises that the concerns expressed in this opinion are also applicable to the guideline on environmental risk assessment of veterinary medicines. An in-depth revision of the guidelines for veterinary medicines, in line with the current state of the science, is recommended. Following the opinion of the SSC the harmonisation of the EU guidelines for risk assessment should be given a high priority.

8. The general environmental legislation on chemicals, including classification and labelling, the associated downstream legislation, the need for comprehensive risk assessment for production and formulation triggered by production volumes, etc., etc. must also be applicable to pharmaceuticals. The base set data requirements (Table 1), together with the knowledge of the effects of structural analogues needs to be used for the identification of the potential environmental hazards.

Specific comments on the CPMP discussion paper

1. The CSTEE agrees to the particular focus of the CPMP discussion paper on the aquatic environment. Although other environmental compartments (air, soil and groundwater) may be at risk, the CSTEE endorses, at this stage, the focus on sewage and /or sewage treatment plants (STPs) as the main emission routes to the environment.

2. For those drugs (and their metabolites) which are persistent and adsorb to sewage sludge, indirect exposure of the terrestrial environment may occur as a result of the application of sewage sludge on agricultural land. This exposure route has not been addressed in the CPMP discussion paper.

3. For any valid assessment of environmental risk use information on pharmaceuticals is essential. This information can be used to decide if exposure of STPs and/or surface waters will occur. If this information shows that exposure to the aquatic environment would indeed occur, basic ecotoxicological information would be required. This information (short-term toxicity to bacteria, algae, daphnids and fish) may then be used to perform a preliminary risk assessment. If, on the basis of this risk assessment, it is concluded that risks may occur, further information may be required in order to refine the risk assessment. This may be additional information on emissions and fate to refine the exposure assessment (predicted environmental concentration or PEC) or chronic ecotoxicological information to refine the effects assessment (predicted no effect concentration or PNEC). Such a tiered approach: (1) preliminary, (2) refined and (3) comprehensive risk assessment is used in both the EU and OECD for risk assessment of industrial chemicals. Such a tiered approach of risk assessment requires information on the use volumes and use patterns as a start. This information is not readily available for pharmaceuticals.

4. The use volume, use-pattern (widespread use and discharge into surface waters and or sewage treatment plants) and, in some cases, the persistence of the pharmaceuticals or their metabolites or degradation products, necessitates research into their long-term environmental risks. Data requirements should be tailored to this. In the CPMP paper the focus is on acute effects and no clear guidance for further research is provided in case of relevant (acute) risks.

5. There may be a need to take into account even low production volume substances if they are used continuously over long periods.

6. The trigger concentration approach (0.01 µg/L) proposed by the CPMP is not scientifically validated. Some pharmaceuticals are known to have effects at lower concentrations (annex 1). The scheme lacks guidance in case the trigger value is exceeded, e.g. on further tests required for fate and effects and on how to integrate this information into a sound tiered risk assessment approach ([1]). The action limit proposed by the CPMP may be underprotective for some highly ecotoxic pharmaceuticals in the case of pseudoestrogens or genotoxic products or be very overprotective for pharmaceuticals which are harmless to the environment. Therefore, it is neither efficient nor effective. Currently there are better alternatives (not necessarily in this order):
   - A scheme along the lines proposed by the US Department of Health and Human Services, Food and Drug Administration (http://www.fda.gov/cder/guidance/1730fnl.pdf) is a good alternative. The scheme presented in Figure 1 of the US FDA (Annex 2) has the advantages

[1] *If, for instance, a persistent substance has a low binding affinity to particles (a low Koc or low adsorption coefficient), the EUSES model predicts that the emission of 1 kg per day to an STP will result in a concentration in surface water of 50 µg/L. This implies that the use of such a drug at a quantity of >200 mg/day will exceed the action limit of 0.01µg/L.*

that it: (a) focuses on exposure, (b) takes processes (microbial inhibition) in sewage treatment plants into account, (c) is a tiered approach, starting with simple acute tests and if necessary continues with chronic tests, and (d) uses internationally harmonised assessment factors.

