Review of Veterinary Medicines in the Environment

R&D Technical Report P6-012/8/TR

A B A Boxall, L Fogg, P A Blackwell, P Kay and E J Pemberton

Research Contractor:
Cranfield Centre for EcoChemistry

Publishing Organisation
Environment Agency, Rio House, Waterside Drive, Aztec West, Almondsbury, BRISTOL, BS32 4UD.
Website: www.environment-agency.gov.uk

Tel: 01454 624400 Fax: 01454 624409

ISBN: 1 85705 780 5

Dissemination Status
Internal: Released to Regions
External: Released to Public Domain

Statement of Use
This document describes a review of the environmental impacts of veterinary medicines in the environment. Data collated as part of the review has been used to identify compounds considered to be high priority for further work.

Research Contractors

This document was produced under R&D Project P6-012/8 by:

Cranfield Centre for EcoChemistry, Cranfield University, Shardlow Hall, Shardlow, Derby, DE72 2GN

Tel: 01332 799000 Fax: 01332 799161

Environment Agency Project Manager

The Environment Agency's Project Manager for R&D Project P6-012/8 was:
Dr Emma Pemberton, National Centre for Ecotoxicology and Hazardous Substances, Evenload House, Howbery Park, Wallingford, Oxon, OX10 8BD

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

tel: 01793-865138 fax: 01793-514562 e-mail: publications@wrcplc.co.uk

CONTENTS

LIST OF FIGURES

LIST OF TABLES

EXECUTIVE SUMMARY

Veterinary medicines are widely used to treat disease and protect the health of animals. Dietary enhancing feed additives may also be incorporated into the feed of animals to improve their growth rates. Because of historic, measurable impacts in the environment, a number of groups of veterinary medicines (i.e. sheep dip chemicals, fish farm medicines and anthelmintics) are known to be of environmental concern. However, the environmental fate, behaviour and effects of other veterinary medicines and their potential environmental impacts are less well understood.

Any new medicine to be placed on the market requires authorisation by the relevant authority. For authorisation specific to the UK, the relevant authority is the Veterinary Medicines Directorate and for EU-wide authorisations it is the European Medicines Evaluation Agency (EMEA). Since 1997, environmental risk assessments have been required for all new veterinary medicines and all other medicines as they come up for review (every 5 years). Guidelines are available for the environmental risk assessment of veterinary medicines within the EU. The approach is performed in 2 phases. In Phase 1 the likelihood of exposure to the environment is assessed and if the product does not meet certain criteria (e.g. if the soil PEC is greater than 100 $\mu g\ kg^{-1}$), then Phase 2 assessment is required. Phase 2 can be performed in two tiers, in the first tier the likely impact of the substance is assessed using a range of standard tests and the second tier involves more detailed investigations into the compartment(s) of interest. The Veterinary International Co-operation on Harmonisation (VICH) is working to harmonise environmental risk assessment approaches across the EU, USA and Japan, with Australia and New Zealand as observers. Guidelines are already available for Phase 1 assessments and draft guidelines are currently being produced for Phase 2 assessments of products used for grazing animals, intensively farmed animals and for use in aquaculture.

To gain a greater understanding of the potential risks to the environment arising from the use of veterinary medicinal products the Environment Agency commissioned Cranfield Centre for EcoChemistry to review the information in the literature on veterinary medicines in the environment. The review considered current regulatory mechanisms, usage, likely exposure routes, environmental fate and behaviour and environmental effects. On the basis of the data collected, an initial identification and prioritisation of those veterinary medicines of most significant environmental concern has been made. This information should assist in 1) guiding the Agency's policy direction; 2) ensuring the Agency's monitoring programme is effectively targeted; and 3) where necessary, enable pollution prevention tools to be applied.

The potential impact of a veterinary medicine on the environment will be determined by a number of factors including:

- amount used;
- usage pattern;
- metabolism;
- persistence in manure and slurry;
- sorption and persistence in the environment; and
- ecotoxicity.

Each of these areas was considered in the review and they are discussed below.

A wide range of veterinary medicinal products are used to treat animals in the UK. Data were available from a number of sources on the identity and usage of many veterinary medicines, including antibacterial agents, sheep dip chemicals and prescribed medicines. Based on the available data, antibacterials are sold in the highest amounts followed by coccidiostats, organophosphate sheep dip chemicals, growth promoters, endoparasitic wormers, general anaesthetics, other neurological preparations, ectoparasiticides, antifungal agents, nonsteroidal anti-inflammatory drugs (NSAIDs), hormones and enteric preparations. Several other therapeutic groups were identified, on the basis of limited information, as potentially important. These were antiseptics, steroids, diuretics, cardiovascular and respiratory treatments and immunological products.

Even if a product is used in large amounts, it may not have the potential to reach the environment in significant quantities. The potential for a veterinary medicine to be released to the environment is determined by a range of factors including the type of treatment; route of administration; the numbers of animals being treated; degree of metabolism; and degradation in slurry or manure prior to application to land.

Treatments used in aquaculture typically have a high potential to reach the aquatic environment, primarily because they are added directly to the environment, whereas the main route of entry to the terrestrial environment will be from the use of veterinary medicines in intensively reared livestock. For livestock treatments, medicines applied topically may have the potential to wash off, whereas medicines applied by other routes may be released to the environment either indirectly (e.g. via the application of manure and slurry to land) or directly (e.g. through the use of veterinary medicines in pasture-reared animals where pharmaceuticals may be excreted directly into the environment). For substances applied orally or by injection there may be the potential for metabolism of the drug by the animal, meaning that reduced amounts of the parent compound are excreted in the faeces and urine. The extent of metabolism will vary according to animal type and age and the class of medicine. For substances used to treat housed livestock, there may also be the potential for degradation during storage of manure and slurry, prior to land spreading. The persistence of major groups of veterinary medicines excreted in manure and slurry varies. Under UK conditions, sulphonamides, beta-lactams, macrolides and aminoglycosides are likely to be degraded. However quinolones and tetracyclines are likely to persist.

Compared to aquaculture treatments and treatments for intensively reared livestock, emissions during the manufacturing of pharmaceuticals and from the treatment of companion animals are likely to be less significant. However, whilst the disposal of waste medicines is subject to a range of controls and guidelines, it is possible that products are inappropriately disposed of to surface waters and refuse and consequently these routes may pose a risk to the environment. Currently there is insufficient information to assess the significance of disposal as a potential source of veterinary medicines in soils, groundwaters and surface waters and this should be investigated further.

Once released to the environment, veterinary medicines may be transported to other environmental compartments or be degraded. The degree to which veterinary medicines sorb to soil (and hence their mobility) varies widely. Consequently the mobility's of different veterinary medicines are also likely to vary widely. Partition coefficients (Kd) range from low (0.61 l kg^{-1}) to high (6000 l kg^{-1}). The sorption of veterinary medicines in different soil types can also vary widely and, unlike many industrial compounds and pesticides, this variation cannot be explained by hydrophobicity and soil organic carbon content. This means that in order to arrive at realistic assessment of the potential for transport and uptake of veterinary medicines in the environment, the Koc (which is used in many exposure models) may not be appropriate

Veterinary medicines can persist in soils for days to years and studies have demonstrated that half-lives are influenced by a range of factors including temperature, pH and the presence of manure. In surface waters, substances may be photodegraded (e.g. the tetracyclines, quinolones, ivermectin and furazolidone), although this degradation route is likely to be of little significance in the UK. Generally, published studies have considered the degradation of the parent compound and limited information is available for transformation products.

A number of studies have determined concentrations of veterinary medicines in environmental media although, with the exception of sheep dip chemicals, these have been on an *ad-hoc* basis and have focused on aquaculture products and antibacterial substances. Compounds used in sheep dip preparations can routinely exceed their EQS. Concentrations of sheep dip chemicals were reported as being as high as 19.2 x 10^6 ng l^{-1} in surface waters and 489 ng l^{-1} in groundwaters. Reported concentrations of aquaculture products were as high as 1 μg l^{-1} in surface waters and 285 μg g^{-1} in sediment. A limited amount of data were available on concentrations of antibacterial agents and anthelmintics to treat livestock Reported concentrations of chlortetracycline, ivermectin and monensin in soil were as high as 42 μg kg^{-1}, 2 μg kg^{-1} and 1 mg kg^{-1}, respectively. Oxytetracycline, tetracycline, chlortetracycline and tylosin were also detected in groundwater.

Information on the effects of veterinary medicines at the field scale is limited. However data are available from laboratory studies on the toxicity of veterinary medicines to individual groups of organisms. The acute and chronic effects of avermectins and sheep dip chemicals on aquatic and terrestrial organisms have been well documented and these substances are known to be toxic to organisms at low concentrations (ng l^{-1} to μg l^{-1}). Concerns have also been raised about the possibility of indirect effects of these substances on predatory species (e.g. birds and bats) although limited information was available on these potential effects. Data were available on the ecotoxicity of other products, in particular antibacterial agents, anticoccidials and performance enhancers. Aquatic toxicity values for these classes were in the mg l^{-1} range whereas the lowest reported effect concentration for the terrestrial species tested was 100 μg kg^{-1}. A number of veterinary medicines have been shown to exhibit endocrine disrupting activity. However, due to limited information, it is difficult to assess the significance of veterinary medicines as a cause of endocrine disruption in the environment.

It is clear from the review that there are a large number and wide variety of veterinary medicines in use and that with the exception of a few groups of compounds, limited

information is available in the public domain on potential environmental impacts. Therefore in order to identify substances of potential concern a prioritisation scheme was developed. The scheme employed a two phased approach. Phase 1, which is described in this report, is essentially an initial broad screen, using only those factors considered most influential in determining risk to the environment. The aim of phase 1 was to identify those veterinary medicines considered to have the greatest potential to impact the environment, and hence the highest priority, with a view to considering their risk to the environment in further detail in future work. It is important to recognise that many compounds identified as high priority in this exercise may not actually cause adverse impacts on the environment. The prioritisation exercise is simply a way of assessing the relative potential for veterinary medicines to cause harm.

