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Occurrence, Fate and Effects of Pharmaceutical Substances in the Environment - A Review

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Abstract

Medical substances (pharmaceuticals) are a group of substances that until recently have been exposed to the environment with very little attention. The reason why they may be interesting as environmental micropollutants, is that medical substances are developed with the intention of performing a biological effect. Especially antibiotics used as growth promoters, as feed additives in fish farms are anticipated to end up in the environment. Very little is known about the exposure routes of the medical substances to the environment. Only few investigations have reported findings of medical substances in other field samples than sediment or treated waste water samples. Several substances seem to be persistent in the environment. This paper outlines the different anticipated exposure routes to the environment, summarises the legislation on the subject and gives an outline of present knowledge of occurrence, fate and effect on both the aquatic and terrestrial environments of medical substances. Present knowledge does not reveal if regular therapeutic use may be the source of a substance carried by sewage effluent into the aquatic system, even though clofibrate, a lipid lowering agent, has been identified in ground and tap water samples from Berlin. Further research would be necessary to assess the environmental risk involved in exposing medical substances and metabolites to the environment. ©1997 Elsevier Science Ltd

Keywords

medical substances, pharmaceuticals, environmental fate, toxicity, legislation.

1. Introduction

Until recently medical substances (pharmaceuticals) have been exposed to the environment with very little attention. New knowledge about the effects of well known xenobiotics (e.g. DDT and PCBs), having a hormone mimicking effect on the reproduction system, in concentrations even down to a few nanograms per litre has emerged. This has taught us to expect unknown effects on nature of substances that we until recently considered to be safe because we would only expect them to be present in trace concentrations (e.g. Colburn and Clement 1992).

The reason why medical substances may be interesting in this context, is that they are developed with the intention of performing a biological effect. They often have the same type of physico-chemical behaviour e.g. are lipophilic in order to be able to pass membranes, are persistant in order to avoid the substance to be inactive before having a curing effect as other harmful xenobiotics. Thus the medical substances have many of the necessary properties to bioaccumulate and provoke effects in the aquatic or terrestrial ecosystems. The yearly exposure of some high volume medical substances may be very large (Table 1).

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Today we actually do not know the fate and effects of the medical substances when they are exposed to the environment. After having an internal curing effect somewhere in the human body, a medical substance will be excreted through urine or faeces as a mixture of metabolites, as unchanged substances or conjugated with an inactivating substituent attached to the molecule, depending on the pharmacology of the substance in concern. (Rang and Dale 1991).

Figure 1 shows the anticipated exposure routes to the environment for different types of pharmaceuticals. Medical substances may roughly, in this context, be divided into medical substances used by humans (F1) or veterinary medicine (F2). The veterinary medicine may further be subdivided into substances used as growth promoters for livestock production, therapeutics in livestock productions, coccidiostatica used for poultry production (F3), therapeutics for treatment of livestock on fields e.g. antiparacetic agents (F4) or as feed additives in fish farms (F5). The medical substances used by humans will enter the sewer system with the urine and faeces (F6) and attend the sewage treatment plant (F7).

As in the case of all other xenobiotics the fate of the substances may be divided in three principal possible fates; i) the substance is ultimately mineralised to carbon dioxide and water, e.g. aspirin (Richardson and Bowron (1985). ii) The substance is lipophilic and not readily degradable so part of the substance will be retained in the sludge (F8). iii) The substance is metabolised to a more hydrophilic form of the parent lipophilic substance but still persistent and therefore it will pass the waste water treatment plant (F9) and end up in the receiving waters (waste water treatment effluents often discharge to rivers) (F10) and may therefore affect the aquatic organisms if the metabolites are biologically active (F11). Clofibrate is an example of a persistent pharmaceutical substance (Richardson and Bowron (1985). Substances that have the potential to be retained in the sludge, will if the sludge is dispersed on fields (F12) be able to affect the micro-organisms and beneficials. The medical substances used for animals in stables as growth promoters will mostly end up in manure (F13). These substances may also affect soil organisms (F14).

A runoff of substances from the fields may be anticipated for hydrophilic substances or metabolites during a rain event in connection with dispersion of sludge and manure (F15). The medical substance used on animals on the field will be urinated or defecated directly on the field (F16) and the exposure will be of a high local concentration and this may also affect soil organisms (F17). It is possible that medical substances dispersed on fields may be mineralised in the soil column or will reach the groundwater as parent compounds and metabolites. Medical substances used in fish farms will be exposed directly to the receiving waters, because the most convenient method of treating fish with antibiotics and chemotherapeutics is by the use of feed additives. However a large portion of the medicated feed administered is not eaten by the fish, but falls through the cages and accumulates on the sea bed (Jacobsen and Berglind 1988) and may affect the aquatic organisms (F18). An unknown portion of marketed human medicinal substances ends in the sewer system as surplus medical substances considered as waste (F19) (Zimmer et al. 1992).
The primary question to raise is whether medical substances at low substance concentrations have any effects at all on organisms at different tropic levels?. Are they persistent in nature or may the micro-organisms mineralise them?. From 1. January 1998 EU will take into operation a directive describing the technical guideline for assessing the risk of the environmental exposure of veterinary medical substances (AEU Note for guidance EM/CAMP/055/96-FINAL).

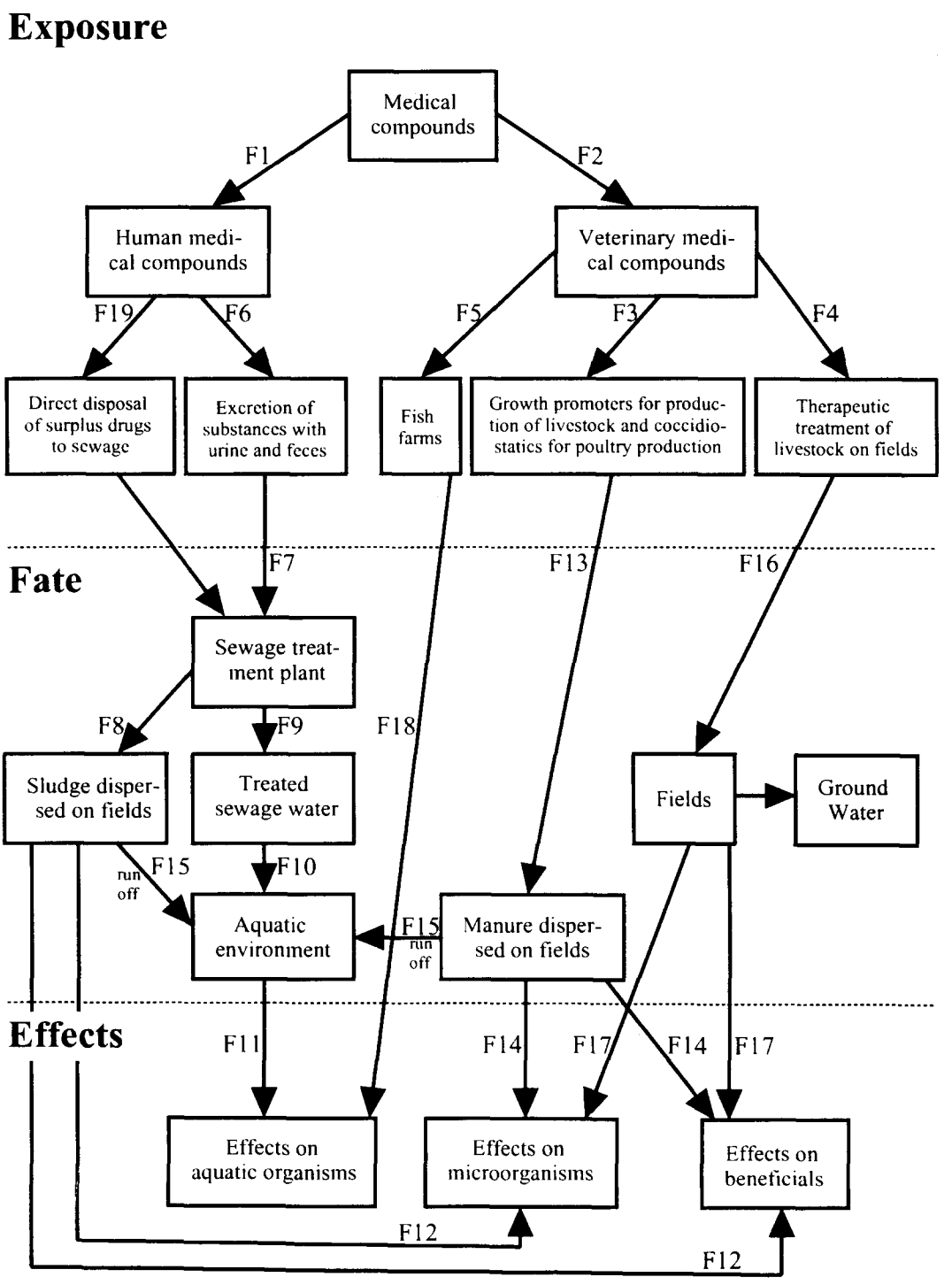

Figure 1. Anticipated exposure routes of both veterinary and human medicinal substances in the environment.

A similar directive have been launched as draft manuscripts covering a risk assessment procedure of the exposure of medical substances for human treatment (III/5504/94 EU draft guideline).

The proposed directives prescribe that a risk assessment should be part of the approval procedure of new medical substances (Cwiertniewicz 1994). The US Food and Drug Administration have already had for several years issued its Environmental Assessment Technical Handbook for FDA-required environmental Assessment (FDA 1985; FDA 1987). But it seems that this legislation is not of high concern, since only very few new medical substances in recent years, to the authors knowledge have, been subjected to a complete risk assessment where a battery of appropriate ecotoxicological tests were included.

The objective of this paper is therefore to give an overview on existing knowledge of the exposures, fates and effects of medical substances on the environment and to discuss this knowledge in the context of the proposed EU directives on environmental risk assessment of both veterinary medical substances and human medical substances.