- The EU risk assessment methodologies for new and existing industrial chemicals which is described in the so-called Technical Guidance Documents (TGD, 1996) can be applied and a computer programme is available (EUSES, 1997). This approach has the advantage that it is (a) an integrated approach to environmental risk assessment, (b) has been developed by the Commission, Member States and Industry, (c) is regularly updated (every 5-7 years), (d) uses a tiered approach to risk assessment, (e) uses the base set as input data thereby referring to internationally agreed OECD test guidelines, (f) includes an STP model which allows the calculation of an exposure concentration in surface water by using in an integrated manner information on use and fate of the chemical. The EUSES model can be used both for local and regional risk assessments.
- The Greater-ER model (Boeije et al., 1997). This is a more specific exposure model, which can be applied for site-specific (GIS-related) predictions of concentration in the aquatic environment. The model is very advanced, has been developed by industry in collaboration with a few modelling expertise centres (universities) in Europe but requires quite some information. It can be linked with effects assessment approaches such as the one described in the TGD. For risk assessment of pharmaceuticals it may be a step too far.

7. By applying the principles laid down in the TGD for new and existing chemicals to those of pharmaceuticals, which may be emitted to the environment, it is also possible to address the issue of additional information in case the PEC/PNEC ratio exceeds the value of 1. The current CPMP draft procedure could also benefit from this, as the required additional information has not been specified in detail.

8. No guidance is provided on the inclusion of metabolites in the environmental risk assessment. No definition is provided on major metabolites and on relevant metabolites. In the guidance document developed by DG Sanco (Sanco/221/2000-rev. 3 March 2001) the following definition is given for major metabolites: *all metabolites, degradation and reaction products that are formed in amounts of ≥ 10% of the applied amount of substance of active ingredient at any timepoint evaluated during the degradation studies in the appropriate compartment (i.e. soil, water and/or sediment) under consideration.* The CSTEE is of the opinion however that it is not appropriate to define a "major metabolite" by its percentage in the excreta alone. Major metabolites should be those which, following excretion, may produce significant adverse effects on environmental species. In making this judgement attention should also be paid to the metabolites which may be transformed in the environment to active moieties (for example hydrolysis of conjugates, reduction of oxidised thiol groups).

9. Excipients may occur at relatively high concentrations. Although generally they are likely not to pose a risk to human health, their environmental risks may be relevant and may need to be assessed as well.

10. It is accepted that the use of drugs that are important in human medicine must be continued (page 2 of the CPMP draft). Nonetheless a proper environmental risk assessment will indicate the need for management measures, including risk reduction and risk mitigation practices.

11. The calculation method for PEC in surface water is not appropriate. Reference is made to approaches described in the TGD. The TGD is currently being updated, involving the methodology for deriving PNECs.

12. The CSTEE notes that labelling of products in order to protect the environment is used in other spheres, e.g. the preparations directive (88/379/EEC). To enhance consumer/patient understanding a harmonised approach to labelling is essential

13. The issue of mixture toxicity is not addressed. The CSTEE notes that the Commission is actively involved in developing a strategy for assessing mixture toxicity. The CSTEE recommends EMEA to develop a procedure for assessing the environmental impacts for those medicinal products that have a common mode of action. We note that some human medicinal products are also used as veterinary medicines or growth promoters. It is important in assessing the risks of human pharmaceuticals that these other sources of environmental exposure are also taken into account.

Conclusions

1. The CSTEE welcomes the discussion paper of the EMEA on environmental risk assessment of pharmaceuticals and is willing to participate in further development of this initiative.

2. The CSTEE endorses the view of the EMEA that procedures need to be introduced to assess the environmental risk posed by medicinal products for human use.

3. There have been very few investigations which identify the levels of pharmaceutical products in the environment and their environmental impacts. However, the CSTEE has concluded a brief literature research which indicates a potential environmental risk of certain medicinal products (Annex 1).

4. It is noted that the EMEA report does not indicate whether the proposed procedure should apply only to new products or also to existing products. The CSTEE recommends that an assessment is conducted of the environmental risk from all medicinal products for which there is substantial use, both prescription only medicines and over the counter preparations (OTCs). However it is appreciated that to complete all the necessary assessments is a large task. The CSTEE therefore provides some initial guidance for establishing priorities for risk assessment.