Using the approach, a total of 56 compounds were assigned to the 'high priority' category. However, there was only sufficient data available to characterise the potential risk for eleven of these compounds. These compounds are, in order of priority (the information in parentheses indicates the treatment scenario(s) that poses a 'high risk' and the environmental compartment of concern for which high toxicity has been demonstrated):

- oxytetracycline (herd and aquaculture scenarios/aquatic compartment)
- chlortetracycline (herd scenario/aquatic and terrestrial compartments)
- tetracycline (herd scenario/aquatic compartment)
- sulphadiazine (aquaculture scenario/aquatic and terrestrial compartments)
- amoxicillin (herd and aquaculture scenarios/aquatic compartment)
- diazinon (herd scenario/aquatic and terrestrial compartments)
- tylosin (herd scenario/aquatic compartment)
- dihydrostreptomycin (herd scenario/aquatic compartment)
- apramycin (herd scenario/terrestrial compartment)
- cypermethrin (herd scenario/aquatic compartment)
- sarafloxacin (aquaculture scenario/aquatic and terrestrial compartments)

It should be noted that whilst an indication is made of the environmental compartment(s) of concern on which the current prioritisation is based for some substances, insufficient hazard data on other compartments has precluded an assessment of the potential risk to those other compartments. It is suggested that these additional data, where absent, are sought to enable a more comprehensive environmental risk assessment to be conducted.

Compounds identified as potentially high priority, but requiring further data were (ranked on the basis of annual usage):

1. trimethoprim
2. baquiloprim
3. amprolium
4. clopidol
5. lasalocid sodium
6. maduramicin
7. nicarbazin
17. morantel
18. flumethrin
19. triclabendazole
20. fenbendazole
21. levamisole
22. ivermectin
23. cephalexin
33. dimethicone
34. poloxalene
35. toltrazuril
36. decoquinate
37. diclazuril
38. phosmet
39. piperonyl butoxide

8. robenidine hydrochloride
9. procaine penicillin
10. procaine benzylpenicillin
11. clavulanic acid
12. monensin
13. salinomycin sodium
14. flavophospolipol
15. neomycin
16. flavomycin
24. florfenicol
25. tilmicosin
26. oxolinic acid
27. lido/ligocaine hydrochloride
28. tiamulin
29. lincomycin
30. clindamycin
31. nitroxynil
32. enrofloxacin
40. amitraz
41. deltamethrin
42. cypromazine
43. emamectin benzoate
44. antiseptics
45. immunological products

A number of recommendations for further work were made. These include

- Obtaining further data to address data gaps and refine the current prioritisation exercise.

- Gaining a greater understanding of the actual risk posed to the environment by those compounds identified as a high priority by undertaking futher, more detailed assessment. Assessments should take into account different treatment scenarios, metabolism, the relative importance of different exposure routes and additional data not considered in the current prioritisation exercise (i.e. persistence, bioaccumulation potential and mobility)

- Consideration of the environmental risks posed by metabolites of those veterinary medicines which undergo significant metabolism following administration to the animal.

- Targeted environmental monitoring to be performed to determine whether those compounds identified as a high priority are present in the environment at ecologically significant levels.

- Development of appropriate pollution prevention tools, where required, on the basis of the outcome of further assessment and targeted environmental monitoring.

In addition to the recommendations described above for further work, a number of more general recommondations regarding the regulatory approvals process, liaison between research groups active in this field and areas requiring further scientific research were made. These include:

- Bringing the regulatory risk assessment regime for veterinary medicines in line with regulatory risk assessment regimes for other chemicals such as industrial chemicals, pesticides and biocides, in light of concerns raised over the use of a ‘trigger concept’, as currently used.

- Validation of existing risk assessment exposure models

- Assessment of endocrine disrupting potential included as part of the regulatory risk assessment regime, once suitable standard testing procedures have been agreed.

- A requirement for applicants to develop suitable analytical methods for environmental analysis as part of the product registration requirements

- Improved liaison between researchers currently engaged in investigating the environmental effects of pharmaceuticals (veterinary and human).

- Further research to establish species sensitivity distributions, indirect effects and likely impacts at the landscape scale for those veterinary medicines identified as being of potentially high environmental risk.

LIST OF ACRONYMS

Organisations:

AHDA	Animal Health Distributors Association
AWVP	Association of Wholesalers to the Veterinary Profession
BVI	British Veterinary Index
CVMP	Committee for Veterinary Medicinal Products
DEFRA	Department of the Environment, Food and Rural Affairs
EA	Environment Agency
EMEA	European Agency for the Evaluation of Medicinal Products
FEDESA	European Federation of Animal Health
IMS	IMS Health
NOAH	National Office of Animal Health
RIVM	National Institute of Public Health and the Environment (The Netherlands)
SEPA	Scottish Environment Protection Agency
VICH	International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
VMD	Veterinary Medicines Directorate

Others:

API	Active pharmaceutical ingredient
CE	Capillary electrophoresis
EIA	Environmental impact assessment
EQS	Environmental quality standard
GC	Gas chromatography
GSL	General sales list medicine
HPLC	High performance liquid chromatography
IPPC	Integrated pollution prevention and control
MAC	Maximum allowable concentration
MS	Mass spectrometry
NMR	Nuclear magnetic resonance spectroscopy
P	Pharmacy medicine
PEC_{soil}	Predicted environmental soil concentration
PML	Pharmacy and merchant list medicine
PNEC	Predicted no-effect concentration
POM	Prescription only medicine
PSU	Periodic safety update report
TLC	Thin layer chromatography
VMP	Veterinary medicinal product

1 INTRODUCTION

Veterinary medicines are widely used in the UK and across Europe to treat disease and protect the health of animals. Dietary enhancing feed additives (growth promoters) are also incorporated into the feed of animals reared for food in order to improve their growth rates. Under Directive 81/852/EEC as amended by 92/18/EEC veterinary medicinal products must be assessed for their quality, efficacy and safety (to both humans and the environment). Only products approved for use by the regulatory authority may be used.

Release of veterinary medicines to the environment occurs both directly, for example the use of medicines in fish farms, and indirectly, via the application of animal manure (containing excreted products) to land. Because of historic, measurable impacts in the environment, a number of groups of veterinary medicines, primarily sheep dip chemicals (Environment Agency, 2001; Environment Agency, 2000; SEPA, 2000; Environment Agency, 1998), fish farm medicines (Davies *et al*., 1998; Jacobsen and Berglind, 1988) and anthelmintics (McKellar, 1997; Strong, 1993; McCracken, 1993; Madsen *et al*., 1990; Ridsdill-Smith, 1988; Wall and Strong, 1987) are known to be of environmental concern. However, there are scant data available in the public domain on the environmental fate, behaviour and effects of other generic groups of veterinary medicines and so their potential environmental impacts are less well understood (Jørgensen and Halling-Sørensen, 2000). With the exception of sheep dip chemicals, the Environment Agency does not currently monitor for veterinary medicines in the environment.

The need for further information in the public domain on the environmental impact of veterinary medicines has been identified as a priority in the recently published Pesticides in the Environment Working Group (PEWG) report (Environment Agency, 2001). In addition, there has been a recent upsurge in interest from both the scientific community and the media in the presence and potential adverse effects of pharmaceuticals in the environment. In response to this the Environment Agency commissioned an assessment of the potential environmental risk of human pharmaceuticals in the environment (Ayscough *et al*., 2000). The study identified gaps in knowledge and as a consequence made a number of recommendations.

To gain a greater understanding of the potential risks to the environment arising from the use of veterinary medicinal products the Environment Agency has commissioned the current review. This considers available data on exposure routes, environmental fate, behaviour and effects of all generic groups of veterinary medicines. On the basis of the data collated, an initial identification and prioritisation of those veterinary medicines of most significant environmental concern has been made.

The outputs from this review will be used to:

- guide Agency policy direction
- ensure that the Agency's monitoring programme is effectively targeted and,
- where necessary, enable pollution prevention tools to be applied

The review is based predominantly on data available in the public domain and involved literature searches of Cranfield University's in-house sources, external databases and the

internet. Contacts were also made with a number of organisations who are active in this area, including: the Veterinary Medicines Directorate (VMD), RIVM, the National Office for Animal Health (NOAH) and research institutes in the US and Europe.

The initial findings were presented at a workshop held on the 29 March 2001. Workshop participants included representatives of the Veterinary Medicines Directorate, the Department for Environment, Food and Rural Affairs (DEFRA), the Scottish Environment Protection Agency (SEPA), English Nature and the pharmaceutical industry. Feedback from the workshop and consultation with the National Office of Animal Health has been an integral part of the production of this report. A summary of the workshop findings is provided in Appendix A.

The report is divided into the following sections:

1. Introduction
2. Environmental assessment of veterinary medicines during registration in the US and EU
3. Veterinary medicine use in the UK and other countries
4. Pathways of environmental contamination
5. Occurrence in the environment
6. Environmental fate
7. Environmental hazard
8. Prioritisation
9. Conclusions
10. Recommendations for further work

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

The project has been divided into two stages. Phase I of the project covers the review and initial prioritisation described herein. The recommendations from this work will then be taken forward in Phase II of the project which is scheduled to start in early 2002.

2 ENVIRONMENTAL ASSESSMENT OF VETERINARY MEDICINES DURING REGISTRATION IN THE EU

2.1 Responsible authorities

In many countries, a pharmaceutical company is required to demonstrate the quality, safety and efficacy of a new pharmaceutical product before it can be marketed. To assess the environmental safety of products a risk assessment is conducted. In the EU, the regulatory authority responsible for assessing applications, is the European Medicines Evaluation Authority (EMEA) (for Europe-wide authorisation) or the Member State's regulatory authority if individual country authorisation is sought. In the UK, the relevant authority is the Veterinary Medicines Directorate (VMD).

To assist companies in performing the environmental risk assessments, a number of guidelines have been developed. The guidelines that are currently in use in the UK and Europe are outlined below.

2.2 Environmental Risk Assessment in the EU

In the EU, under EU Directive 81/852/EEC as amended by Directive 92/18/EEC it is necessary, when applying for a marketing authorisation for a veterinary product, to assess any potential harmful effects which the use of the product may cause to the environment and identify any precautionary measures which may be necessary to reduce such risks. This means that an environmental risk assessment has been performed on all new products produced since 1997. Older products are being assessed as they come up for renewal of marketing authorisations (applications for these are required every 5 years).