2. Occurrence and Exposure of Medicinal Compounds to the Environment

Potential quantities

Table 1 shows some examples of the consumption of some high volume pharmaceuticals used in Denmark (5.2 million inhabitants) in 1995. It was possible to obtain these numbers from the Danish Drug Administration (pers. comm.) as number of defined daily doses (millions). These numbers were then recalculated into tonnes of active substance. The table shows that several substances are used in quantities (1 to 30 tonnes) of active substance.

The risk that a substantial quantity of substances may end up in the environment is therefore present. A total of 110 tonnes antibiotics are used as growth promoters in livestock production, as feed additives in fish farms or as coccidiostatica in poultry production per year (Plantedirektoratet, pers. comm.). Calculations have indicated that 70 - 80 % of drugs administered in fish farms end up in the environment, and drug concentrations with antibacterial activity are found in the sediment underneath fish farms (Samuelsen et al. 1992). Because a major part of medical substances applied in human treatment may be metabolised by the liver a substantial amount will be exposed as metabolites. Over 30 percent of all medical substances developed in the period from 1992 to 1995 are lipophilic (Solubility less than 100 mg/l) (DFH Lægemiddelforskning, 1996). The total usage of some veterinary pharmaceuticals applied in Sweden (antibiotics and antiparasitics) 1988 to 1993 and in Norway (antibiotics) is discussed in Björnerot et al. (1996) and Lunestad (1992a). During the period studied, the total usage of antibacterial substances remained stable in Sweden at approximately 35 tonnes of active substance annually. The use of antibiotics for growth-promoting purposes was prohibited in Sweden in 1986 and became available by veterinary prescription only. Total amount of coccidiostatics was around 10 tonnes annually and other antiparasitic drugs 7.7 tonnes annually. A study conducted in 1985 by Richardson and Bowdon on the exposure of human pharmaceutics to the River Lee, in England, showed that approximately 170 pharmaceutical chemicals were found to be used in excess of one tonne annually giving a predicted concentration of 0.1 µg/l or above in the River Lee. The medical substances investigated for environmental impact is primarily the antibiotics, used as growth promoters in livestock production, feed additives for fish farms and coccidiostatics to poultry industry (e.g. Migliore et al. (1997); Schneider (1994); Eckman (1994); Addison (1984); Bhat-

tachara and Taylor (1975), the antiparacetic agent (e.g Wratten and Forbes 1996; Sommer (1992a); Sommer et al.(1992b); Sommer and Overgaard Nielsen (1992c). Very little is known about the appearance, fate and effects of compounds for human treatment e.g. hormones and antinoleptic agents.

3. Pharmacological fate of medical substances before entering the environment.

Pharmaceuticals for human treatment are also often used in high quantities, as shown in Table 1. Compounds like Ibuprofen or Furosemid which both are on the top ten list of pharmaceuticals used in Denmark in 1995 may be used as examples.

They are used in yearly amounts of 33 tonnes and 4 tonnes respectively (Lægemiddelstatestik (1995) WHO (1995)). Most medical substances e.g. ibuprofen, are metabolised to phase I or phase II metabolites before being retrieved from the body with the urine and may be exposed to the environment as such. Phase I reactions usually consist of oxidation, reduction or hydrolysis, and the products are often more reactive and sometimes more toxic than the parent drug. Phase II reactions involve conjugation, which normally results in inactive compounds. Both phase I and phase II reactions changes the physical chemical behaviour of the substance because metabolisation always renders the metabolites more water soluble than the parent compounds. Berger et al. (1986) showed that chloramphenicol glucoronide and N-4-acetylated sulphadimidine, both phase II metabolites, was converted to respectively chloramphenicol and sulphadimidine in samples of liquid manure, and thus reactivated, the phase II metabolites into the parent compounds. Figure 2 shows an overview of the metabolisation of parent compound into phase I and phase II metabolites. Thus, often it is not only the parent compound which should be the subject for a risk assessment but also the main metabolites. For a comprehensive understanding of drug metabolisation see Gibson and Skett (1986).

Table 1. Consumption in Denmark (5.2 millions inhabitant) of some high volume medical substances in 1995.

Substances	DDD per year millions[a]	DDD WHO grams[b]	Applied weight tons
Human treatment			
Single substances			
Ibuprofen	27.7	1.2	33.2
Furosemid	91.9	0.040	3.7
Estrogens in comb. with gestoden or desorgestrel	58.3	$6.5*10^{-5}$	$3.8*10^{-3}$
Estradiol	24.3	0.002	0.049
Therapeutic groups			
Antibiotics	25.1	1.5	37.7
Analgesic (NSAID-type)	56.6	0.5	28.3
Hypotensiva	41.0	0.010	0.41
Diuretica (loop)	95.3	0.040	3.8
Anti-astmatics	110.5	0.015	1.7
Psychleptics	147.5	0.050	7.4
Veterinary treatment			
Growth promoters (livestock production pigs)[c]			
Single substances			
Carbadox			1.181
Olaquindox			16.213
Avilamycin			1.665
Avoparcin			5.690
Bacitracin			7.910
Flavomycin			0.048
Monesin			5.007
Salinomycin			0.850
Spiramycin			0.507
Tylosin			52.275
Virginiamycin			2.590
Therapeutics applied in livestock production[d]			
Antibiotics			49.687
Therapeutic applied in poultry industry			
Coccidiostatics			16.165
Antibiotics feed additive			2.491
Fish farms, feed additives[e]			
Single substances			
Branzil (Trimetoprim and Sulfamethizol)			3.356
Oxolinic acid and Inoxyl			0.208
Oxytetracycline			0.082
Sulfa contaning substances (therapeutics)			0.182

Sources:
a. Defined Daily Doses in millions (pers.comm. Danish Drug Administration)
b. Anatomical Therapeutic Chemical (ATC) index. WHO (1995)
c. Pers. comm. Plantedirektatoriet, Lyngby, Denmark.
d. Pers. comm. Plantedirektoratet, Lyngby, Denmark
e. Pers. comm. Velje Amt, Teknik og Miljø. Tilsyn med dambrug (1995).

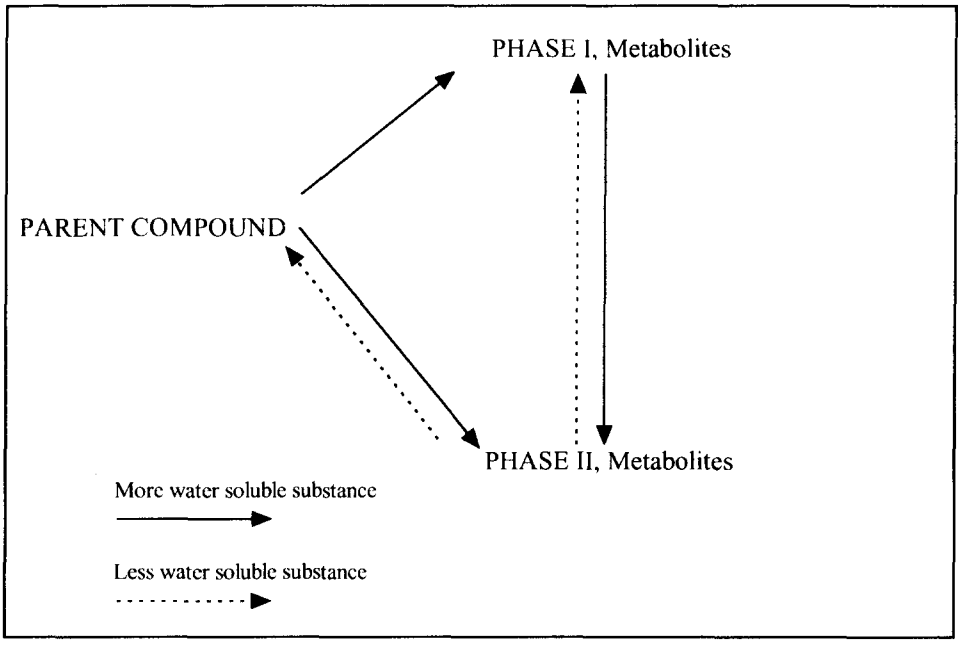

Figure 2. An overview of the metabolisation of parent compound into phase I and phase II metabolites. Solid lines indicates a transformation into a more water soluble compound. Dotted lines indicates a reactivation of the phase II metabolites into a less water soluble compound.

4. Occurrence in the environment

Table 2 gives an overview of found literature references describing occurrence of medical substances in the environment.

Ground water pollution

A few references may be found in the literature concerning findings of metabolites originating from medical substances in ground water. A landfill in Florida which received wastes from the Jackson Naval Air Station in 1968 and 1969 including wastes from the naval base hospital, has contaminated a nearby shallow ground water (Eckel et al. 1993). The authors reported the presence and persistence of pentobarbital, meprobamate and phensuximide in the 21 years old anaerobic ground water plume. Holm et al. (1995) describes findings and distributions of organic compounds originating from waste from the pharmaceutical industry in the down gradient of a landfill. The authors reported findings of e.g. different sulfonamides (concentrations up to 5 mg/l), propylphenazone (1,2-dihydro-1,5 dimethyl-4-(1-methylethyl)-2-phenyl-3H-pyrazol-3-one) (concentrations up to 4 mg/l), 5,5-Diallylbarbituric acid (concentrations up to 0.2 mg/l). All three medical substances which have been used for treatment of humans in the period between 1940's and 1970's. As a common practice in that period, waste from pharmaceutical industries were disposed of at landfills

Table 2. Occurrence of medical compounds in the environment.