5. The CSTEE agrees that consideration of the aquatic compartment is particularly important. However since it is widespread practice to dispose of sewage sludge to land, impact on terrestrial ecosystems must also be evaluated.

6. In the view of the CSTEE the proposed threshold of 0.01µg/l is not scientifically based. Several pharmaceuticals have been identified that have adverse environmental impacts below this concentration (Annex 1).

7. The CSTEE recommends the CPMP to adopt the environmental risk assessment methodologies described in the Technical Guidance Documents for risk assessment of industrial chemicals. The TGD is better supported, scientifically and the result of a consensus approach based on an effective dialogue between Industry, the EU Member States and the Commission. Moreover, the methodologies described in the TGD can be easily adapted for medicinal products. The adoption of the same data requirements and the same risk assessment methodologies for human pharmaceuticals would also save time and resources and would also lead to a further harmonisation of risk assessment methodologies used in the European Union.

8. The CSTEE proposes that the fate and effects of both the active principal and important major metabolites must be taken into account. Initial guidance for such major metabolites is given.

9. Medicinal products are biologically active and may affect other biological functions than those in the treated patients. For example, the risks for biological processes in STPs are a clear target for all anti-microbial drugs. This may lead to a disruption of the microbial purification processes in the STP and lead to indirect effects in surface waters (oxygen depletion, ammonia intoxication, etc). Again, effects on microbial processes are part of the base-set and risk assessment methodologies are clearly given in the TGD and EUSES.

10. Chronic reproduction studies addressing relevant endpoints should be required for those drugs with a potential for endocrine disruption or other reprotoxic effects.

11. The CSTEE wishes to draw the attention of EMEA to the Commissions initiative in developing a strategy for assessing the risks from exposure to mixtures. It suggests that EMEA consider developing a procedure for examining the environmental impacts of medicinal products with common modes of actions.

12. The CSTEE proposes that the potential of excreted medicinal products (and their metabolites) to promote antimicrobial resistance among environmental microorganisms and other ecological effects on microbial communities is included in the assessment of antibacterial agents.

13. The CSTEE recognises that the concerns expressed in this opinion are also applicable to the guideline on environmental risk assessment of veterinary medicines. An in-depth revision of the guideline for veterinary medicine, in line with the current state of the science, is recommended. Following the opinion of the SSC (2000) the harmonisation of the EU guidelines for risk assessment should be given priority.

Table 1. Information required for the technical dossier ("base set") referred to in Article 7 (1) of the seventh amendment of Directive 67/548/EEC (1992).

1. Identity: trade name, chemical name, formulae composition, spectra, methods of analysis
2. Quantity, functions, applications
3. Precautionary measures, emergency measures
4. Physical properties:
    a. melting point, boiling point
    b. relative density
    c. vapour pressure
    d. surface tension
    e. solubility in water
    f. n-octanol/water partition coefficient
5. Chemical properties
    a. Flashpoint
    b. (auto)flammability
    c. explosive properties
    d. oxidizing properties
6. Toxicological properties
    a. acute toxicity (2 routes)
    b. skin/eye irritation
    c. sensitization
    d. subacute toxicity
    e. genotoxicity (2 tests)
    f. reproductive toxicity (existing substances)
7. Ecotoxicological properties
    a. acute toxicity for fish, daphnia and algae)
    b. inhibition of bacteria
    c. ready biodegradability
    d. hydrolysis
    e. adsorption/desorption screening test
8. Methods for rendering the substance harmless

Annex 1. Short review of the environmental risks of medicinal products for human use.

1. Introduction and scope

Recently, the Committee for Proprietary Medicinal Products (CPMP) of the European Agency for the Evaluation of Medicinal Products (EMEA) finalised a discussion paper on environmental risk assessment of pharmaceuticals. A proposal (CPMP, 2001) has been made for: (1) the environmental risk assessment of medical products when administered to patients and (2) for labelling provisions, i.e. an outline of the information that applicants could provide on precautionary and safety measures to be taken, for the purpose of reducing the risks to the environment, with regard to the administration to patients, and to storage and disposal of waste products.

Pharmaceuticals appear in a wide variety on the EU market. The number of medical prescriptions is overwhelming. The mode of toxic (pharmaceutical) action of these drugs is very diverse (Martindale, 1999) and their relevance to human health is evident.