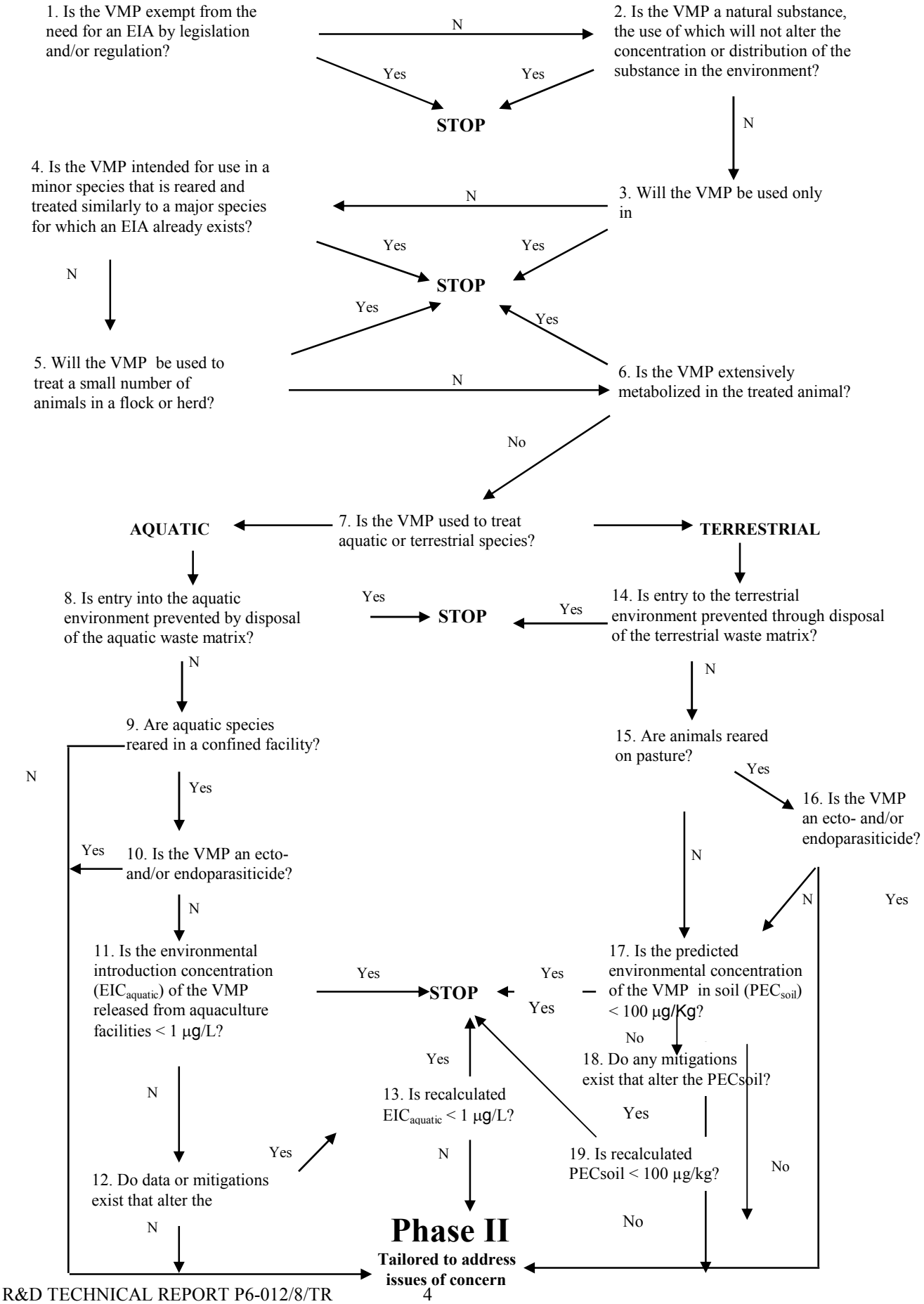
The assessments are performed in 2 phases (CVMP, 1997). The approaches used for the Phase 1 and Phase 2 assessments are described in the following sections.

2.2.1 Phase 1

In the first phase (Phase 1), the potential for environmental exposure is assessed according to the intended use of the veterinary medicine.

Since July 2001, guidelines developed by the Veterinary International Co-operation on Harmonisation (VICH, 2000) have been available for Phase 1 assessments. The Phase 1 assessment makes use of a decision tree, the questions used in the decision tree and the approach used is illustrated in Figure 2-1.

Figure 2-1 Phase 1 decision tree (VICH, 2000)



2.2.2 Phase 2

The phase 2 assessment is performed in two parts, Tier A and Tier B. Assessment will stop at tier A if the product has been shown to present no risk. The decision tree used for Phase 2 assessments of veterinary medicines, other than fish medicines, is illustrated in Figure 2-2. The approach used for fish medicines is shown in Figure 2-3.

In Tier A, the possible fate and effects of the drug and/or its major metabolites are assessed in more detail than in Phase 1. Depending on the characteristics of the drug, tests may be required on aquatic species (fish, daphnids and algae), earthworms and plants. There may also be a need to determine the degradation half-life of the active substance in the environmental compartment(s) of interest. Typical tier A studies include:

- degradation rates in 3 soils
- acute earthworm toxicity study
- phytotoxicity study
- adsorption-desorption studies, in 3 soils
- acute toxicity tests with daphnids, algae and fish
- effects on soil microorganisms

If the product exhibits insecticidal activity then additional studies on dung fauna (1 species of dung fly, 1 species of dung beetle) and grassland invertebrates also need to be assessed.

If after Tier A there is an indication that the compound poses an environmental risk and that any proposed risk management strategies are inadequate, then further assessment (tier B is required). Tier B involves the refinement of the risk assessment using studies of effects on the fauna and flora within the environmental compartments that are likely to be affected, typical Tier B tests include:

- degradation in soil (DT50) and soil transformation pathway
- sublethal effects on earthworms
- field studies
- tests for effects on soil microflora
- tests with grassland invertebrates
- tests on terrestrial vertebrate wildlife

2.2.2.1 Development of Phase 2 guidelines by VICH

Harmonised, Phase 2 guidance documents are currently under development by VICH (available in draft form). The guidance is divided into three sections, covering products used in aquaculture; the treatment of intensively reared animals; and the treatment of animals on pasture..

Figure 2-2 Phase II – Tier A: Decision tree for medicines other than fish medicines (adapted from CVMP, 1997)

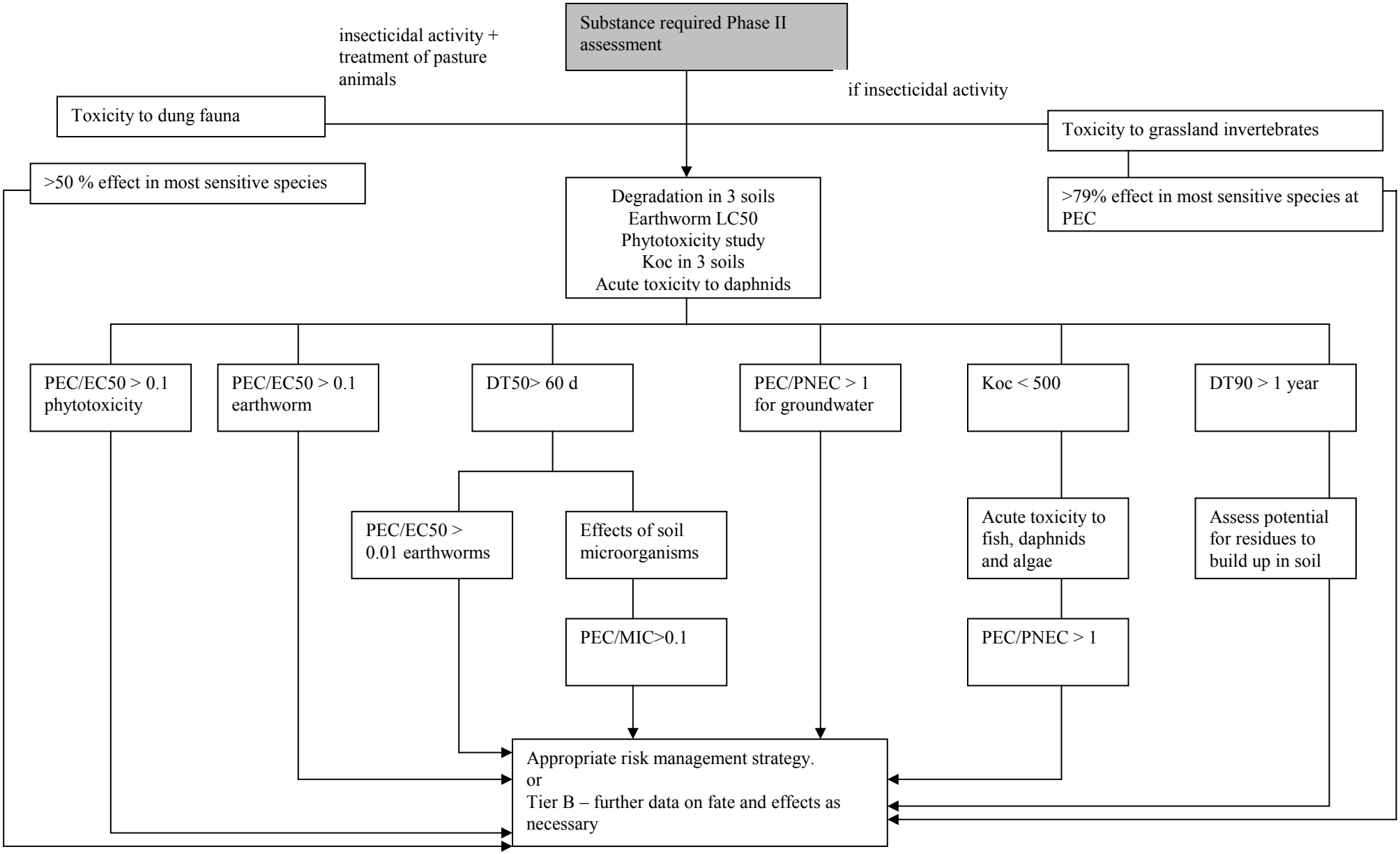
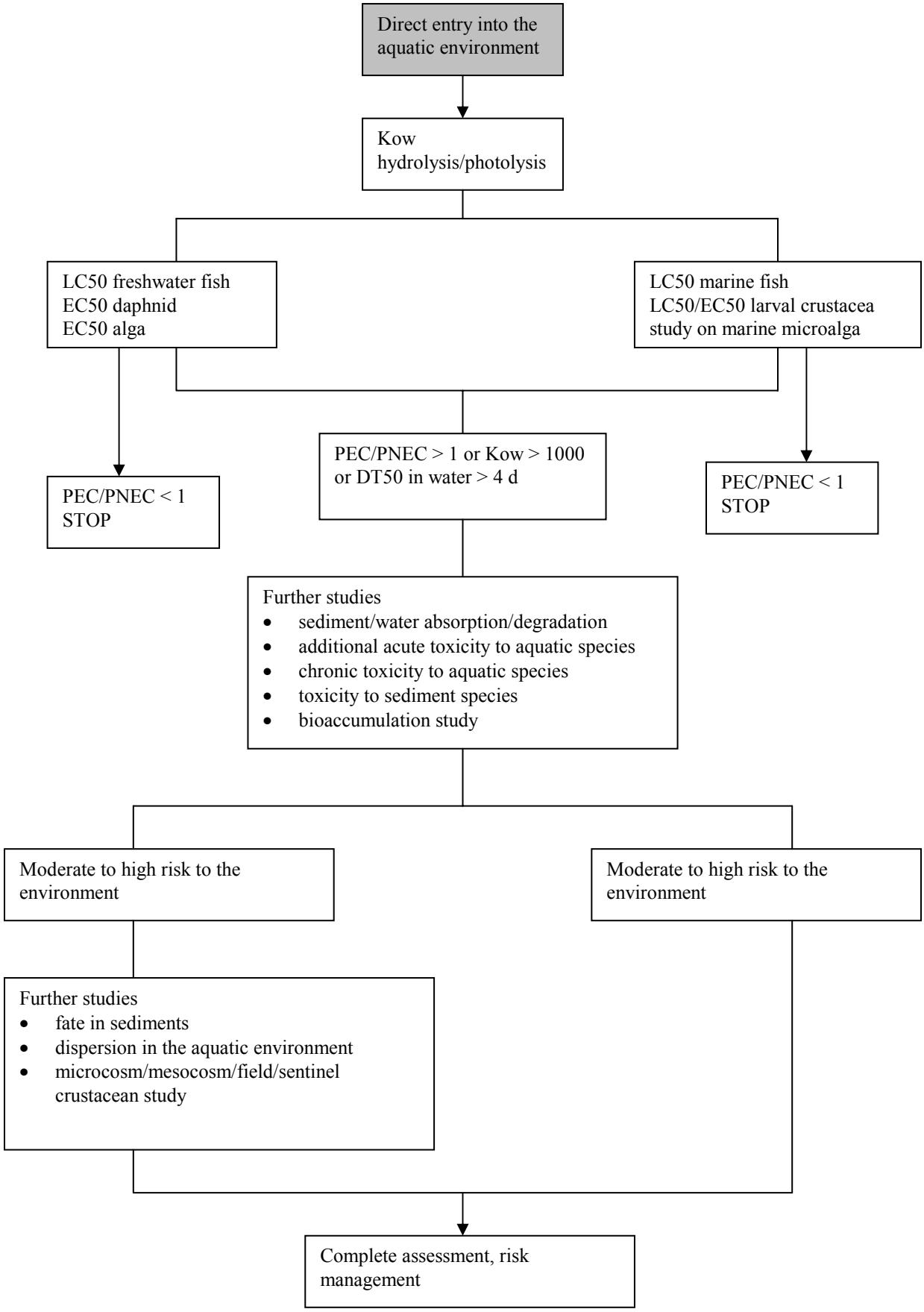