Medical compound or residue	Therapeutic use	Concentration in the environment	Sphere / conditions	Reference
Human treatment				
Aspirin	Analgesic (Pain killer)	~1µg/l < 50 - 1510	Sewage effluent Effluent from sedimentation tank	Richardson and Bowron (1985) Stumpf et al. (1996)
Bleomycin	Antinoplastic agent	11-19 ng/l < 5 -17 ng/l 5-13ng/l	Sewage treatment plant effluent (radioimmunno assay) River water Potable water	Aherne et al. (1990)
Caffeine	Psychomotor stimulants	~1µg/l >1µg/l 16- 292 µg/l	Sewage effluent Potable water Effluent waste water	Richardson and Bowron (1985) Rogers et al. (1986)
Clofibrate Clofibric acid	Lipid lowering agent	~ 40ng/l < 0.5 - 1750 ng/L < 0.5 - 220 ng/l < 5 - 180 ng/L < 50 - 1560	River water River water Berlin River water Europe River water Effluent sedimentation tank	Richardson and Bowron (1985) Heberer (1995) Stumpf et al. (1996)
Cyclophosphamide	Antinoplastic agent (chemotherapy)	146 ng/l (estimated 1-10 µg/l)	Treated hospital effluent from sewage treatment plant	Steger-Hartmann et al. (1996)
Dextropropoxyphene	Analgesic agent	~1µg/l	River water	Richardson and Bowron (1985)
Diazepam	Anxiolytic agent	<1µg/l ~10ng/l ~10ng/l	Sewage effluent River water Potable water	Waggott (1981)
Dichlorfenac	Analgesic agent	up to 2 µg/l 15 - 304 ng/l 38 - 489 ng/l	Effluent from sedimentation tank River Rhine Different rivers	Stumpf et al. (1996)
Erythromycin	Antibiotic	~1µg/l	River water	Watts et al. (1983)
Estrogen	Hormone	measurable conc.	Treated sewage water for irrigation	Shore et al. (1992)
Estrogen	Hormone	0.2 to 0.5 nmol/l	Raw sewage water, Tel Aviv, Israel	Shore et al. (1993)
Estrogen/estradiol and estrone	Hormones	10µmol/day	Daily excreate with urine from pregnant women	Fostis (1987)
Ethinylestradiol	Hormone	< 0.2 ng/L 0.3 - 0.5 ng/L 2 -1 5 ng/l 1 -3 ng/l < 5 ng/l	Surface water Effluent from sedimentation tank River water Reservoir Drinking water	Kalbfus (1995) Aherne and Briggs (1989)

Table 2 (continued). Occurrence of medical compounds in the environment.

Medical compound or residue	Therapeutic use	Concentration in the enviornment	Sphere / conditions	Reference
Ibuprofen	Analgesic agent	up to 12 µg/l < 5 - 41 ng/l 17 - 139 ng/l	Effluent sedimentation tank River Rhine Different river water samples	Stumpf et al. (1986)
Ifosfamide	Antinoplastic agent (chemotherapy)	24 ng/l (estimated 1-10 µg/l)	Treated hospital effluent from sewage treatment plant	Steger-Hartmann et al. (1996)
Indometacin	Analgetic agent	< 5 - 26 ng/l 17 -121 ng/l	River Rhine Different rivers	Stumpf et al. (1996)
Methaqualone	Hypnotics	~1µg/l	Sewage effluent	Richardson and Bowron (1985)
Methotrexate	Antinoplastic agent (chemotherapy)	~1µg/l <6.25 ng/l <6.25 ng/l	Sewage effluent River water Potable water	Aherne and English (1985)
Morphinan structure	Narcotic analgesic	<1µg/l	River water	Richardson and Bowron (1985)
Norethisterone	Hormone	8-20 ng/l < 17 ng/l < 10 ng/l < 10 ng/l	Effluent from sedimentation tank River water Reservoir Drinking water	Aherne and Briggs (1989)
Oral contraceptive	Hormone	<0.2µg/l <0.1µg/l	River water Sewage effluent	Aherne and English (1985)
Penicilloyl groups	Antibiotic	>25 ng/l >10 ng/l	River water Potable water	Richardson and Bowron (1985)
Sulphamethoxazole	Antibiotic	~1µg/l	River water	Watts et al. (1983)
Tetracycline	Antibiotic	~1µg/l	River water	Watts et al. (1983)
Theophylline	Psycomotor stimulant	~1µg/l	River water	Watts et al. (1983)
Testosterone	Hormone	0.8 to 1.1 nmol/l	Raw sewage water, Tel Aviv, Israel	Shore et al. (1993)
Veterinary treatment				
Ivermectin	Antiparacitic agent	> 60% 2%	Excreated with feces the 3 first days after injection. (dose 0.3 mg/kg of cattle body weight) conc. in urine (see above)	Chiu et al. (1990)
Testrosterone and estrogen	Hormones growth promoters	1 µmol / g manure	Chicken manure	Shore et al. (1988)
Oxytetracycline	Antibiotic (feed additive in fish farm)	0.1-11 µg / g sediment	Sediment	Björklund et al. (1990; 1991) Coyne et al. (1994) Poliquen et al. (1993) Weston et al. (1994) Kerry et al. (1995b)
		285 µg / g sediment	Sediment	Samuelsen et al. (1992a)

with no leachate collection systems. The chemicals may have entered the surrounding aquifers as a part of the leachates (Holm et al. 1995).

Contamination of tap water by clofibric acid (metabolite of a blood lipid regulator in human medical care) was investigated by (Stan et al. 1994; Stan and Linkerhägner 1992). These papers showed that samples taken from different districts of Berlin, all containing clofibric acid in concentrations between 10 and 165 ng/l. Clofibric acid was additionally detected in all surface water samples from the Berlin area. Clofibric acid was also found in samples of surface waters taken from several rivers in other areas of Germany. These findings support the hypothesis that clofibric acid is a substance of considerable persistence in the environment and that regular therapeutic use is the source of clofibric acid which is carried by sewage effluent into the aquatic system (Stan et al. 1994; Stan and Linkerhägner 1992).

River water pollution

Watts et al. (1983) reported the presence of several antibiotics (erythromycin, sulphamethoxazole, tetracyclines) and theophylline, in river water samples. They used field desorption mass spectrometry and high performance liquid chromatography. Aherne (1984) and Aherne et al. (1985) have used immunoassay techniques for the detection of methotrexate, progesterone, norethisterone and ethinyloestradiol in various river and potable water samples. Detection limits of between 5 and 10 ng/l were achieved. Several findings of antinoplastic agents (chemotherapeutics) are found in treated hospital waste water effluents (Steger-Hartmann et al. 1996; Aherne et al. 1990). This indicates that genotoxic agents might find way to the receiving waters.

Sediment pollution

Several investigations describes findings of antibiotics in sediment cores from medication in fish farms. (Bjørklund et al. (1990; 1991); Coyne et al. (1994); Kerry et al. (1995); Weston et al. (1994); Samuelsen et al. (1992a; 1992b). Oxytretracycline, an antibiotic agent, was found in concentrations varying between 0.1 and 4.9 mg / kg dry matter (Jacobsen and Berglind 1988).

Ocean pollution

A deep-water dumpsite, receiving 30 to 280 million litres of pharmaceutical waste yearly, in the period from 1972 to 1983, were established offshore in the United States, at 74 km north of Arecibo, Puerto Rico, and covered an area of about 500 Km^2 (Lee and Arnold 1983). No information was available on the content or occurrence of the wastes.

Soil pollution

Chlortetracyclines was found in soil amended with poultry manure (Warman and Thomas 1981). It was demonstrated that drug metabolites excreted by medicated livestock (e.g., as glucuronides) are decomposed by bacterial action in the liquid manure and reconverted into the active drugs. Due to the application of manure to agricultural soils, multiple drug resistance developed in livestock micro flora, even in the intestinal flora of untreated pigs. Thus, multiple-resistant

strains found their way into the food chain (Berger et al. (1986)). Shore et al. (1988) presented findings of testosterone and estrogen, used as growth promoters, in chicken manure. A paper published by Goll van (1993) estimates that if the total amount of growth promoters used in the Netherlands were spread over all the 2 million hectares of Dutch arable land, a yearly average of 130 mg antibiotic and antibiotic metabolites per m^2 of arable land would be found. If this amount were located in the top ten cm of the field, a concentration of 0.87 mg/ kg of soil should be expected..

5. Environmental fate

Table 3 gives an overview of the present knowledge of the fate of medical substances in the environment.

Biodegradation in sediments

The persistence of oxytetracycline (OTC), in bottom deposits from fish farms has been investigated by Jacobsen and Berglind (1988). Bottom deposits from four locations were sampled at different intervals after medication and analysed for OTC. The drug was found in concentrations varied from 0.1 to 4.9 mg/kg dry matter and are therefore capable of causing antimicrobial effects up to 12 weeks after administration. There was no correlation between concentration and time after medication or depth at sampling site. OTC is therefore relatively persistent in anoxic sediments. A conservative estimation of a half-life of approximately 10 weeks was estimated through a pilot study. The authors indicate that the data may give a rough idea of the persistence of this agent in marine sediments. Possible effects on sulphide ion activity in the sediment due to OTC was suggested by the authors.

A study performed by Hektoen et al. (1995) shows a comparison of the persistence of oxytetracycline (OTC), oxolinic acid (OA), flumequine (FLU), sarafloxacin (SAR), florfenicol (FLO), sulfadiazine (SDZ) and trimethroprim (TRM) in marine sediments. Polyethylene boxes were filled with sediment, the antibacterial compound added and placed on the sea at approximately 15 m depth for a period of 180 - 230 days. Sediment cores were analysed for residues of the antibacterials in four intervals from 1 to 7 cm. OTC, OA, FLU and SAR were found to be very persistent in the sediment. In the deeper layer of the sediment the initial concentrations of these compounds were present after 180 days and a calculated half-life of more than 300 days was estimated. The residues in the top layer of the sediment depurated more rapidly. The removal of these substances from the sediment were according to the authors, most probably due to leaching and redistribution rather than degradation. The quinolones were found to adsorb to the sediment. SDZ and TRM were less persistent than the quinolones. The concentration of FLO decreased rapidly in the sediment with a calculated half-life of 4.5 days, and a metabolite, florfenicol amine, was identified in the sediment.

Sewage sludge

Richardson and Bowron (1985) examined a number of pharmaceutical substances for their biodegradability during sewage treatment. The substances were selected for biodegradation studies on basis of their high quantity in use, their potential for being noxious or on basis of literature reviews that indicated that the drug had the potential to survive sewage treatment. The methods for testing were those recommended by the Department of Environment, Standing

Table 3. Fate of medical compounds in the environment.