The occurrence of pharmaceuticals in the environment and the question whether they pose a risk to the environment has received considerable attention over the last 10 years. Research activities were aimed at summarizing the potential risks of pharmaceuticals in the aquatic environment. Römbke et al. (1996) provided an excellent report on this subject. Similar types of documents have been published by Jorgensen and Halling-Sorensen (2000) and by Derksen (2000). Aspects of the environmental fate of pharmaceuticals have been published by e.g. Richardson and Bowron (1985) and Halling-Sorensen et al. (1998). Webb (2000) has published an inventory of their environmental effects. He also provided a preliminary risk assessment of some human pharmaceuticals. A few papers have been published on the endocrine-disruptive effects of pharmaceuticals, e.g. CSTEE (1999) and Larsson et al. (1999). In all these papers the focus is on the aquatic environment.

The occurrence of pharmaceuticals in surface waters and groundwater has drawn the attention from the drinking water producers (Mons et al., 2000). In order to provide some insight into the relevance of environmental exposure and effects of pharmaceuticals for human use conferences have been organised (Pharmaceuticals in the Environment, 2000) and special issues of scientific journals have been published (Chemosphere, 2000). Currently, the Health Council of the Netherlands is drafting an advise to the Minister of Health, The Minister of Agriculture and the Minister of the Environment (Gezondheidsraad, 2001). Other relevant sources of information are e.g. Ayscough et al. (2000) and Daughton and Ternes (1999).

This annex summarises some of these sources of literature in order to provide a context to the question of the CPMP to the CSTEE. The focus of this quick scan is on the relevance of pharmaceuticals to the aquatic environment. Risks related to groundwater, drinking water, and the terrestrial environment are excluded in this short review. No attempt is made to provide an in-depth review on the environmental risks of pharmaceuticals. For this short review existing reviews were used and in many cases it was not possible to check the primary sources of the literature on which these reviews were based.

2. Use and emissions

For every environmental risk assessment information on the emissions to the environment is a prerequisite. This would require information on (1) the actual use, (2) the use pattern and on (3) the metabolism of the pharmaceutical in human beings, so that the emissions and emission routes of both the parent compound and relevant metabolites can be estimated.

Actual use. The information on the use of pharmaceuticals for humans in the EU is not ready available. This holds in for drugs in general and even for popular drugs. Information on use volumes (or sales or EU production or import volumes) of the most important pharmaceuticals in the EU (kg/year) is not readily available. Some information on the use of drugs can be obtained only on the basis of frequencies of medical prescriptions (Stichting Farmaceutische Kengetallen, 1997; Römbke et al., 1996). Some problems with this indirectly obtained information are evident. Some very popular drugs can be obtained without medical prescription and some uncertainty remains as to the number of tablets present in such a prescription (Table 2.1). This can easily introduce an error of approximately one order of magnitude (a factor of 10). Even higher errors can occur for those drugs, which can be obtained without medical prescription (the so-called over the counter or OTC drugs). Recently, Ternes (2000) estimated the sold quantities of selected human pharmaceuticals in Germany (Table 2.2). It can be concluded that for a country like Germany for instance up to 100t of an individual drug can be prescribed on an annual basis.

Use pattern. Oral uptake or injection is the main uptake routes of pharmaceuticals in human beings. It is assumed that faecal and urinary excretion are the major routes of elimination and therefore of emissions into the environment. This could lead to a direct emission to surface waters or in the case of wastewater treatment in a sewage treatment plant (STP) to indirect exposure to the aquatic environment. Volatile pharmaceuticals can lead to direct exposure of air and disposal of old (not used) pharmaceuticals could lead to emissions to soil or groundwater. In the Netherlands it is estimated that 8.3% of the prescribed pharmaceuticals are not used. In Belgium this is 5% (Derksen, 2000). In the Netherlands, most of these non-consumed products are treated as special chemical waste and incinerated. Therefore, diffuse pollution of surface waters is regarded the most relevant exposure route of the environment (Rombke et al., 1996, Derksen, 2000, Gezondheidsraad, 2001). The application of sewage sludge on land may result in indirect exposure of the soil. Jorgensen and Halling-Sorensen (2000) have provided a clear scheme (Figure 1).