Figure 2-3 Phase II – Tier A and B: Decision tree for fish medicines



2.3 Environmental Risk Assessment Models

In order to support the environmental risk assessment process, a number of approaches have been developed for predicting concentrations of veterinary medicines in soil, groundwater and surface waters (e.g. Spaepen *et al*., 1997; WRc-NSF, 2000; Montforts, 1999). An overview of each model is presented in Table 2-1 and discussed below. It should be noted that, because of a lack of monitoring data, none of the models described below have been validated.

2.3.1 Uniform approach for predicting environmental concentrations of veterinary medicines (Spaepen *et al*., 1997)

In order to harmonise the environmental assessments of veterinary products, the European Federation for Animal Health (FEDESA) developed a uniform scheme for calculating predicted environmental concentrations (Spaepen *et al*., 1997). The scheme provides a sequence of standard equations and a database containing information on three major agricultural species: cattle, pigs and poultry. The database also contains information on the agricultural practices and relevant regulations for various regions within the EU. Inputs to the model are the dose and treatment regime. If information is available on metabolism and/or degradation this can be incorporated into the calculation. The output from the model is a predicted soil concentration.

2.3.2 ETox (Montforts, 1999)

The ETox models developed by Montforts (1999) predicts concentrations of veterinary medicines using scenarios that are specific to agricultural practices in the Netherlands.

The model is more complex than the uniform approach and can be used for medicines that are given internally (e.g. oral and injection treatments) or medicines applied externally (e.g. udder disinfection treatments). A range of input pathways are considered, i.e. direct excretion of dung and urine onto a field; spreading of manure and slurry and direct spillage onto a field. The following groups of organisms are considered: cows (milk cows, suckling cows, beef cows), pigs (fattening pigs, sows) and poultry (hens, broilers and turkeys). The outputs from the model include concentrations of the veterinary drug in soil, groundwater, surface waters and biota).

2.3.3 VETPEC (WRc-NSF)

VETPEC is a combination of 4 existing models, namely: a Mackay fugacity model for partitioning in soils; PESTAQ and PESTCAT models for transport to groundwater and river water respectively and the uniform approach of Spaepen *et al.* (1997) which is described above. The model considers a range of animals, including cows, pigs, broiler chickens, laying hens, turkeys and lambs and predicts concentrations in soil, groundwater and surface waters in three UK catchments (the Cotswolds, Otter Valley and Herefordshire). The model allows the user to produce outputs of likely concentration distributions that reflect the variability

Table 2-1 Exposure assessment models developed for use on veterinary medicines

	Scenarios available						
	Animals	Location	Husbandry	Administration route	User Inputs	Outputs	Validation status
Uniform approach	cows pigs poultry	Europe Member states	Intensively reared livestock	Internal treatment	dose treatment regime metabolism degradation data	concentration in slurry and soil	not validated
Etox	cows poultry pigs	The Netherlands	Intensively reared livestock Grazing animals	Internals and external treatments	dose treatment regime metabolism degradation rate Kow	concentration in slurry, manure, soil, groundwater, surface waters and biota	not validated
VETPEC	cows pigs poultry sheep	3 UK catchments	Uses stocking densities at the county level	Internal treatment	dose treatment regime vapour pressure Koc molecular weight solubility	concentrations in soil, groundwater and surface waters	not validated

in possible input variables, this output can then be used for probabilistic risk assessment purposes.

2.4 Discussion

Current guidelines for the assessment of the environmental risk of veterinary medicinal products have been described. A two-phase approach is used. In the first phase, the potential for the environment to be exposed to the veterinary medicine is assessed. Depending on the results of the Phase 1 assessment, Phase 2 may be required involving a series of experimental studies to assess the ecotoxicity, environmental fate and behaviour of the substance.

Trigger values are used in Phase 1 to identify substances that require a Phase 2 assessment. The trigger value for fish medicines is 1 $\mu g\ l^{-1}$; this is based on data on the ecotoxicity of human medicines. The trigger value for substances released to soils is 100 $\mu g\ kg^{-1}$, this is based on a dataset on the toxicity of 30 substances to earthworms, plants and microbes.

The approach of using a trigger value as in the Phase I assessment for veterinary medicines has a number of limitations. Using a specific concentration as a trigger for the need to obtain data on a chemicals ecotoxicity, fate and behaviour assumes that any chemical present in the environment will only cause harm if present above the trigger concentration. Clearly the definition of the trigger value will be reliant on an appropriate data set to ensure all modes of toxic action are reflected and a sufficient level of environmental safety has been afforded.

For example, the data obtained in this review (Chapter 7) for effects on terrestrial organisms do not support the use of the 100 $\mu g\ kg^{-1}$ trigger. Whilst all the test results were higher than the trigger, a large proportion were within 1 or 2 orders of magnitude of the trigger. If safety factors are incorporated to account for the uncertainties in the test results, both intra species and in extrapolating from lab to field, to derive predicted no-effect concentrations, then a large proportion of the values would be lower than the trigger (Table 2-2). In fact using the data available, a trigger value of 2–3 $\mu g\ kg^{-1}$ appears to be more appropriate.

Table 2-2 Estimation of predicted no effect concentrations using available data on terrestrial ecotoxicity of veterinary medicines (excluding ectoparasiticides and endectocides)

No and type of tests data available	No of substances	Range ($\mu g\ kg^{-1}$)	Safety factor recommended by EC (EC, 1996)*	PNEC ($\mu g\ kg^{-1}$)
LC50	0	-	1000	-
1 NOEC	9	250-50000	100	2.5
2 NOECs	9	100-24000	50	2
3 or more NOECs	9	30-2000000	10	3

* - based on EC Technical Guidance Document on Environmental Risk Assessment

Whilst recognising the need to limit animal testing to a minimum, a more appropriate method of assessing risk to the environment would be to eliminate the use of a trigger and obtain a 'base-set' of appropriate toxicity data for each chemical. A comparison of the predicted environmental concentration (PEC) with the predicted no-effect concentration (PNEC) can then be determined. A PEC: PNEC ratio greater than one indicates a potential risk to the environment and triggers the need for further data to address the risk and refine the assessment.

2.5 Summary

- Any new medicine to be placed on the market requires authorisation by the relevant authority. For authorisation specific to the UK, the relevant authority is the Veterinary Medicines Directorate and for EU-wide authorisations it is the European Medicines Evaluation Agency (EMEA). Since 1997, environmental risk assessments have been required for all new veterinary medicines and all other medicines as they come up for review (every 5 years).

- Guidelines are available for the environmental risk assessment of veterinary medicines within the EU. The approach is performed in 2 phases. In Phase 1 the likelihood of exposure to the environment is assessed and if the product does not meet certain criteria (e.g. if the soil PEC is greater then 100 $\mu g\ kg^{-1}$), then Phase 2 assessment is required. Phase 2 can be performed in two tiers, in the first tier the likely impact of the substance is assessed using a range of standard tests and the second tier involves more detailed investigations into the compartment(s) of interest.

- The Veterinary International Co-operation on Harmonisation (VICH) is working to harmonise environmental risk assessment approaches across the EU, USA and Japan, with Australia and New Zealand as observers. Guidelines are already available for Phase 1 assessments and draft guidelines are currently being produced for Phase 2 assessments of products used for grazing animals, intensively farmed animals and for use in aquaculture.

- Risk assessment models are available to support the different approaches. However, none of these have been validated.

- Based on analysis of the data contained in this review and using EU recommended uncertainty factors, it appears that the current soil trigger is inadequate.

3 VETERINARY MEDICINE USE IN THE UK

3.1 Introduction

The quantity of veterinary medicines released into the environment will be determined by a range of factors which includes, the quantity used, the degree of metabolism in the animal and degradation during storage of manure prior to land spreading. In order to prioritise veterinary medicines in terms of their potential environmental impact, quantitative information is required on the usage of veterinary medicines (metabolism and degradation are discussed in Chapter 6 of this report).