Medical compound or residue	Therapeutic use	Process	Fate	Sphere / conditions	Reference
Human treatment					
Amitriptyline	Antidepressant	Biodegradation	Non-biodegradable	Sewage treatment	Richardson and Bowron (1985)
Ampicillin	Antibiotic	Biodegradation	48% biodegradable	Sewage treatment	
Aspirin	Analgesic (pain killer)	Biodegradation	Readily biodegradable	Sewage treatment	
Caffeine	Psychomotor stimulans	Biodegradation	Readily biodegradable	Sewage treatment	
Chlorhexidine	Desinfection	Biodegradation	Non-degradable	Sewage tratement	
Clofibrate	Lipid lowering agent	Biodegradation	Non-degradable	Sewage tratement	
Codeine phosphate	Narcotic analgesic	Biodegradation	Non-degradable	Sewage tratement	
Cyclophosphamide	Antioplastic agent (chemotherapy)	Biodegradation	not degradable	Lab. scale sewage treatment plant	Steger-Hartmann et al. (1996)
		Biodegradation	not degradable at	Closed bottle test (OECD 301D) 5 mg/l within 57 days	Kümmerer et al. (1996)
Dextropropoxyphene	Analgesic	Biodegradation	Non-degradable	Sewage tratement	Richardson and Bowron (1985)
Ephedrine	Astma, nasal decongestion	Biodegradation	Readily degradable after acclimatisation	Sewage treatment	Richardson and Bowron (1985)
Erythromycin	Antibiotic	Biodegradation	Non-degradable	Sewage treatment	Richardson and Bowron (1985)
Estrogen	Hormone	Biodegradation	Persistent in sewage and lake water		Shore et al. (1993)
Estrogen and diethylstilbistrol	Hormones	Biodegradation	Persistent in soil and feces		Gregers-Hansen (1964) Zondek and Sulman (1943)
Ibuprofen	Analgesic (pain killer)	Biodegradation	Inherently bio-degradable	Sewage treatment	Richardson and Bowron (1985)
Ifosfamide	Antioplastic agent (chemotherapy)	Biodegradation	not degradable	Lab. scale sewage treatment plant	Steger-Hartmann et al. (1996)
		Biodegradation	not degradable at 5 mg/l within 57 days	Closed bottle test (OECD 301D)	Kümmerer et al. (1996)
Meprobamate	Hyponotics	Biodegradation	Non-degradable	Sewage treatment	Richardson and Bowron (1985)
Methyldopa	Hypertension	Biodegradation	Non-degradable	Sewage treatment	
Metronidazole	Antiprotozoal, antibiotic	Biodegradation	Non-degradable	Sewage treatment	
Naproxen	Analgesic (pain killer)	Biodegradation	Non-degradable	Sewage treatment	
Nicotinamide	Treatment of pellagra	Biodegradation	Readily degradable	Sewage treatment	
Paracetamol	Mild analgesic	Biodegradation	Readily degradable after acclimatisation	Sewage treatment	

Table 3 (continued). Fate of medical compounds in the environment.

Medical compound or residue	Therapeutic use	Process	Fate	Sphere / conditions	Reference
Sulphamethoxazole	Antibiotic	Biodegradation	Non-degradable	Sewage treatment	Richardson and Bowron (1985)
Sulphasalazine	Antibiotic	Biodegradation	Non-degradable	Sewage treatment	
Tetracycline	Antibiotic	Biodegradation	Non-degradable	Sewage treatment	
Theobromine	Hypertension	Biodegradation	Readily degradable after acclimatisation	Sewage treatment	
Theophylline	Psychomotor stimulans	Biodegradation	Readily degradable	Sewage treatment	
Tolbutamide	Hypoglycaemic agent	Biodegradation	Non-degradable	Sewage treatment	
Veterinary treatment					
Avermectin B_1a	Antiparacetic agent	Biodegradation	$T_{1/2}$ = 14-28 days	Conc. 0.1-1ppm, different soils in lab.	Bull et al. (1984)
			$T_{1/2}$ = 28-56 days	test. (Lufkin fine sandy loam and Huston clay) Conc. 50 ppm, different soils in lab.test as above.	
		Leaching	No leaching potential		
		Plant uptake	Minor uptake of residues		
		Mobility	Koc = $4.76*10^3$	Immobile in different soils	Gruber et al. (1990)
Bacitracin	Antibiotic - growth promoter	Biodegradation	$T_{1/2}$ = 22.5 days (20°C) $T_{1/2}$ = 12 days (30°C)	Feces (5%) / soil matrix	Gavalchin and Katz (1994)
Bambermycin	Antibiotic - growth promoter	Biodegradation	Persistance < 25 days (over 20°C)	Feces (5%) /soil matrix	Gavalchin and Katz (1994)
Carbadox	Antibiotic - growth promoter	Biodegradation	No informations excist.		Goll van (1993)
Ceftiofur sodium	Antibiotic	Biodegradation	$T_{1/2}$ = 22.2 days (pH = 5) $T_{1/2}$ = 49 days (pH = 7) $T_{1/2}$ = 41.1 days (pH = 9)	Aerobic degradation in soils; clay loam, sand and silty clay loam.	Gilbertson et al. (1990)
		Photodegradation	minimal		Gilbertson et al. (1990)
		Hydrolyse	$T_{1/2}$ = 100.3 days (pH = 5) $T_{1/2}$ = 8.0 days (pH = 7) $T_{1/2}$ = 4.2 days (pH = 9)	Water	
Chloramphenicol	Antibiotic	Primary degradation		In liquid manure the main metabolite chloramphenicol glucoronide is craked by bacterial to chloramphenicol. Thus reactivating the parent drug.	Berger et al. (1986)
Chlortetracycline	Antibiotic - growth promoter	Biodegradation	After 30 days at 30°C, 44% of added compound remaind. At 20°C and 4°C, 88% and 100% were persistent after 30 days.	Feces (5%) / soil matrix	Gavalchin and Katz (1994)

Table 3 (continued). Fate of medical compounds in the environment.

Medical compound or residue	Therapeutic use	Process	Fate	Sphere / conditions	Reference
Efrotomycin	Antibiotic - growth	Sorption Desorption	Koc = 580-11000 Only 50% of sorbed dose was desorped even with organic solvents.	Different soils	Yeager and Halley (1990)
Enrofloxacin	Antibiotic	Excretion from	10 % unmetabolised animals		Vancutsum et al. (1990)
Erytromycin	Antibiotic - growth promoter	Biodegradation	$T_{½}$ = 11.5 days (20°C). At 4°C, 97% of the activity remained during 30 days.	Feces (5%) / soil matrix	Gavalchin and Katz (1994)
Florfenicol	Antibiotic - feed additive fishfarms	Biodegradation	$T_{½}$ = 4-5 days.	Degrades to persistent amine metabolite at all sediment dephts.	Lunestad et al. (1993)
Flumequine	Antibiotic - feed additive	Biodegradation	$T_{½}$ = 150 days	Surface sediment	Lunestad et al. (1993)
Furazolidone	Antibiotic	Biodegradation	$T_{½}$ = 50 hrs to 2 months		Roij de and Vries de (1982)
	Antibiotic - feed additive fish farms	Biodegradation	Readily degraded to inactive metabolite	Surface sediment	Ervik (1993)
Ivermectin	Antiparasitic agent	Biodegradation	Persistence in dung < 6 days	End of spring, field conditions (spain).	Lumaret et al. (1993)
		Biodegradation	$T_{½}$ = 93 - 240 days	Laboratory, dark, 22°C in soil / feces mix.	Halley et al. (1989)
		Biodegradation	$T_{½}$ = 1 - 2 weeks	Outdoor, summer soil / feces mixture	Halley et al. (1989)
		Photodegradation	$T_{½}$ = 3 hours	Outdoor, thin dry film on glass, sunlight	Halley et al. (1989)
Monensin	Antibiotic - growth promoter	Biodegradation	Persistent under an-aerobic conditions. (after 10 weeks 60-70% unchanged). More degradable under aerobic conditions.	Lab. experiments with feces	Donoho (1984)
		Biodegradation	Primary degradation within 33 days with or without manure.	Field experiments, soils	Donoho (1984)
Neomycin	Antibiotic	Excretion	Efter oral intake 97% will be excreated via lifestock feces.		Carli et al. (1982)
Oxolinic acid	Antibiotic - feed additive fish farms	Biodegradation	$T_{½}$ = 150 to 1000 days	Supeficial sediment at various sediment deepts (up to 7 cm)	Ilektone et al. (1993) Samuelsen et al. (1992b)
Oxytetracycline	Antibiotic - feed additive fish farms	Binding to sediment	$T_{½}$ = 30 to 142 days	Surface sediment at different conditions	Samuelsen (1989) Poliquen et al. (1992;1993) Ervik (1993)
		Biodegradation	$T_{½}$ = 9 days and 419 days	At two different locations with anoxic cond.	Björklund et al. (1990)
		Wash-out from sediment	At a sediment conc. of 285 µg / g sediment, the maximum water conc. was predicted to 0.11 µg/l. At sediment conc. of 10.9 µg/g sediment a similar water conc. of 0.016 µg/l was estimated	Sediment	Smith and Samuelsen (1996)

Table 3 (continued). Fate of medical compounds in the environment.