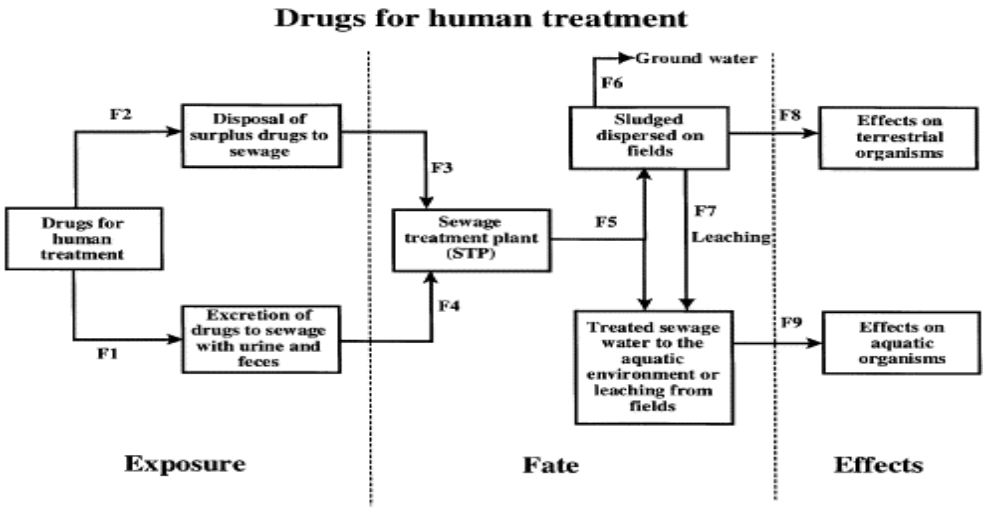

Figure. 1. Anticipated exposure routes of drugs for human treatment in the environment (Jorgenson and Halling-Sorensen, 2000). Drugs may enter the environment as a result of their use in human beings and their disposal. They may be degraded, adsorbed or even be reactivated in STPs as a result of microbial activity. The discharge of STP-effluent in surface waters or use of sewage sludge on agricultural land may lead to exposure of surface water, aquatic sediments, groundwater, and agricultural land (terrestrial ecosystems).

Metabolism. In order to predict emissions into the environment, it is necessary to obtain information about the metabolism in human beings in order to estimate the releases of the parent compound and their relevant metabolites. The degree, rate and pattern of metabolism vary greatly among pharmaceuticals and the information is generally not available for environmental exposure assessment. Halling-Sorensen et al. (1998) has recently published a review on this.

In case no information is provided on metabolism in human beings, assumptions are necessary for the predictions of emissions to STPs. A worst-case assumption would be to assume 0 % metabolism in human beings. This solves the problem on how to predict the emissions of the parent compound but it does not solve the problem of the emission of potent (very active) metabolites.

Table 2.1. Top ten of popular pharmaceuticals in the Netherlands in 1997 (Source: Stichting Farmaceutische Kengetallen, 1998). The Netherlands has 16 million inhabitants

Pharmaceutical	Category	Administration	Prescriptions (millions)[2]
Paracetamol[1]	Analgesic/ anti-inflammatory drugs/antipyretic	tablet 500 mg	2.3
Oxazepam	Sedative	tablet 10 mg	2.2
Diclofenac(sodium)	Analgesic/ Anti-inflammatory drug	tablet 50 mg	1.2
Aspirin (acetylsalicylic acid)[1]	Analgesic/ Anti-inflammatory drugs/antipyretic	tablet 80 mg	1.2
Ethinyloestradiol/ Levonorgestrel	Contraceptive (synthetic oestrogen resp.progestogen	tablet 30 + 150 µg	1.2
Temazepam	Sedative	capsule 10 mg	1.2
Furosemide or frusemide	Diuretic	tablet 40 mg	1.1
Doxycycline	Antibacterial	tablet 100 mg	1.0
Omeprazol(sodium)	Gastro-intestinal drug (inhibits secretion of gastric acid)	capsule 20 mg	1.0
Temazepam	Sedative	capsule 20 mg	0.8

1 Paracetamol and aspirin are generally sold without medical prescription.
2 Drugs are generally sold in a package containing more than one tablet.