In the UK, veterinary medicines are classified into three major legal classes, namely: prescription only medicines (POMs), general sales list medicines (GSL) and pharmacy and merchant list medicines (PMLs) (VMD, 2000). Prescription only medicines can only be prescribed for use on animals by a vet and are distributed solely through the Association of Wholesalers to the Veterinary Profession (AWVP). Medicines on the general sales list and pharmacy and merchants list may be acquired from a veterinarian. However, since they do not require prescription they may also be distributed via pharmacies or pet shops or, through the Animal Health Distributors Association (AHDA), to other outlets such as saddlers and feed merchants. Other legal categories of veterinary medicinal products include pharmacy (P), controlled drug (CD), medicated pre-mix requiring MFS prescription (MFS), medicated pre-mix not requiring an MFS prescription (MFSX) and zootechnical feed additive (ZFA). Of these, only medicated pre-mixes and zootechnical feed additives may be distributed through AHDA. Figure 3-1 illustrates the distribution routes of the major legal classes of veterinary medicinal products within the UK.

Data on amounts and/or sales of veterinary medicines in the UK were obtained from a number of sources, including:

- survey data obtained from International Medical Statistics (IMS) Health
- Veterinary Medicines Directorate (VMD) data on the sales of antimicrobial substances and sheep dip chemicals in the UK
- data in the published literature on the use of sheep dip chemicals

The VMD and IMS data sets are discussed in more detail below.

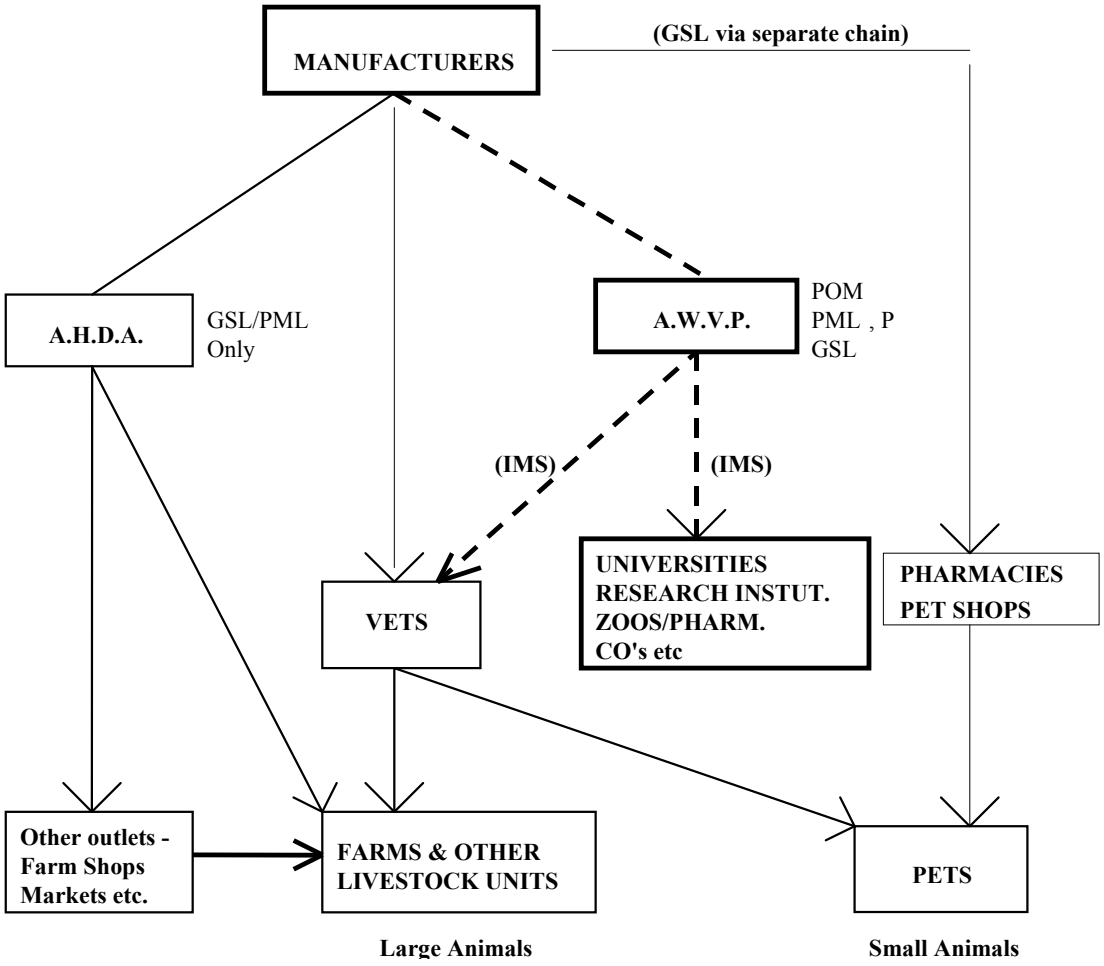
3.1.1 IMS data

IMS collate and analyse data provided by the British Veterinary Index (BVI) on sales of veterinary medicines and pharmaceutically related products to veterinary practices and other home market purchase points in the UK. The BVI data represents sales data for 3300 veterinary practices, 93 % of those registered within the UK (Royal College of Veterinary Surgeons, pers. comm.). As illustrated in Figure 3-1, data are only collected for veterinary medicines that are distributed to veterinary practices, zoos, research institutes and animal hospitals/centres via the Association of Wholesalers to the Veterinary Profession (AWVP). This includes veterinary medicines that are only available by prescription (known as

Prescription Only Medicines, (POMs)) as well as non-prescription medicines (GSL, PML, P, MFS, etc.). The data collected by IMS data do not cover the following distribution routes:

- direct sales from companies to veterinary surgeons;
- the sale of general sales list (GSL) or other non-prescription medicines through members of the Animal Health Distributors Association (AHDA);
- the sale of GSL or other non-prescription medicines through pharmacies and pet shops

Usage data obtained from IMS Health regarding prescription only medicines can thus be regarded as complete. IMS usage data for other categories of veterinary medicinal products (GSL, PML, P, MFS, etc.), whilst providing a good indication of the major usage compounds within a therapeutic/chemical group, may not represent total sales. It is considered that usage data for these compounds may be an underestimate of the actual total sales.



▬▬▬▬▬▬▬ distribution routes covered by IMS data

Figure 3-1 Veterinary market distribution channels (Figure provided by IMS)

For the purposes of the current review, data was provided by IMS for each product (expressed in terms of the numbers of units sold in the year 2000). A Microsoft Access database was constructed to convert the product sales data into amounts of each active ingredient distributed in 2000. The quantities of active ingredient in each product were obtained from the Compendium of Datasheets for Veterinary Products, 2000-2001 (NOAH, 2000). The database was then interrogated to obtain information on total amounts of each active ingredient sold.

3.1.2 Veterinary Medicines Directorate data

The Veterinary Medicines Directorate (VMD) requests that every marketing authorisation holder supplies data on the amounts of product sold each year (companies are in any case legally required to provide this data every 5 years as part of the Periodic Safety Update Report (PSU)). VMD have collated, and were able to provide, data on antimicrobial compounds, organophosphate sheep dips, coccidiostats and growth promoters. It is anticipated that data from recent PSUs will be available in a few years time for a broader range of products (VMD, pers. comm.). The usage data provided by VMD covers all the distribution routes shown in Figure 3-1 (e.g. both through AHDA and AWVP).

3.2 Usage by therapeutic group

It was not possible to obtain a complete data set on usage of all veterinary medicines. The IMS dataset represents a wide range of products but does not cover all supply routes. For example, sheep dips will be distributed and sold via the Animal Health Distributors Association (AHDA) and so are not included within the IMS dataset.

Data obtained from VMD is limited in terms of product types, but for those products covered provides a comprehensive picture of usage. However, together the two data sets are likely to reflect the general picture of usage of veterinary medicines in the UK.

3.2.1 Ectoparasiticides and endectocides

Ectoparasiticides are antiparasitic veterinary medicines used to control external parasites in livestock. Endectocides are antiparasitic veterinary medicines used to treat both internal and external parasites. Both ectoparasticides and endectocides are used to treat parasites in a wide range of animals.

If uncontrolled, ectoparasites (mites, blowfly, lice, ticks, headfly and keds) can cause significant financial loss and severely affect the welfare of sheep within the UK. Consequently, many sheep in the UK are routinely treated with ectoparasiticides. Currently in the UK, there are 5 main product types available and a range of active substances approved for use (Table 3-1)(VMD, 2001).

Data are available on the number of sheep treated with the different classes of ectoparasiticides in 1993, 1997 and 1999 (Liddel, 2000) and are presented in Figure 3-2. In 1999, approximately 40 million sheep were treated with an organophosphate dip, 7.4 million

were treated with a synthetic pyrethroid dip, 21 million sheep received a pour-on treatment and 9 million sheep received an endectocide injection.

Table 3-1 Veterinary medicinal products currently authorised in the UK for use as ectoparasiticides in sheep (VMD, 2001)

Product	**Indication for use**		
	sheep scab	**blow fly strike**	**lice, ticks and keds**
Organophosphorous sheep dips:			
diazinon	x	x	x
Non-organophosphorous sheep dips:			
Synthetic pyrethroids:			
flumethrin	x		x
cypermethrin	x		x
Amidines:			
amitraz			x
Spray and pour-ons:			
Synthetic pyrethroids:			
deltamethrin		x	x
cypermethrin		x	x
alphacypermethrin		x	x
Others:			
cypromazine		x	
Injectables:			
Macrocyclic lactones*:			
ivermectin	x		
doramectin	x		
moxidectin	x		

* Also used to treat gastro-intestinal nematodes, lungworms and nasal bots

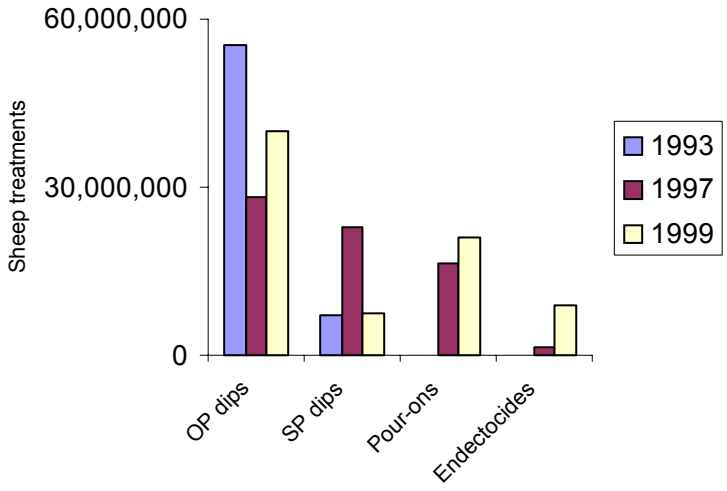


Figure 3-2 Number of sheep treated with the different types of ectoparasiticide in 1993, 1997 and 1999 (Liddel, 2000).