Medical compound or residue	Therapeutic use	Process	Fate	Sphere / conditions	Reference
Penicillin	Antibiotic	Biodegradation	Inactivation due to combination of microbial induced enzymatic and chemical hydrolyse	Feces (5%) / soil matrix	Gavalchin and Katz (1994)
Streptomycin	Antibiotic	Biodegradation	Complete adsorption to clay fraction of the soil.	Feces (5%) / soil matrix	Gavalchin and Katz (1994)
Sulphadimidine	Antibiotic	Primary degradation		In liquid manure the main metabolite N-4-acetylated sulphadimidine is craked by bacterial to sulphadimidine. Thus reactivating the parent drug	Berger et al (1986)
Sulphatrimetroprim	Antibiotic	Biodegradation	Within one year 75 % undegrated	Surface water	Goll van (1993)
Tetracycline	Antibiotic Fish pond	Photodecomposition		Seven tetracycline metabolites were found under conditions similar conditions as fish pond cultures	Oka et al. (1989)
Tylosin	Antibiotic - growth promoter	Biodegradation	At 4°C, 40% of the compound remained active after 30 days of incubation. At 20°C and 30°C inactivation occured rapidly	Feces (5%) / soil matrix	Gavalchin and Katz (1994)

Committee of Analyst (1981) and King (1981). Kümmerer et al. (1996) showed that some antinoplastic agent were persistent in sewage sludge.

Soils

Avidov et al. (1990) investigated the involvement of treated soils with different soil micro-organisms in the degradation of diphenimid, an antibiotics applied in agriculture, compared to nontreated soils.

The degradation of ceftiofur sodium, a wide-spectrum cephalosporin antibiotic, was studied by Gilbertson et al. (1990) in different soils. Fortification of cattle faeces with [^{14}C]ceftiofur showed that it was quickly degraded to microbiological inactive metabolites. Sterilisation of the cattle faeces inhibited the degradation of the substance which suggests that micro-organisms or heat labile substances may be responsible for the degradation. The $T_{1/2}$ values of aerobic degradation of ceftiofur sodium in California, Florida and Wisconsin soils were found to be 22.2, 49.0 and 41.4 days respectively. The persistence of medical substances occurring in liquid manure in the food chain is outlined by Berger et al. (1986). An investigation performed by Donoho (1984) showed that monecin, an antibiotic applied as growth promoter for swines, is degradable in manure and soil.

The use of sulfonamide in the production of a structure analogous herbicide asulam, motivated Walker (1978) to study the biodegradation of both compounds in soil. From a soil which had been exposed to asulam, he isolated *a Flavobacterium sp.* capable of degrading 172 mg sulphanilamide / L in a synthetic medium with no other carbonsources added.

The aerobic biodegradation of sarafloxacin hydrochloride, a fluroquinolone antibiotic for use against poultry diseases was tested in three different soils. Sarafloxacin treatment demonstrated mineralization to $^{14}CO_2$ amounting to 0.58%, 0.49% and 0.57% in loam, silt loam, and sandy loam soils, respectively, during 80 days test duration (Marengo et al. 1997).

Binding properties to sediments and soils

Hektoen et al. (1995) reports that quinolones such as oxolinic acid (OA), flumequine (FLU) and sarafloxacin (SAR) were found to adsorb to sediment of marine origin. In spite of the binding properties between OA and the sediment, the sediment with added OA had antibacterial activity throughout the experiment of 180 days. This is in accordance with the results of Hansen et al. (1992); however Björklund et al. (1991) found no antibacterial activity of OA in fish farm sediment from brackish water 10 days after the addition of drug.

The sorption of efromycin, an antibiotic, developed as a growth promoter in swine, was investigated by Yeager and Halley (1990) in five soils of various properties. Sorption occurred within 7 hours. Sorption distribution constants ranged from 8 to 290. Classifying efromycin as immobile in most soils (Koc = 580 to 11000). Avermectin was also determined immobile in three different soils by Gruber et al. (1990).

Transport

The transport processes of medical substances in the environment is not well covered in the literature. The mobility of

avermectin, an antiparacetic agent , is described by Gruber et al. (1990). From the pesticide research, it is well known that after agricultural treatment, pesticide may move below the ground in both the saturated and unsaturated zones and, depending of the water mobility, end up as parent compound or metabolites in the aquatic environment (Kruger 1992). It is therefore anticipated that antibiotics may have the same fate if manure containing antibiotics are spread on fields just before a rain event. Several antibiotics posses the same physico-chemical properties as the pesticides known to be able to run-off to surface waters.

Abiotic processes

Hydrolysis and photodegradation of ceftiofur sodium was investigated by Gilbertson et al. (1990). Hydrolysis of ceftiofur was accelerated by increasing pH. The $T_{1/2}$ values at pH 5, 7 or 9 were 100.3, 8.0 and 4.2 days, respectively, at 22 °C and dramatically increased at 47 °C. The photodegradation experiment showed that after initial degradation for several days the rate of degradation decreased to a minimum, probably due to a protective film formed from degradation products. Oka et al. (1989) presented seven metabolites of tetracycline after photodecomposition under conditions similar to natural waters in a fish culture pond.

6. Toxic Effects

An outline is given below of the present knowledge of toxic effects due to medical substances on different species from different trophic levels e.g. micro-organisms, phytoplankton, crustaceans, found in the literature. The same results are summarised, as effect concentrations, in Table 4. Effects as resistant development (antibiotics) and genotoxicity are also presented in this section. Possible environmental effects of antibiotic residues in animal manure are summarised by Gool, van (1993).

Micro-organisms

Ibuprofen, 2-(4-isobutylphenyl)propionic acid, which has analgesic, anti-inflammatory and antipyretic properties (Reynolds 1989), and is taken orally to treat mild to moderate pain of rheumatism and other musculo-skeletal disorders. Sanyal et al. (1993), draws to attention the potential antimicrobial activity of Ibuprofen's in terms of Minimum Inhibitory Concentration (MIC values), against certain dermatophyte fungi. Anti-fungal activity of ibuprofen was enhanced by lowered pH. These authors also noted that *Staphylococcus aureus* was susceptible to ibuprofen. Elvers and Wright (1995) showed that Ibuprofen inhibited growth of the Gram-positive bacteria, but that two Gram-negative species were unaffected. Growth of *Staphylococcus aureus* was suppressed by ibuprofen concentrations greater than 150 µg/ml at initial pH 7. At pH 6, such concentrations prevented growth. The antibacterial activity of ibuprofen was affected by pH, being more effective at values below pH 7.

Phytoplankton

Streptomycin prevented growth of six blue-green algae species in an investigation performed by Harrass et al. (1985), at concentrations (0.09 to 0.86 mg/l) substantially lower than needed to prevent growth of 7 of 8 green algae tested.

Table 4. Toxic effects of medical compounds on the environment.

Medical compound or residue	Therapeutic use	Test organisms	Toxicity	Sphere / conditions	Reference
Human treatment					
Clofibrate	Lipid lowering agent	Algae	EC10 = 5.4 mg/l EC50 = 12 mg/l	Growth inhibiton	Kopf (1995)
		Daphina magna	LC10 = 17.7 mg/l LC 50 = 28.2 mg/l	Acute test	
			NOEC = 0.01 mg/l LC10 = 0.0084 mg/l LC 50 = 0.106 mg/l	Reproduction test	
Diazepam	Psycopharmaca	*Daphnia magna*	LC50 = 13.9 mg/l LC50 = 4.3 mg/l		Lilius et al. (1995) Calleja et al. (1993)
Diethylstibestrol	Hormone	*Oedogonium cardiacum* (Algae)	LC_{50} > 10 mg/l	Algal toxicity test	Coats et al. (1976)
		Daphnia magna	LC_{50} = 4 mg/l		
		Culex pipiens	LC_{50} = 4		
		Physa sp.	LC_{50} > 10 mg/l		
		Gambusia affinis (Moskito fish)	LC_{50} > 1 mg/l		
Diethylstibestrol acetat	Hormone	*Oedogonium cardiacum* (Algae)	LC_{50} > 10 mg/l	algal toxicity test	Coats et al. (1976)
		Daphnia magna	LC_{50} = 10 mg/l		
		Culex pipiens	LC_{50} = > 10 mg/l		
		Physa sp.	LC_{50} > 10 mg/l		
		Gambusia affinis (Moskito fish)	LC_{50} > 10 mg/l		
Estrogen	Hormone	Alfalfa plants	0.02-2nmol/l signifi-catly increased plant growth. 200-2000nmol/l signi-ficantly decreased plant growth.	Irrigation water	Shore et al. (1992)
17α-Ethinylestradiol	Hormone	Algae	EC10 = 0.054 mg/l EC50 = 0.84 mg/l		Kopf (1995)
		Daphnia	NOEC = 0.01 mg/l EC10 = 0.0125 mg/l EC50 = 0.105 mg/l	Reproduction test	
		Daphnia	EC10 = 3.2 mg/l EC50 = 5.7 mg/l	Acute test	
Hospital wastewater containing Mitomycin C and/or Cisplatin	Antinoplastic agent (chemotherapautic)	Umu C test (bacteria)	Genotoxic activity	Hospital waste water samples	Giuliana et al. (1996)

Table 4 (continued). Toxic effects of medical compounds on the environment.