Table 2.2. Estimation of sold quantities of selected pharmaceuticals used in human medicine in 1997 in Germany (Ternes, 2000).

Pharmaceuticals in human medicine	Quantity in tonnes
Bezafibrate	45
Carbamazepine	80
Metoprolol	52
Sulfamethoxazol	60
Diclofenac	75
Ibuprofen	180
Acetylsalicylic acid	>500
Iopromide	130
17α-ethinylestradiol	0.050

3. Environmental fate

Once excreted by human beings, pharmaceuticals and relevant metabolites may enter the aquatic environment. Generally, wastewater is treated in a sewage treatment plant before discharge to surface waters takes place. Therefore, information on the degradation (degradation rates and routes) under relevant aerobic and anaerobic conditions is crucial, together with information of basic physicochemical characteristics such as water solubility. Halling-Sorensen et al. (1998) have provided some information on the degradation of pharmaceuticals. Research was reviewed on 27 pharmaceuticals both in STPs and in degradation studies in the laboratory. Their study comprised analgesics, antibiotics, cardio-vascular drugs, oncolytics and hormones. Degradation of these drugs varied from readily biodegradable to non-ready biodegradable and some drugs were even persistent. Information on anaerobic degradation is generally not available. An interesting observation was that for some drugs metabolism which deactivates the parent compound (e.g. clofibric acid) into a glucuronide may be activated again in STPs as a result microbial deglucorination (Gezondheidsraad, 2001) and lead to pollution of surface waters including the North Sea.

4. Concentrations in the environment

Information on the occurrence of drugs in surface waters is available for a number of countries in the EU. Estimated concentrations for pharmaceuticals for the UK for the River Lee are given in Table 4.1.

Table 4.1. Estimated drug concentrations in the river Lee (Richardson and Bowron, 1985)

Drug	Classification	Concentration (µg/l)
Amitriptyline	Antidepressant	0.88
Ampicilline	Antibiotic	7.90
Acetylsalicyclic acid	Analgesic	14.6 (161*)
Chlorotetracycline	Antibiotic	0.15
Clofibrate	Lipid regulating agent	6.30
Codeine + dhc	Opioid analgesic	1.17
Coffeine	Analgesic	0.29
Dextropropoxyphene	Analgesic	3.20
Diazepam	Antidepressant	0.44
Epedrine	Sympathomimetic	0.44
Erythromycine	Antibiotic	2.20
Ibuprofen	Analgesic	9.50
Indomethacine	Analgesic	1.32
Meprobamate	Antidepressant	2.60
Methyldopa	Antihypertensive agent	17.50
Metronidazol	Antibiotic	0.29
Naproxen	Analgesic	2.30
Nicotinamide	Vitamine	2.00
Oxytetracycline	Antibiotic	6.70
Paracetamol	Analgesic	84.10 (340*)
Phenylpropanolamine	Sympathomimetic	0.29
Salicylic acid	Dermatological agent	0.29
Sulfamethoxazine	Antibiotic	7.20
Sulfasalazine	Sulfonamide	1.80
Tetracycline	Antibiotic	2.90
Theobromine	Xanthine	0.29
Tolbutamide	Antidiabetic agent	2.20

* including self medication , **DHC = dihydrocodeine

In Table 4.2 Van Vlaardingen and Montforts (1999) have summarised PECs of pharmaceuticals in Germany.

Table 4.2. Estimated concentrations of selected human drugs in German surface water using EU Draft Guideline III/5504/94 (Van Vlaardingen and Montforts, 1999).