In terms of amounts of each product type, data were available from the VMD on the sales of organophosphate sheep dip product for the years 1984-1998 (reported in Pepper and Carter, 2000) (Figure 3-3). In 1998, 50.2 tonnes of organosphosphate sheep dip were sold in the UK.

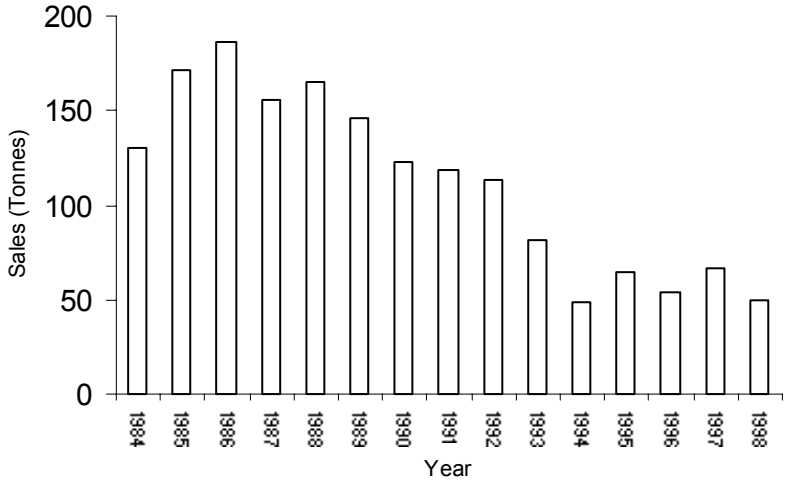


Figure 3-3 Sales of organophosphate sheep dips 1984-1998 (VMD)

Whilst there was no data available on the other classes of ectoparasiticides used on sheep, an estimate of usage can be made for synthetic pyrethroids and macrolide endectins by extrapolating from the organophosphate usage data and using the information on number of animals treated in Liddel (2000) (calculations are shown in Appendix B).

Using 1998 data, the amount of pyrethroids used in dip is estimated to be around 5.8 tonnes. The total amount of macrocyclic lactones administered to sheep in 1999 as endectocide treatments is estimated to range from 90-180 kg.

Complete usage data of other ectoparasiticides (i.e. phosmet, emamectin benzoate and piperonyl butoxide) used in agriculture, aquaculture and for treating companion animals were not available.

3.2.2 Antibiotics

Antibiotics are used in the treatment and prevention of bacterial diseases (Gustafson and Bowen, 1997). Whilst their use follows similar principles to those used in human medicines, there are some differences. The most significant is that livestock and poultry are raised in large numbers, and it is therefore necessary to treat the entire flock or herd at risk.

In the UK, data are available on the sales of antimicrobial products used as veterinary medicines or growth promoters (VMD, 2001a). This data was based on information provided to the Veterinary Medicines Directorate by the pharmaceutical industry. In 1999, a total of 448 tonnes of antimicrobials were sold in the UK, 383 tonnes were used to treat food animals (including aquaculture), 28 tonnes of antimicrobials were used for growth promotion and 37 tonnes were used to treat non-food animals (i.e. horses, dogs and cats) (VMD, 2001a).

Information was also available on sales of individual antimicrobial therapeutic groups and these are summarised in Table 3-2. Tetracyclines were the most widely used antibacterial medicines, followed by potentiated sulphonamides, β-lactams, macrolides, aminoglycosides, fluoroquinolones and others.

Table 3-2 Sales of antimicrobial therapeutic products (tonnes active ingredient) in 1999 (VMD, 2001a)

Therapeutic group	Sales in 1999 (Tonnes)
Tetracyclines	192
Trimethoprim/sulphonamides	82
β lactams	52
Macrolides	29
Aminoglycosides	20
Fluoroquinolones	1
others*	7
Total	*383*

* includes lincosamides, tiamulin, oxolinic acid

Whilst data were not available from VMD for individual antimicrobial substances, data were available from IMS for these compounds (Table 3-3). The total amounts of each therapeutic

class calculated from the IMS data are significantly lower than the amounts obtained by VMD. For example, VMD estimated that 192 tonnes of tetracyclines were sold in the UK, this compares to an estimate of 16.3 tonnes using the IMS data). This is because selected distribution routes are not included in the IMS survey. For example, medicated feedstuffs are distributed through AHDA members and VMD have estimated that in 1999, 307.5 tonnes of therapeutic antimicrobials were distributed via this route.

Table 3-3 Amounts of individual antimicrobial active substances sold in the UK in 2000 through veterinary wholesalers (data obtained from IMS Health)

Therapeutic class	Active substance	Usage (Kg)
Tetracyclines	oxytetracycline	8495
	chlortetracycline	6256
	tetracycline	1517
Sulphonamides	sulphadiazine	14224
	sulphadimidine	4933
	formosulphathiazole	859
	sulphadoxine	545
β lactams	amoxicillin	17432
	procaine penicillin	7223
	procaine benzylpenicillin	2811
	clavulanic acid	2194
	ampicillin	1487
	benzatine penicillin	1363
	cloxacillin	1324
	cephalexin	1310
	benzylpenicillin	1273
	phenoxylethylpenicillin	834
Aminoglycosides	dihydrostreptomycin	5978
	neomycin	1079
	apramycin	466
Macrolides	tylosin	5144
Fluoroquinolone	enrofloxacin	799
2,4-diaminopyrimidine	trimethoprim	2955
Pleuromutilin derivatives	tiamulin	1435
Lincosamides	lincomycin	721
	clyndamycin	688

3.2.3 Endoparasiticides

Endoparasiticides are antiparasitic agents that are used to control internal parasites. They include anthelmintics (wormers) for the control of gastrointestinal worms, lungworms and flukes as well as antiprotozoals and coccidiostats which are included in feeding stuffs mainly for therapeutic or prophylactic purposes (Bowen, 1995).

3.2.3.1 Anthelmintics

A wide range of active ingredients are used to treat gastrointestinal worms, liver fluke and lung worms in either poultry, cattle, sheep and horses. These include compounds of the chemical groups: macrolide endectins, pyrimidines and azoles. Usage data were available from IMS on the amounts of individual endectocide substances distributed via AWVP members. However, whilst this information gives an indication of the major usage compounds, it is considered to be an underestimate of the actual total amounts used as many of the compounds are distributed through other routes. Table 3-4 shows that ivermectin, a macrolide endectin, was sold in the highest amounts (although this may include the sheep treatments described above) followed by the pyrimidines, azoles and nitroxynil.

Table 3-4 Amounts of endectocide anthelmintics distributed through AWVP members in the UK in 2000 (based on data provided by IMS Health)

Chemical group	Active substance	Usage (Kg)
Macrolide endectins	ivermectin	3995
Pyrimidines	pyrantel emboate	3780
	morantel	2086
Azoles	triclabendazole	1267
	fenbendazole	1092
	levamisole	934
Others	nitroxynil	684

3.2.3.2 Coccidiostats and antiprotozoals

Coccidiostats and antiprotozoals are often incorporated into feed stuffs for medicinal purposes. This includes prophylactic use for the prevention of diseases such as coccidiosis and swine dysentry and therapeutic use for the treatment of diseases.

Data from a report published by VMD shows that in the UK in 1999, the sale of coccidiostats reported to the VMD was 66 tonnes (active ingredient) (VMD, 2001a). However, the report states that it was not possible to obtain the full data and it is expected that total sales of coccidiostats are higher than this amount. Sales of individual compounds were not reported.

Apart from one individual substance (dimetridazole), usage data provided by IMS on individual compounds is largely unavailable since many compounds are classified either MFS, ZFA, GSL or PML and are therefore distributed through routes other than those covered by AWVP. However, the following compounds are considered to be potential major usage compounds within the therapeutic group; amprolium, clopidol, lasalocid acid, maduramicin, narasin, nicarbazin and robenidine hydrochloride.

Data provided by IMS on sales of antiprotozoals indicates 0.18 tonnes were sold in 2000, the three highest use compounds being toltrazuril, decoquinate and diclazuril. As with the coccidiostats, many antiprotozoal compounds may be distributed through routes other than those covered by AWVP. The total amount reported by the IMS data is thus considered an underestimate.

3.2.4 Antifungals

Antifungal agents are used topically and orally to treat fungal and yeast infections. The most common uses include treatment of ringworm and yeast infections. Data were available from IMS on the amounts of antifungal agents distributed through the AWVP. The major active substances were chlorhexidine, miconazole and griseofulvin. Quantities sold in 2000 are summarised in Table 3-5. Apart from the biguanide/gluconate group, data for other antifungal groups is considered complete as the substances used are classified as prescription only medicines.

Table 3-5 Amounts of antifungal agents distributed through AWVP members in the UK in 2000 (based on data provided by IMS Health)

Chemical group	Active substance	Usage (Kg)
biguanide/gluconate	chlorhexidine	828
azole	miconazole	828
other	griseofulvin	408

3.2.5 Aquaculture

A range of substances are used in aquaculture to treat mainly sea lice infestations and furunculosis. The medicines may be applied by injection, in feed or via cage treatments. Currently, there are 11 active substances that are approved for use in the UK, namely: oxytetracycline, oxolinic acid, amoxycillin, co-trimazine, florfenicol, sarafloxacin, emamectin benzoate, cypermethrin, teflubenzuron, azamethiphos and hydrogen peroxide.

Data were available from VMD on the amounts of antimicrobials (oxytetracycline, oxolinic acid, amoxycillin, florfenicol, sarafloxacin and co-trimazine) sold for use in aquaculture (VMD, 2001a). Between 1993 and 1998 there was a decline in sales of the antimicrobials, even though the amount of fish produced has risen from 55000 tonnes to 143000 tonnes. In 1999, a total of 4 tonnes of antimicrobials were sold for use in aquaculture. Despite many of the treatments being POM, no data were available from the IMS dataset or other sources on the amounts of individual veterinary medicines used in the UK in aquaculture.

3.2.6 Hormones

Whilst they are now banned as growth promotors, hormones have other uses, including to induce ovulatory oestrus, suppression of oestrus, systemic progesterone therapy, and treatment of hypersexuality. Data were available on the amounts of hormones distributed through AWVP (Table 3-6). The major active substances used were altrenogest and progesterone. All hormones are classified prescription only and usage data for this group is considered complete.

Table 3-6 Amounts of hormones distributed through AWVP members in the UK in 2000 (based on data provided by IMS Health)

Active substance	Usage (Kg)
altrenogest	380
progesterone	85
medroxyprogesterone	7
delmadinone acetate	1.4
methyltestosterone	1.2
estradiol benzoate	0.5
benzyl alcohol	0.5
melatonin	0.4
oestradiol benzoate	0.2
ethinyloestradiol	0.002

3.2.7 Growth promoters

Growth promoters (also called digestive enhancers) are antibiotic compounds added to animal feed stuffs to improve the efficiency of food digestion.