Medical compound or residue	Therapeutic use	Test organisms	Toxicity	Sphere / conditions	Reference
Ibuprofen	Analgesic (pain killer)	*Trichphyton rubrum* (dermatophytes)	MIC = 5- 10 µg/ml	MIC = minimum inhibitory concentration at pH = 5	Sanyal et al. (1993)
		Trichophyton mentagrophytes (dermatophytes)	MIC = 5 - 20 µg/ml		
		Trichophyton tonsurans (dermatophytes)	MIC = 20 -40 µg/ml		
		Microsporum fulva (dermatophytes)	MIC = 10 - 40 µg/ml		
		Epidermophytes floccosum (dermatophytes)	MIC = 20 - 40 µg/ml		
		Candida albicans (pathogenic yeast)	MIC = 140 - 160 µg/ml		
		Staphylococus aureus (bacteria)	MIC = 40 - 80 µg/ml		
		Mucor sp.	MIC = 120 - 140 µg/ml		
		Staphylococus aureus (bacteria)	MIC = 150 µg/ml at pH = 7 MIC = 50 µg/ml at pH = 6		Elvers and Wright (1995)
		Daphnia magna (water flea)	EC_{50} (48 hours) = 9.06 to 11.5 mg/l. NOEC ca 3 mg/l	Acute toxicity	Knoll, BASF (1995)
		Lepomis machrochirus (bluegill sunfish)	LC_{50} (96 hours) = 173 mg/l NOEC 10 mg/l.	Acute toxicity	
		Mysidopsis bahia (mysid)	NEL (96hours) > 100 mg/l NOEC = 30 mg/l	Acute toxicity	
		Cyprinodon variegatus (sheepshead minnow)	NEL (96 hours) > 300 mg/l	Acute toxicity	
		Selenastrum capricornutum (freshwater green algae)	NEL (96 hours) > 30 mg/l		
		Skeletonema costatum (saltwater, diatom)	EC_{50} (96 hours) = 7.1 mg/l		
		Microtox® (bacteria)	EC_{50} (5 mins) = 12.3 mg/l		
Kanamycin	Antibiotic	Bacteria		Antibiotic resistence developed in envionmental samples	Leff et al. (1993)
Metronidazol	Antibiotic	*Chlorella sp.* (green algae)	EC_{10} (72 hours) = 2.03 mg/l		Lanzky and Halling-Sørensen (in press)
		Selenastrum carpricronutum (freshwater green algae)	EC_{10} (72 hours) = 19 mg/l		
Neomycin	Antibiotic	Bacteria		Antibiotic resistence developed in environmental samples	Leff et al. (1993)
Nicotin		*Daphnia magna*	LC50 = 3.7 mg/l LC50 = 5.7 mg/l		Lilius et al. (1995) Calleja et al.(1993)
Propanolol HCl	beta-receptorbloker	*Daphnia magna*	LC50 = 17.7 mg/l LC50 = 3.1 mg/l		Lilius et al. (1995) Calleja et al. (1993)

Table 4 (continued). Toxic effects of medical compounds on the environment.

Medical compound or residue	Therapeutic use	Test organisms	Toxicity	Sphere / conditions	Reference
Veteranry treatment					
Ampicillin	Antibiotic	Sediment bacteria *Vibrio harveyi*	Antibiotic resistance > 100 mg/l	 growth rate	Sandaa et al. (1992) Thomulka et al. (1993)
Amitriptylin	Psycopharmaca	*Daphnia magna*	EC50= 5.0 mg/l		Lilius et al. (1995)
Amprolium	Antiprotozoal	Nitrifying bacteria	No effect at 204µg / g manure of amprolium		Warman (1980)
Aureomycin	Antibiotic	Nitrifying bacteria	No effect at 22.5 µg / g manure of auromycin		Warman (1980)
Avermectin B1	Antiparasetic agent	*Musca vetustissima* (Bushfly)	No bush flies survived from egg to adult following cattle injectioon of 200µg/kg		Ridsdill-Smith (1988)
		Onthophagus binodis (dung beetle)	Not affected in dung of cattle treated with avermectin B1		Ridsdill-Smith (1988)
Avilamycin	Antibiotic - growth promoter	Anaerobic digestion	No overall effects on gas production		Sutton et al. (1989)
Bacitracin	Antibiotic - growth promotor	*Daphnia magna*	LC_{50} (24 hours) = 126 mg/l LC_{50} (48 hours) = 30 mg/l		Brambilla et al. (1994) Migliore et al. (1997)
		Artemia salina	LC_{50} (24 hours) = 34 mg/l LC_{50} (48 hours) = 21.8 mg/l		
		Daphnia Magna	LOEC = 5 mg/l EC50 (24 hours) = 126 mg/l EC50 (48 hours) = 30 mg/l		Di Delupis et al. (1992)
		Plants		Effects on plants mean root weight and mean stalk . Leaves weight dramatically reduced.	Brambilla et al. (1994)
Bromocyclen	Antiparacitic agent	Algae	EC10 > 100 mg/l EC50 > 100 mg/l		Kopf (1995)
		Daphina magna	LC10 = 0.4 mg/l LC 50 = 0.7 mg/l NOEC = 0.1 mg/l LC10 = 0.064 mg/l LC 50 = 0.353 mg/l	Acute test Reproduction test	
Carbadox	Antibiotic - growth promoter	Mutagensity test			Cihak et al. (1983)
			No effect on overall manure composition		Kreuzer (1994)
Chloramphenicol	Antibiotic	*Vibrio harveyi*	EC50 = 0.16 mg/l	Biolumicens test	Thomulka et al. (1993)

Table 4 (continued). Toxic effects of medical compounds on the environment.

Medical compound or residue	Therapeutic use	Test organisms	Toxicity	Sphere / conditions	Reference
Chlortetracycline	Antibiotic	*Phaseolus vulgaris* (Pinto bean plants)	At conc. up to 160 ppm in solution top dry weight were reduced 71-87% and root dry weight were reduced 66-94 %. All plants died at 160 ppm treatment level.	liquid lab. testsolution	Batchelder (1981)
		Raphanus sativus L. (Edible radish) *Triticum aestivum* L. (wheat) *Zea mays* L. (corn)	At sub. conc. up to 160 ppm stimulation of growth and N uptake was observed in a sand loam soil.		Batchelder (1982)
		Phaseolus vulgaris (Pinto bean plants)	At sub. conc. up to 160 ppm decrease of plant hights, top and root dry weight was observed		
		Soil biological activity	no effect	soil ammended with antibiotic contaning poultry manure	Warman and Thomas (1981)
		Methane production	18 mg/l antibiotic inhibited mesophilic anaerobic digestion of swine manure		Fedler and Day (1985)
Flumequine	Antibiotic	*Artemia salina*	LC_{50} (24 hours) = 477 mg/l LC_{50} (48 hours) = 308 mg/l LC_{50} (72 hours) = 96 mg/l		Brambilla et al. (1994) Migliore et al. (1997)
		Aeromonas salmonicida Bacteria	MIC (24 hours) = 4µg/ml (Tryptone soya broth) MIC (24 hours) = 128 µg/ml (Tryptone plus sea water ion) MIC (72 hours) = 16 µg/ml (Tryptone soya broth) MIC (72 hours) = 256 µg/ml (Tryptone plus sea water ion) MBC (24 hours) = 16 µg/ml (Tryptone soya broth) MIC (24 hours) = 2048 µg/ml (Tryptone plus sea water ion) MIC (72 hours) = 32 µg/ml (Tryptone soya broth) MIC (72 hours) = 256 µg/ml (Tryptone plus sea water ion)	MIC = minimum inhibitory concentration MBC = minimum bactericidal concentration	Pursell et al. (1995)
		Plants		Effects on plants mean root weight and mean stalk . Leaves weight dramatically reduced.	Brambilla et al. (1994)

Table 4. (continued) Toxic effects of medical compounds on the environment.

Medical compound or residue	Therapeutic use	Test organisms	Toxicity	Sphere / conditions	Reference
Furazolidone	Antibiotic feed-additive fish farm	Sediment bacteria	Antibiotic resistance		Nygaard et al. (1992)
		Chlorella pyrenoidosa (algae)	EC50= 1.3 mg/l	Algal toxicity test	Canton and Van Esch (1976)
		Dapnia magna	LC50 = > 30 mg/l		
		Salmo gairdneri	LC50 = > 30 mg/l		
		Lebistes reticulatus (guppy)	LC50 = 25 mg/l		
Ivermectin residues	Antiparasitic agent	*Neomyia cornicina* (dung-dwelling Diptera)	No larvel development at 0.16 mg / kg dung after injection with 200 µg / kg body weight (steers)		Lumaret et al. (1993)
		Euroniticellus fulvus (dung beetle)	Slight delayed development at 0.06 mg / kg dung after injection with 200 µg / kg body weight (steers)		
Ivermectin H_2B_{1a}	Antiparasitic agent	*Daphnia magna*	LC_{50} (48 hours) = 0.025 ppb NOEC (48 hours) = 0.01 ppb		Halley et al. (1989)
Ivermectin monosaccharide	Antiparasitic agent	*Daphnia magna*	LC_{50} (48 hours) = 0.4 ppb NOEC (48 hours) = 0.1 ppb		
Ivermectin H_2B_{1a} - aglycone	Antiparasitic agent	*Daphnia magna*	LC_{50} (48 hours) > 17 ppb NOEC (48 hours) > 9 ppb		
Ivermectin	Antiparasitic agent	*Daphnia magna*	to some extent toxic		Nessel et al. (1989)
		Salmo gairdneri (Rainbow trout)	LC_{50} (96 hours) = 3.0 mg/l NOEC (96 hours) = 0.9 mg/l		Halley et al. (1989)
		Lepomis macrochines (Bluegill sunfish)	LC_{50} (96 hours) = 4.8 mg/l		
		Eisemia foetida (Earthworm)	LC_{50} (28 days) = 18-100 mg/kg soil		Halley et al. (1989)
		Chlorella pyrenoidosa (green algae)	NEL > 9.1 mg /l		

Table 4 (continued). Toxic effects of medical compounds on the environment.

Medical compound or residue	Therapeutic use	Test organisms	Toxicity	Sphere / conditions	Reference
Ivermectin residues	Antiparasitic agent	*Musca vetustissima* (Bush fly)	Inhibited larvel development for 7 to 14 days after animal treatment.		Wardhaug et al (1996)
		Musca domestica (house fly)	Inhibited larvel development for 7 to 14 days after animal treatment.		
Ivermectin	Antiparasitic agent	*Haematobia irratans*	56 days 63 days 42 days	Sensitivity of dipteran larvae, indicated by days post-treatment until adult emergence from dung equalled that of control	Miller et al. (1981) Fincher (1992) Schmidt (1983)
		Musca autumnalis	14 days	Sensitivity of dipteran larvae, indicated by days post-treatment until adult emergence from dung equalled that of control	Mayer et al. (1980)
		Neomyia cornicina	32 days 17 days	Sensitivity of dipteran larvae, indicated by days post-treatment until adult emergence from dung equalled that of control	Wardhauge et al. (1988) Lumaret et al. (1993)
		Stomoxys calcitrans	14 days	Sensitivity of dipteran larvae, indicated by days post-treatment until adult emergence from dung equalled that of control	Schmidt (1983)
		Cyclorrapha	> 30 days 42 days	Sensitivity of dipteran larvae, indicated by days post-treatment until adult emergence from dung equalled that of control	Madsen et al. (1990) Sommer et al. (1992b)
		Nematocera	20 days 0 days	Sensitivity of dipteran larvae, indicated by days post-treatment until adult emergence from dung equalled that of control	Madsen et al. (1990) Sommer et al. (1992b)
		Ontophagus gazella	17 days 21 days	Sensitivity of coleopteran larvae, indicated by days post-treatment until adult emergence from dung equalled that of control	Sommer and Nielsen (1992c) Fincher (1992)
		Aphodius spp.	10 days 13-14 days 14 days	Sensitivity of coleopteran larvae, indicated by days post-treatment until adult emergence from dung equalled that of control	Madsen et al. (1990) Sommer et al. (1992b) Strong and Wall (1994)

Table 4 (continued). Toxic effects of medical compounds on the environment.