Drug	Classification	Amount prescribed (kg)	Concentration (µg/l)
Acetylcysteine	Mucolytic	106,949	1.83
Acetylsalicyclic acid	Analgesic	135,357	2.32
Ambroxol	Mucolytic	16,568	0.28
Bacitracine	Antibiotic	128	0.002
Bromhexine	Mucolytic	451	0.01
Clenbuterol-HCl	Sympathomimetic	2	0.00003
Clofibric acid	Lipid regulating agent	2,679 **	0.05
Codeine	Opioid analgesic	4,124	0.07
Diclophenac	Analgesic	31,606 ++	0.54
Doxycycline	Antibiotic	13,034 +++	0.22
Erythromycin	Antibiotic	215,663	3.69
Oestradiol	Sex hormone	702	0.01
Oestriol	Sex hormone	313	0.005
Ethinyloestradiol	Sex hormone	10 *	0.0002
Iphosphamide	Antineoplastic agent	+	+
Norethisterone	Sex hormone	245	0.004
Oxytetracycline	Antibiotic	700	0.01
Paracetamol	Analgesic	209,887	3.59
Pentoxyverine	Cough suppressant	961	0.02
B-sitosterol	Lipid regulating agent	11,674	0.20
Spironolactone	Aldosterone-antagonist	27,758	0.48

* Schweinfurth & Lange (1995) and Schmidt (1995): 50-93 kg.

** Heberer (1995) and Stumpf et al. (1996): including all metabolised derivatives of all clofibric acid (Clofibrate, Etofibrate, Etonyllinefibrate) approximately 15,000 – 21,000 kg.

\+ No information available .

++ Stumpf et al. (1996): approximately 48,000 – 72,000 kg (including salves etc. up to ca. 720,000 kg).

+++ Schmidt (1995)

Kümmerer (2000) has reported measured concentrations in German surface waters in the ng/L to µg/L range. Similar observations were made by Mons et al. (2000) and by Derksen (2000). Derksen (2000) gathered information for the Netherlands.

A recent study carried out by the Gezondheidsraad (2001), based on a review by Derksen (2000), summarized maximum measured concentrations of drugs in hospital effluents, influents and effluents of STPs, surface water, groundwater, drinking water and sediment. In this review it was shown that individual drugs occur in concentrations up to 100 µg/L in aqueous media, whereas in sediments concentrations

of more that 100 mg/kg have been detected. Similar observations were made in a recent ESF/EEA report (ESF/EEA, 2001). From these monitoring studies it is difficult to draw general conclusions with regard to specific drugs, as measured and predicted concentrations were obtained from different geographical regions, at different sites, in different media and at different times. Nevertheless, it can be concluded that pharmaceuticals are detected in effluents, surface waters and groundwater in ranges of ng/L to µg/L. It is very likely that at certain places close to STPs or in surface waters, which are mainly composed of effluents of STPs, relatively high concentrations may be observed. Relatively high concentrations may also be expected in the case of hospital effluents. Changes in the pattern of medical treatment (e.g. cancer treatment at home) may lead to increased concentrations in sewage. The prediction of environmental concentrations is hindered by the fact that information on the actual use of pharmaceuticals is difficult to obtain.

5. Environmental effects

Most of the information on the ecotoxicity of pharmaceuticals is related to acute or short-term toxicity to aquatic species. Recently, Derksen (2000) performed a literature search into the aquatic toxicity of pharmaceuticals. A total of 456 data were found for 76 compounds and 6 metabolites. Only for a few (18) studies pharmaceuticals information on chronic aquatic toxicity (*Daphnia magna*) is available. Some info was also available on *Vibrio fischeri* (38 studies) and waterplants (20 studies). This information is given in Table 5.1.

Webb (2000) in Table 5.2 has provided similar information on the aquatic toxicity. He showed that the human pharmaceuticals vary in toxicity of over 6 orders of magnitude. The most toxic compounds with acute endpoints of 1 mg/L or less were: Alendronate (used for the treatment of metabolic bone disease), Amitriptyline (an anti-depressant), Carvedilol (an antihypertensive and anti-angina drug), Ethinyl Oestradiol (an oestrogen), Fluticasone (a corticosteroid antiastmatic), Fluoxetine (an anti-depressant), Fluvoxamine (an anti-depressant), Midazolam (an anaesthetic), Paclitexel (an anti-neoplastic) and Thioridazine (an anti-psychotic drug). The variation in toxicity is also depicted in Table 5.3.

Probably more important than information on the acute toxicity of these compounds is the profound lack of chronic aquatic toxicity. Both in the Derksen (2000) and Webb (2000) studies very few chronic data were given. A clear exception is Ethinyl Oestradiol for which several fish chronic toxicity studies have been performed which show its very high toxicity to fish (e.g. Larsson et al., 1999). A few chronic data were available for only 20 compounds. Again, this is similar to the findings of Derksen (2000).