Data published by VMD on the sale of growth promoters are available for the period 1993 to 1999 (VMD, 2001a). From 1993 to 1998, sales of antimicrobial growth promoters remained largely static. However, in 1999, sales fell by 69% to 28 tonnes and the proportion of antimicrobials used for growth promotion fell from 17% in 1998 to 7% in 1999. This decrease is considered to be due to the ban by the EU in mid-1999 of those growth promoters that confer cross resistance to antimicrobials in human medicine (VMD, 2001a).

Usage data on individual antimicrobial compounds used as growth promoters is limited. Information provided by IMS indicates only 0.0075 tonnes of one compound, monensin, was used in 2000. Since many compounds are classified ZFA or PML and are distributed through routes other than those covered by AWVP it is likely that this is a gross underestimate of the total sales of antimicrobial growth promoters in the UK. Other compounds identified as potentially major usage growth promoters include flavophospolipol and salinomycin sodium.

3.2.8 Others

Several other therapeutic groups that are used as veterinary medicines in significant quantities were identified using the IMS data. These included anaesthetics, euthanasia products, analgesics, tranquilisers, nonsteroidal anti-inflammatory drugs (NSAIDS) and enteric preparations. The major usage compounds for each therapeutic group are listed in Table 3-7.

Most of the compounds are classified prescription only and usage data provided by IMS can therefore be considered complete for most therapeutic groups. However lido/lignocaine hydrochloride, a local anaesthetic, and the bloat remedies dimethicone and poloxalene are non-prescription only medicines and are thus sold through routes other than those covered by AWVP. Consequently, actual usage for these groups may be higher than reported.

Table 3-7 Other active substances that are distributed through AWVP members in significant quantities (based on IMS Health data)

Therapeutic group	Active substance	Usage (Kg)
Anaesthetics	isoflurane	9608
	halothane	4134
	procaine hydrochloride	2143
	lido/lignocaine hydrochloride	166
Euthanasia products	pentobarbitone sodium	2680
Analgesics	metamyzole	607
Tranquilisers	phenobarbitone	663
NSAIDS	phenylbutazone	129
	caprofen	117
Enteric bloat preparations	dimethicone	269
	poloxalene	118

In addition to the above, the following ‘other’ therapeutic groups have also been identified as potentially important: antiseptics, steroids, diuretics, cardiovascular and respiratory treatments, locomoter treatments and immunological products. However, insufficient information was available to identify individual compounds and usage within each of these groups.

3.3 Summary

- Information has been obtained on the UK usage of a range of veterinary medicines. The information described above has been summarised (Appendix C) and represents a relative ranking of veterinary medicine usage in the UK based on available data. It should be borne in mind that because of lack of a complete data set on sales or usage of all veterinary medicines, some compounds that are used in large quantities may have been omitted.

- Data were available from IMS Health on the sales of veterinary products in the UK distributed through the AWVP. Data were also available from the Veterinary Medicines Directorate for sales of antibacterial substances, organophoshate sheep dips, coccidiostats and growth promoters. Data available in the open literature on the numbers of sheep treated with organophosphate dips, synthetic pyrethroid dips and macrolide injections enabled usage for the latter two to be estimated.

- The data from VMD covered sales of all antibacterial agents and organophosphate dips in the UK, the data on antibiotics and sheep dip chemicals are therefore likely to accurately reflect use in the UK. Total sales data provided by VMD for growth promoters is also considered complete, however data regarding coccidiostats is reported as possibly being an underestimate of the total sales.

- The IMS data only considers the distribution of substances through AWVP members. This includes prescription only medicines, pharmacy and merchant list medicines, pharmacy and general sales list medicines. Sales of substances direct to vets, through AHDA members, pharmacies and pet shops are therefore not accounted for. As prescription only medicines can only be prescribed by a veterinarian and the BVI audit data represents sales from 93% of veterinary practices, it is likely that the majority of prescription only medicines are sold through AWVP members and thus covered by the IMS data. IMS usage data for categories of veterinary medicinal products other than prescription only medicines (i.e. GSL, PML, P, MFS, ZFA, etc.) whilst providing a good indication of the major usage compounds within a therapeutic/chemical group may not represent total sales as they may be distributed through routes other than those covered by the AWVP. It is considered that usage data for endoparasitic wormers, biguanide/gluconate antifungals, antiprotozoals, local anaesthetics, enteric preparations and several antimicrobial therapeutic groups (pleuromutilins, lincosamides and ‘others’) may be an underestimate of the actual total sales.

- Whilst data was provided by VMD on the total amounts of coccidiostats and growth promoters sold, information regarding what individual compounds are used within these two therapeutic groups was very limited. Informed judgement has been used to identify the potentially major usage compounds for each of these two groups.

- With the exception of antibacterial agents, no data were available on the amounts of veterinary medicines used in aquaculture. This is surprising since many aquaculture medicines are prescription only medicines and hence should have been included in the data provided by IMS Health.

- Based on the available data, overall, antimicrobials are sold in the largest amounts followed by coccidiostats, organophophate sheep dip chemicals, growth promoters, endoparasitic wormers, general anaesthetics, other neurological preparations, ectoparasiticides, antifungals, anti-inflammatory preparations (NSAIDS), hormones and enteric preparations.

- Several 'other' therapeutic groups have also been identified as potentially important; antiseptics, steroids, diuretics, cardiovascular and respiratory treatments, locomotor treatments and immunological products. However, insufficient information was available to identify individual compounds and usage within each of these groups

- Discussion should be held with the VMD, and industry bodies to identify classes of substances that may not be fully represented in the current data set.

- VMD anticipate that data from recent PSUs, and hence data on total usage for a broader range of veterinary products, will be available in a few years time.

4 PATHWAYS OF ENVIRONMENTAL CONTAMINATION

4.1 Introduction

Veterinary medicines enter the environment by a number of different pathways. Currently the environmental risk assessment of veterinary medicinal products is only concerned with emission at or after use of the product (i.e. application and excretion) (Montforts, 1999). However, emission may occur at any stage in a products lifecycle, including production and during the disposal of the unused drugs, containers and waste material containing the product (manure, fish water and other dirty water) (Montforts, 1999).

4.2 Routes of entry into the environment

The major routes for veterinary medicines into the environment are illustrated in Figure 4-1 to Figure 4-4. A summary of the possible emission routes to the environment is given below. The importance of individual routes into the environment for different types of medicine will vary according to the type of treatment, the route of administration and the type of animal being treated.

4.2.1 Emissions during manufacturing and formulation

During the manufacture of active pharmaceutical ingredient (API) and formulation of the finished drug product, raw materials, intermediates or the active substance may be released to the air, to water in wastewater, and to land in the form of solid waste. In England and Wales (SEPA in Scotland), the Environment Agency regulate releases to the environment from such processes.

Manufacture and formulation of pharmaceuticals and pesticides (under which sheep dips are covered) are 'prescribed processes' under the Integrated Pollution Control (IPC) Regulations. Releases of prescribed substances to air water or land are subject to controls over the amounts released. Prescribed substances are listed in a schedule to the Regulations. For processes and substances subject to control under IPC, there is a requirement for the manufacturer to apply BATNEEC (best available methods not entailing excessive cost) in order to achieve the BPEO (best practicable environmental option), ensuring releases to the environment are as clean as technology allows, without entailing excessive cost and without causing any harm. Technical Guidance Notes are available for industry sectors providing guidance on best available techniques for control of pollution from the process, levels of release achievable by their use and aspects of monitoring specific to the process.

A European Directive for Integrated Pollution Prevention Control (IPPC) (Directive 96/61/EC) came into force in 1999. This will gradually replace the UK IPC Regulations and is being phased in gradually for different industrial sectors. Pesticide and pharmaceutical manufacture will come under IPPC in approximately 2006 (Environment Agency, pers. comm.).

Discharges to water that are not authorised under IPC require the consent of the Environment Agency under the Water Resources Act. Consents specify legally binding limits on the composition of the discharge in terms of the description, volume and total amount of substances that can be discharged. However, limits on consents tend to focus on water quality parameters such as pH and Biological Oxygen Demand (BOD) rather than specifying concentration limits for specific active ingredients.

The main route of release of drugs into the environment is probably via process waste effluents produced during the cleaning of active pharmaceutical ingredient and manufacturing equipment used for coating, blending, tablet compressing and packing (Velagaleti and Gill, in press). Biological and chemical degradation processes such as biotransformation, mineralisation, hydrolysis and photolysis are thought to remove most drug residues before process waste effluents or sludge solids are discharged to surface waters/sewage treatment works or released to land (Velagaleti and Gill, in press). In addition, a number of practices are often implemented by the industry to reduce waste generation and material losses. These include process optimisation, production scheduling, materials tracking and waste stream segregation (USEPA, 1997). Losses to the environment arising during the manufacture or formulation of veterinary medicine products are likely to be minimal.

Manufacturing plants employ a number of treatment methodologies and technologies to control and treat emissions and minimise the amounts of waste produced. These include the use of condensers, scrubbers, adsorbent filters and combustion or incineration for recovery and removal in air emissions. Neutralisation, equalisation, activated sludge, primary clarification, multimedia filtration, activated carbon, chemical oxidation and advanced biological may be used for treatment for waste waters (USEPA, 1997). Details of the main releases to the environment associated with the manufacture and formulation of pharmaceuticals and benchmark release levels permitted under IPC are given in the Technical Guidance Document for Speciality Chemicals (IPC S2 4.02) (Environment Agency, 1999).