Medical compound or residue	Therapeutic use	Test organisms	Toxicity	Sphere / conditions	Reference
		Copris hispanus	16 days	Sensitivity of coleopteran larvae, indicated by days post-treatment until adult emergence from dung equalled that of control	Wardhaugh et al. (1988)
		Euoniticellus fulvus	10 days	Sensitivity of coleopteran larvae, indicated by days post-treatment until adult emergence from dung equalled that of control	Lumaret et al. (1988)
Kanamycin	Antibiotic	Sediment bacteria	Antibiotic resistance		Sandaa et al. (1992)
Moxidectin residues	Antiparasitic agent	*Musca vetustissima* (Bush fly)	No effect on larvea survival, but delayed development was observed.		Wardhaug et al. (1996)
		Musca domestica (House fly)	No effect on larvea survival, but delayed development was observed.		
Nitrofurazone		*S. capricornutum* (algae)	EC50 = 1.45 mg/l	algal toxicity test	Macri and Sbardella (1984)
		Daphia magna	LC50 = 28.67 mg/l		
Novobicin	Antibiotic	Sediment bacteria	Antibiotic resistance		Sandaa et al. (1992)
		Vibrio harveyi	LC50 = 0.08 mg/l	Biolumisens test	Thomulka et al. (1993)
Oxolinic acid	Antibiotic feed-additives, fish farm	Sediment bacteria	Antibiotic resistance		Nygaard et al. (1992)
Oxytetracycline	Antibiotic	*Phaseolus vulgaris* (Pinto bean plants)	At conc. up to 160 ppm in solution top dry weight were reduced 71-87% and root dry weight were reduced 66-94 %. All plants died at 160 ppm treatment level.	liquid lab. testsolution	Batchelder (1981)
		Raphanus sativus L. (Edible radish) *Triticum aestivum* L. (wheat) *Zea mays* L. (corn)	At sub. conc. up to 160 ppm stimulation of growth and N uptake was observed in a sand loam soil.		Batchelder (1982)
		Phaseolus vulgaris (Pinto bean plants)	At sub. conc. up to 160 ppm decrease of plant hights, top and root dry weight was observed		

Table 4 (continued). Toxic effects of medical compounds on the environment.

Medical compound or residue	Therapeutic use	Test organisms	Toxicity	Sphere / conditions	Reference
		Sediment bacteria	Antibiotic resistance		Husevåg et al. (1991) Sandaa et al. (1992) Samuelsen (1992a) Nygaard et al. (1992) Kerry (1995a) Kerry et al. (1995b)
Streptomycin	Antibiotic	*Vibrio harveyi* Blue green algae *Chlorella vulgaris* *Scenedesmus obliquus* *Chlamydomonas reinhardtii*	LC50 = 19 mg/l growth prevented at 0.09 to 0.86 mg/l growth prevented at 21 mg/l growth prevented at 0.66 mg/l	Biolumicens test	Thomulka et al. (1993) Harrass et al. (1985)
Sulphadimethoxine	Antibiotic	*Artemia salina*	LC_{50} (24 hours) = 1.8 g/l LC_{50} (48 hours) = 0.9 g/l LC_{50} (72 hours) = 0.5 g/l LC_{50} (96 hours) = 19 mg/l		Brambilla et al. (1994)
		Plants		Effects on plants mean root weight and mean stalk. Leaves weight dramatically reduced.	Brambilla et al. (1994)

Chlorella vulgaris, *Scenedesmus obliquus* and *Ulothrix sp.* grew in active streptomycin concentrations less than 21 mg/l, while *Chlamydomonas reinhardtii* growth was prevented at concentrations of 0.66 mg/l. Algal growth in sublethal concentrations of streptomycin was slowed or delayed, and the maximum density attained by several species was decreased. Result published by Lanzky and Halling-Sørensen (in press) showed that *Chlorella sp.* are sensitive (EC_{10} = 2.03 mg/l and EC_{50} = 12.5 mg/l) to metronidazole.

Plants

Batchelder (1981; 1982) showed that effects of the antibiotics chlortetracycline and oxytetracycline on plants vary from species to species. The most sensitive plant species in the Batchelder study was pinto beans when they were grown on sandy loam soil.

Crustaceans/copopods

The acute toxicity of furazolidone, 3-[(5-Nitrofurfurylidene)amino]-2-oxazolidinone, which are largely used in medicated fish feed, have been investigated by Macrì et al (1988). The authors found a significant toxicity of the compound on *Daphnia Magna*, while *Artemia salina* proved to be the less sensitive. Migliore et al. (1997) showed the toxicity of several agricultural antibiotics to *Artemia*.

Acute toxicity of four antibiotics; aminosidine, bacitracin , erythromycin and lincomycin, all used as feed additive or mass therapy in intensive farming, on *Dapnia magna* Straus has been performed by Dojmi di Delupis et al. (1992). EC_{50} values after 48 hours was found in the range of 30 mg/l to 500 mg/l with Bacitracin as the most potent.

Lee and Bird (1983) found that the calanoid copepods *Temora turbinata*, if raised in pharmaceutical waste concentrations above 1 ppm, resulted in smaller adult size, reduced egg production rates and an abnormal growth pattern.

Crustaceans/amphipod

Lee and Arnold (1983) studied the toxic effects of ocean-dumped pharmaceutical wastes on the marine amphipod *Amphitoe valida*. The toxic effects increased with increasing duration of exposure to waste concentration. Amphipods chronically exposed to waste concentrations above 1% had lower survival rates and reduced fecundity when compared to control groups. The parent amphipods exposed to 3% waste had 100 % mortality after three weeks, while those exposed to less than 2 % waste were able to survive over 2 months. Larvae of the amphipod survived shorter periods than the parents. No offspring were recorded for amphipods exposed to 3% waste (Lee and Arnold 1983).

Nicol et al. (1978) have shown that the pharmaceutical wastes disposed of at the Puerto Rico dumpsite were toxic to many invertebrates. Toxic levels were about 0.05 - 5% of the waste concentration, depending on species employed in the bioassay.

Fish

Only very few informations are outlined in the literature concerning the effects of medical substances on fish species.

The performed ISO laboratory assays with ibuprofen shows that the compound is almost non-toxic on bluegill sunfish and sheepshead minnow (Knoll, BASF 1995).

Mosquito Larvea

Macrì et al. (1988) showed that furazolidone had a significant toxic effect on the mosquito larvae *Culex pipiens* Larvae

Insects

The potential of animal excreted residues of anthelmintics to adversely affect the development and survival of non-target organisms, important in the process of dung degradation and nutrient cycling, was first recognised in the 1970s. Whereas drugs such as piperazine, thiabendazole and levamisole has little or no effect on dung beetle breeding, formulations of coumaphos, dichlorvos and phenothiazine adversely affected their survival and reproduction for at least 4 to 5 days after treatment (Blume et al. 1976).

Phenothiazine was also implicated in deleterious changes in the botanical composition of pastures (Southcott (1980), whereas residues of dichlorvos delayed dung degradation (Lumaret 1986)

The 1980´s saw the introduction of a new class of compounds known as macrocyclic lactones. Comprising the avermectin (doramectin, abamectin and ivermectin) and the milbemycins (moxidectin), these drugs are excreted in faeces of treated livestock, partly as unaltered drug. No data are available on the insecticidal properties of doramectin residues in dung, but effects of faecal residues of abamectin and ivermectin are reported on a wide range of arthropods. In the late 80´s Wall and Strong (1987) discovered that avermectin, an antiparasitic drug for cattle treatment, had an effect on dung degrading insects and delay in degradation of pats from cattle treatment was observed. The environmental aspects and effects of avermectin have also been investigated by e.g. Sommer C. (1992a); Sommer et al. (1992b); Sommer and Overgaard Nielsen (1992c) and Holter (1993). Results show that the duration of effects after treatment of ivermectin on dung degrading organisms is depended of e.g. species, temperature, soil composition and type of livestock.

Resistant development

Antibacterial resistance is a threat to the efficacy of antibacterial substances. Since it is generally agreed that the extent of usage of antibacterial substances is closely related to the development of antibacterial resistance, it is important to investigate this feature. The development of resistance to antimicrobial agents by many bacterial pathogens has compromised traditional therapeutic regimens, making treatment of infections more difficult. Three factors have contributed to the development and spread of resistance: mutation in common genes that extend their spectrum of resistance, transfer of resistance genes among diverse micro-organisms, and increases in selective pressures that enhance the development of resistant organisms. Resistance to kanamycin and neomycin in the bacterial assemblage of a coastal plain stream of South Carolina, US, was detected by growth of colonies on media containing antibiotics (Leff et al. 1993). Attrassi et al. (1993) reported resistance of bacterial flora to some antibiotics from water, mussels and

sediments sampled at three marine sites, localised in Marocco. Resistance to penicillin and ampicillin common to all sites, polluted or not, was frequent. However bacterial resistance to erythromycin, tobramycin, chloramphenicol and tetracycline was limited to polluted sites by slaughter house effluents or sewage. Multi-resistens was frequent: more than 55% of strains resisted at least one antibiotic and more than 20% carried plasmids. Antibiotic resistance in sediment bacteria are often found in locations with fish farms. Several papers e.g., Samuelsen et al. (1992a); Husevåg et al. (1991); Sandaa et al. (1992); Nygaard et al. (1992), have all reported findings of sediment bacteria resistant to various antibiotics used as feed additives in fish farms.