In conclusion it may be stated that standard acute toxicity tests with their focus on short-term effects play an important role in a tiered approach of environmental risk assessment. They do not provide the most appropriate basis for risk assessment given the intended specific mode of toxic action/potency of pharmaceuticals in general. The profound lack of chronic ecotoxicity data hinders an adequate assessment of the risks of pharmaceuticals.

Table 5.1. Summary of available acute ecotoxicity data (LC50 and EC50 values) for human pharmaceuticals (Derksen, 2000)

Ecotoxicity Range	Number	Frequency (%)	Cumulative (%)
<0.1 mg/L	9	7.0	7.0
>0.1-1 mg/L	6	4.7	11.7
>1-10 mg/L	23	18.0	29.9
>10-100 mg/L	31	24.2	53.9
>100-1,000 mg/L	43	33.6	87.5
>1,000 mg/L	16	12.5	100
Total	128	-	-

Table 5.2. Summary of available acute ecotoxicity data (LC50 and EC50 values) data for human pharmaceuticals (Webb, 2000).

Ecotoxicity Range	Number	Frequency (%)	Cumulative (%)
<0.1 mg/L	2	1.9	1.9
>0.1-1 mg/L	8	7.5	9.3
>1-10 mg/L	22	20.3	29.9
>10-100 mg/L	31	29.0	58.9
>100-1,000 mg/L	37	34.6	93.5
>1,000 mg/L	7	6.5	100
Total	107	-	-

Table 5.3. Toxicity of seven major groups of human drugs for the aquatic environment - Based on information provided by Derksen (2000).

Substances	*Extremely toxic (EC_{50} < 0.1 mg/l)*	*Very toxic (EC_{50} 0.1 – 1 mg/l)*	*Toxic (EC_{50} 1-10 mg/l)*	*Harmful (EC_{50} 10-100 mg/l)*	*Not toxic (EC_{50} > 100 mg/l)*
Cardiovascular products		D			
Anti-epileptics			C		D, E
Analgetics			D	D,E	
Cytostatics		A		D,E	
Antibiotics	A	B			
Antidepressants		D			
Roentgen contrast fluids					A,B,D, E

Most sensitive taxonomic group: A: micro-organisms; B: algae; C: Cnidaria; D: crustacea; E: fish

6. Risk characterisation

Webb (2000) has performed an initial risk assessment for the UK on the basis of an UK population of 57.6 million and a specific water consumption of 259 litres/capita/day. The assumptions used in this worst-case analysis were:

1) no metabolism of the drug in human beings and a 100% loss to drain
2) no removal in STPs (i.e. no adsorption to sludge, no volatilisation and no biodegradation)
3) no dilution in surface waters (i.e. dilution factor is 1; effluent = surface water)
4) Homogeneous distribution of use in the UK.

From this analysis for 60 compounds, which according to Webb (2000) probably account for over half of all known pharmaceuticals consumption in tonnage terms, the PEC/PNEC ratio was <1 in all but eight cases. Webb mainly used acute toxicity data for his analysis. This result indicates that the major fraction of human pharmaceuticals pose negligible risk to the aquatic environment. It also indicates that a small but relevant fraction may show a risk to the aquatic environment. The relevant compounds with PEC/PNEC ratios > 1 were: Paracetamol/Acetominophen, Aspirin, Dextropropoxyphene, Fluoxetine, Oxytetracycline, Propranolol, Aminotriptyline and Thioridazine. The highest PEC/PNEC ratio was found for Paracetamol. Webb (2000) concluded that further refinement of the assessments was needed for these chemicals. This will require: (1) transparent information on the actual use volumes and use patterns, (2) detailed information on the 4 assumptions given above (metabolism, fate in STPs, dilution factors and use patterns, e.g. use in hospitals) and (3) information on chronic aquatic ecotoxicity.

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Annex 2

Tiered approach to fate and effects testing as proposed by the US Department of Health and Human Services, Food and Drug Administration (http://www.fda.gov/cder/guidance/1730fnl.pdf) in their document: Guidance for Industry. Environmental Assessment of Human Drug and Biologics Applications 1998).

Figure 1
Tiered Approach to Fate and Effects Testing