Genotoxicity

In recent years there has been an increasing interest in the genotoxicological effects connected to the spreading of genotoxins in the environment. The attention has been focused on the aquatic environment especially testing of surface water samples used as drinking water, waste water and sludge samples. Several papers also report of bacterial mutagens in the urine of patients in therapeutic treatment with medical substances e.g. tinidazole, prescribed against protozoal infections, (Espinosa-Aquirre et al., 1996), metronidazole (Connor et al.1977) general studies (Mortelmans et al. 1981; Monteith et al. 1987).

Giuliana et al. (1996) analysed the genotoxic potential of 800 native (unconcentrated samples) waste water from a hospital with the umuC test. Genotoxic activity was found in 13 % of the samples. The highest genotoxic activity occurred in the morning hours, but genotoxic samples were detected also during the day and at night. 96% of the genotoxic waste water samples revealed a genotoxic potential without growth inhibition of the bacteria monitored as OD600, in the same way as antinoplastic drugs like mitomycin C or cisplatin. 4% of the genotoxic waste water samples showed combined cytotoxic and genotoxic activities as seen in control experiments using glutaraldehyd containing disinfectants and certain antibiotics. Due to the fact that the samples were unconcentrated a considerable amount of genotoxic substances is released to the environment especially during morning hours. Similar findings were reported by Gartiser et al. (1994) and Giuliana et al. (1994) with and without metabolic activation of Ames test.

7. Legislation

For several years the environmental fate and effect requirements for veterinary drugs have been in place in the US. The Food and Drug Administration (FDA) issued the final rule requiring compliance for human pharmaceuticals under the National Environmental Policy Act (NEPA) in 1985. In March 1987, FDA prepared and issued its Environmental Assessment Technical Handbook for FDA-required environmental Assessment (Cwiertniewicz 1994; FDA 1985; FDA 1987). Finally in 1995, FDA issued its guidance for industry for the submission of an environmental assessment in human drug application and supplements.

In Europe the legislation on the area has first been initiated in the beginning of the 90's and it distinguishes between medical substances which do not contain (or consists of) genetically modified organisms (GMOs) and medical substances which do contain (or consists of) genetically modified organisms (GMO). These two groups are further divided into veterinary medicinal products and human medicinal products. All new EU policy making will include an

environmental dimension. This means that all new draft EU laws (in transport, agriculture, fisheries, medicine etc) i.e., also pharmaceuticals, will be assessed for potential environmental impact. Directive 81/852/EEC (as amended since 1. April 1993) is known as the "technical directive" concerning veterinary medical products. It outlines in sections on ecotoxicity the basic requirements of conducting an environmental risk assessment. A note for guidance (EMEA/ CVMP/055/96-FINAL) issued in 1997 gives a detailed technical guidelines for assessing the risk of veterinary medical substances.

The technical directive for human medicinal products (EU directive 75/318/EEC) does not include any reference to ecotoxicity or ecotoxicology and there are apparently no plans about doing this. In this way it differs from its veterinary counterpart (EU derective 81/852/EEC) which is described above. Therefore, except for very few GMO-containing products, the legislation do not specify how to conduct environmental risk assessments for human medicinal products. A detailed technical draft guideline III/5504/94 issued in 1994 indicated that the same approach applicable for veterinary also would apply for human medicinal substances. This technical guideline has not yet been finalised. Rumours says that because the FDA have never rejected the application for marketing a human medical substance due to environmental risk consequences FDA will reduce the law. The EU is therefore waiting for this decision later this year to finalise the technical guidelines. It is expected to appear in a less demanding form than that appearing in the draft versions. For a comprehensive discussion on these issues see (Irwin 1994a; 1994b and Cwiertniewicz 1994).

Thus, presently it seems that only the veterinary guidelines are expected to invoke, in the context of the relevant characteristics of any affected environment, the various descriptors used in ecotoxicological evaluations.

The scientific reason for this different treatment of the veterinary and human drug is quite obscure.

8. Discussion

Exposure assessment

Some high volume medical substances are probably released to the environment at the same order of magnitude as other xenobiotics known to be found in nature. Examples are antibiotics used as growth promoters in livestock production, as feed additives in fish farms, or as cocciostatics in poultry production. Several investigations, e.g. Jacobsen and Berglind (1988) and Samuelsen (1992a; 1992b), report findings of antibiotics in sediment cores originating from medication in fish farms. Three investigations published in the literature present findings of medical substances in ground water (Eckel et al. 1993; Holm et al. 1995; Stan et al. 1994). Even though the substances found in ground water probably originates from spills, it is surprising that these substances have been transported through the soil to a ground water plume without being mineralised. The literature also presents the finding of a substance, clofibrate, used in human treatment to decrease cholesterol level in blood, that normally is expected to be metabolised in the liver to a more water soluble conjugated form of clofibrinc acid. In all samples analysed from different water samples, originating from the surroundings of Berlin, the substance was found as the free acid clofibrinic acid. This result indicates that the phase II metabolites, which the liver often transform medical substances into, will be hydrolysed in nature. The unconjugated metabolites are often more hydrophobic than the phase II conjugated substances, which enables them to bioaccumulate.

Berger et al. (1986) showed that the excretion from medicated domestic cattle contain a considerable amount of medicinal compounds, which may stress the agricultural environment. Thus, they also demonstrated that the main phase II metabolites are transformed by bacterial activities in liquid manure. They are thus dependent of the compound in question to reactivate to the original compounds or relatively active phase I metabolites.

Present knowledge can not reveal if regular therapeutic use, on humans or animals, may be the source of a substance carried by sewage effluent into the aquatic system.

Several papers have reported that antibiotics are persistent in sediment cores e.g. Jacobsen and Berglind (1988), Hektoen et al. (1995). Only one paper reports the metabolization of a compound released to nature. Florfenicol is rapidly metabolised to florfenicol amine in sediment cores (Hektonen et al. 1995).

Although that a huge amount of antibiotics, in Denmark alone more than 100 tonnes active substance, are used as growth promoters only few information's exists, to the authors knowledge, of occurrence, persistence or fate of these antibiotics when they are dispersed with manure on the fields. From the literature it is known that 30 to 90 % of an administrated dose of most antibiotics to humans and animals is excreted with the urine as active substance (Rang and Dale 1991).

A few investigations reports the finding and fate of hormones in the environment (Shore et al. 1988; Gregers-Hansen 1964).

Informations about the physico chemical parameters describing the environmental fate of medical substances are difficult to obtain. As a result it is practically impossible to estimate predicted environmental concentration (PEC) of any medical substances with the available knowledge.

Effect assessment

The few toxic effect data presented in the literature (see table 4), often quantified as effect concentration data (EC) or maximum inhibition concentration (MIC), for various medical substances are usually performed on very few species e.g. micro-organisms, phytoplankton, crustaceans, mosquito larvae and amphipod. Results are mostly given for antibiotics. Only few studies reveal the effect of substances used for human treatment. One of them outlines the effect of Ibuprofen on micro-organisms. Recent published results shows that metronidazole, a compound used for treatment of anaerobic micro-organisms, is rather potent on the green algae *Chlorella sp.* (Lanzky and Halling-Sørensen, in press).

All toxicity test presented in the literature are performed as acute toxicity tests. Due to the fact that at least some of the antibiotics exposed to the environment are found to be rather persistent, it would be more relevant to perform life cycle test on organisms representing different trophic layers to identify the hazard of the substance in question rather than to perform acute toxicity tests. Since medical substances often have a specific mode of action it would be more accurate to assess these compounds by use of assays that would reveal e.g. endocrine activity or hormone activity instead of acute toxicity. The presence of antibiotics in manure and other waste may cause the following problems as indicated by Macrí et al (1988); (1) if the manure is used as fertiliser it may produce adverse

effects on ground-nitrifying bacteria, (2) the introduction of waste containing antibacterial drugs to treatment plants that use bacteria (e.g., methane production) may cause disruption of the purification processes. (3) if the waste may have toxic effects on aquatic and/or terrestrial ecosystems it may consequently interfere with trophic chains. The risks of this contamination to the different aquatic and/or terrestrial organisms are yet unknown. Informations in the literature of the antibiotic resistant which may spread between micro-organisms are quite sparse. One study revealed that effluent waste water from hospitals to some extent was genotoxic. Also the anticipated effects of hormones and antioplastic agents on the environment are discussed in the literature. Especially these two groups of substances may have effects at even low substance concentrations, wherefore it is important to investigate the impact of these substance groups on the environment. The only group of medical substances which have been investigated to some extents is the antiparasetic agents used as therapeutics for livestock on fields.

Because our knowledge is so sparse on the subject it is not possible to conduct thorough environmental risk assessments for any substance. The object is not to forbid the use of medical substances. Nature will probably never stand over the health of mankind. The object is to develop a sound frame for performing necessary risk assessment and to estimate risks on sound knowledge.

9. Conclusions

Very little is known about the exposure routes of the medical substances to the environment. Most investigations report on the exposure and effects of antibiotics in sediments originating from administration of antibiotics as feed additive to fish farms or growth promoters. Only a few investigations have reported findings of medical substances in other field samples. Medical substances have been detected in sediment samples originating from antibiotics in feed additives and in ground water samples originating from spills. I seems that at least some antibiotics are persistent in sediments and that several antibiotics were found to adsorb to sediments of marine origin. Concerning medical substances for human treatment the knowledge is practically zero. One study showed that quite a number of high volume substances were persistent in the sewage treatment plant.

Present knowledge can therefore not reveal if regular therapeutic use may be the source of a substance carried by sewage effluent into the aquatic system, even though one compound has been identified in ground and tap water samples from Berlin. In conclusion, further research in this hitherto little explored field would be necessary to assess the environmental risk involved in exposing medical substances to the environment.

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