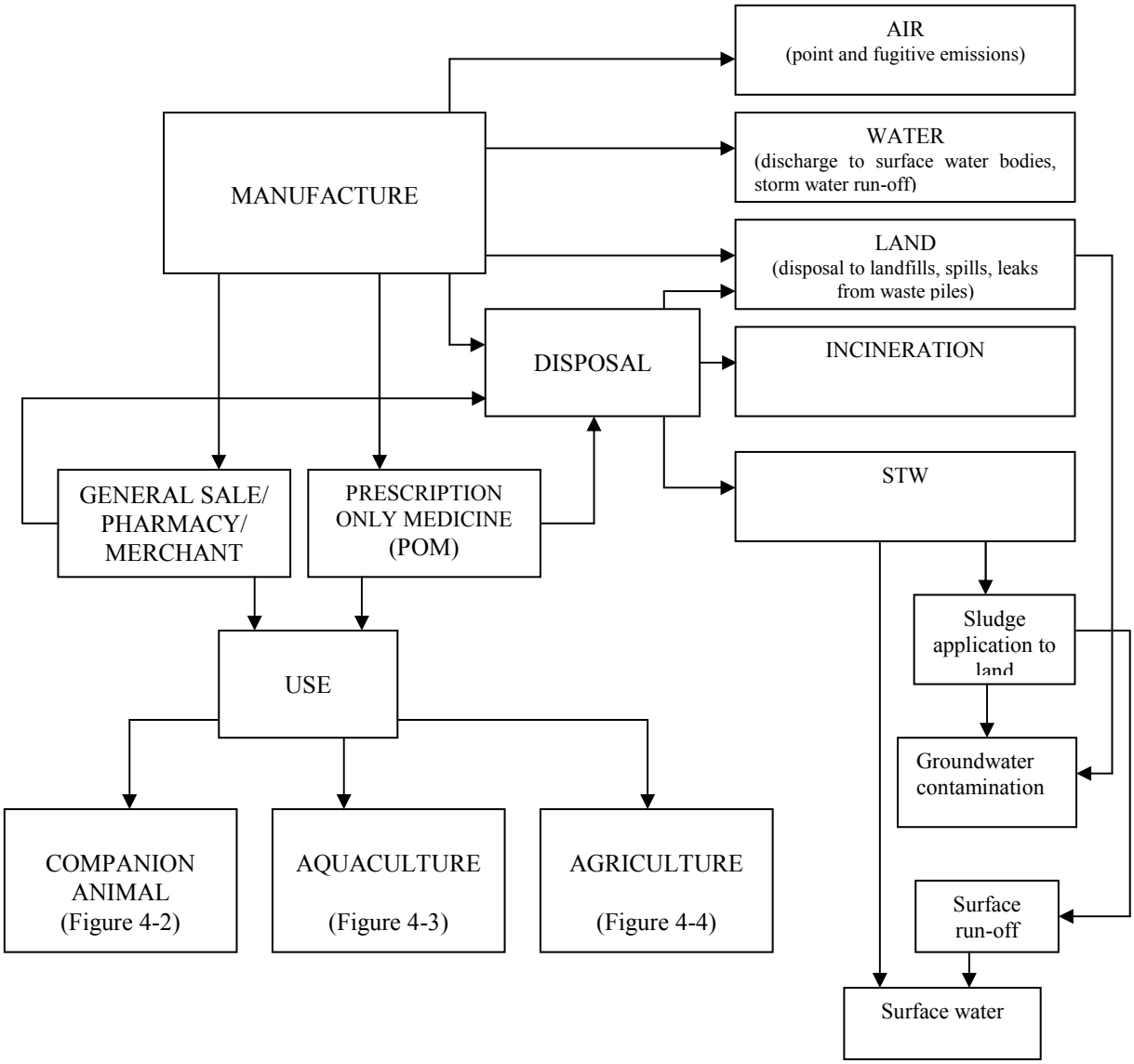


Figure 4-1 Pathways of veterinary medicines to the environment

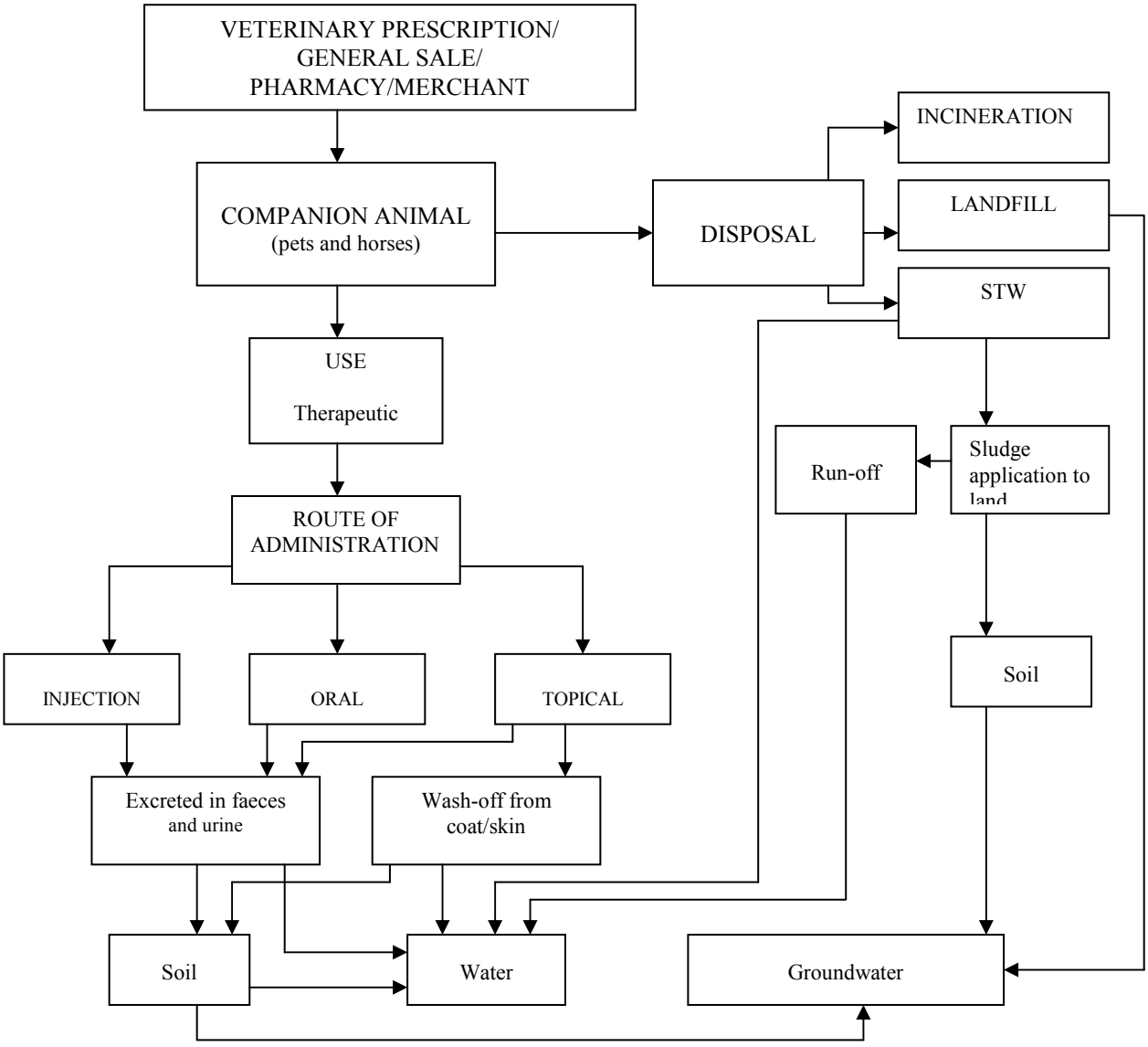


Figure 4-2 Pathways of veterinary medicines, used for treatment of companion animals, to the environment

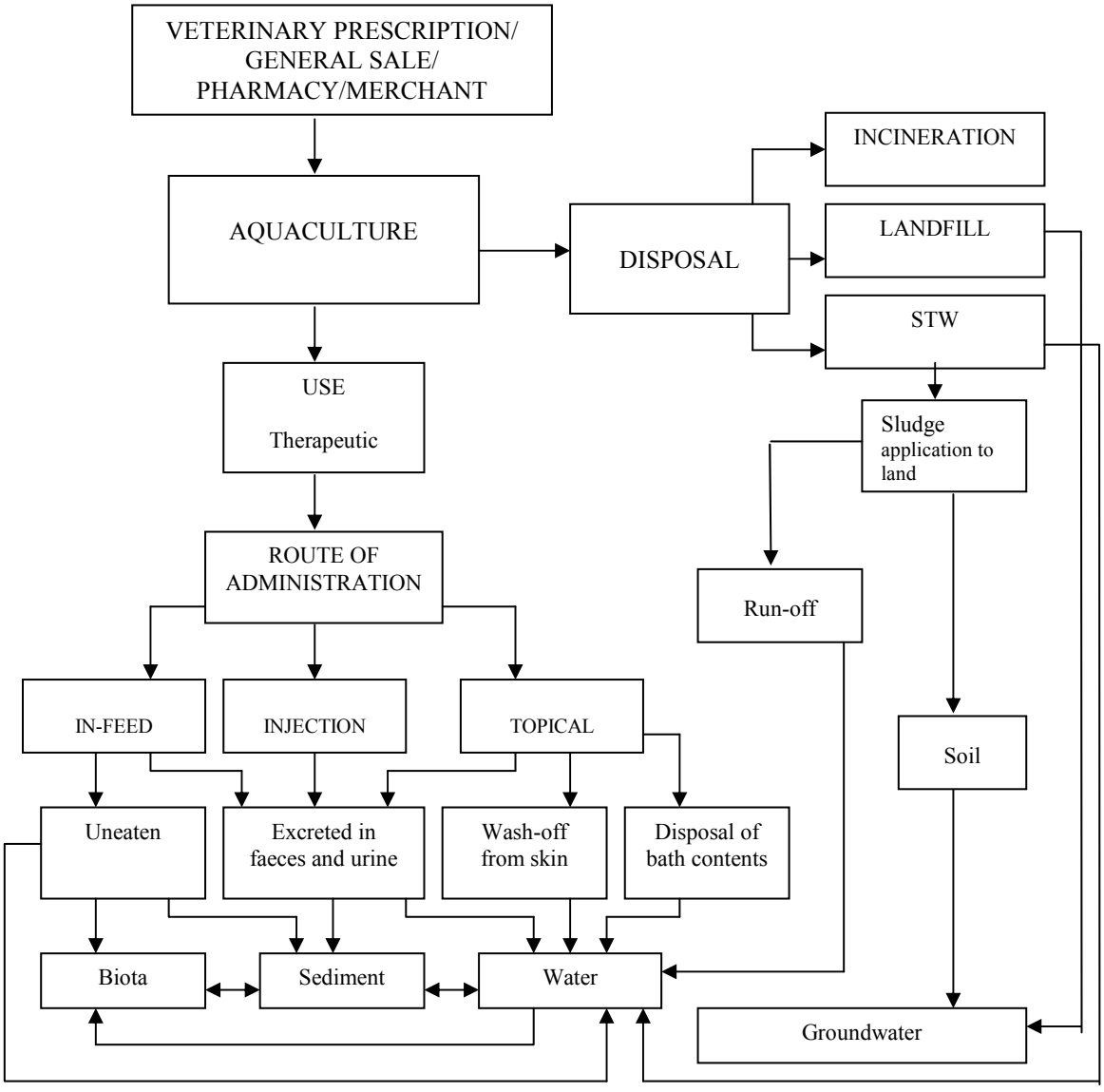


Figure 4-3 Pathways of veterinary medicines, used in aquaculture, to the environment

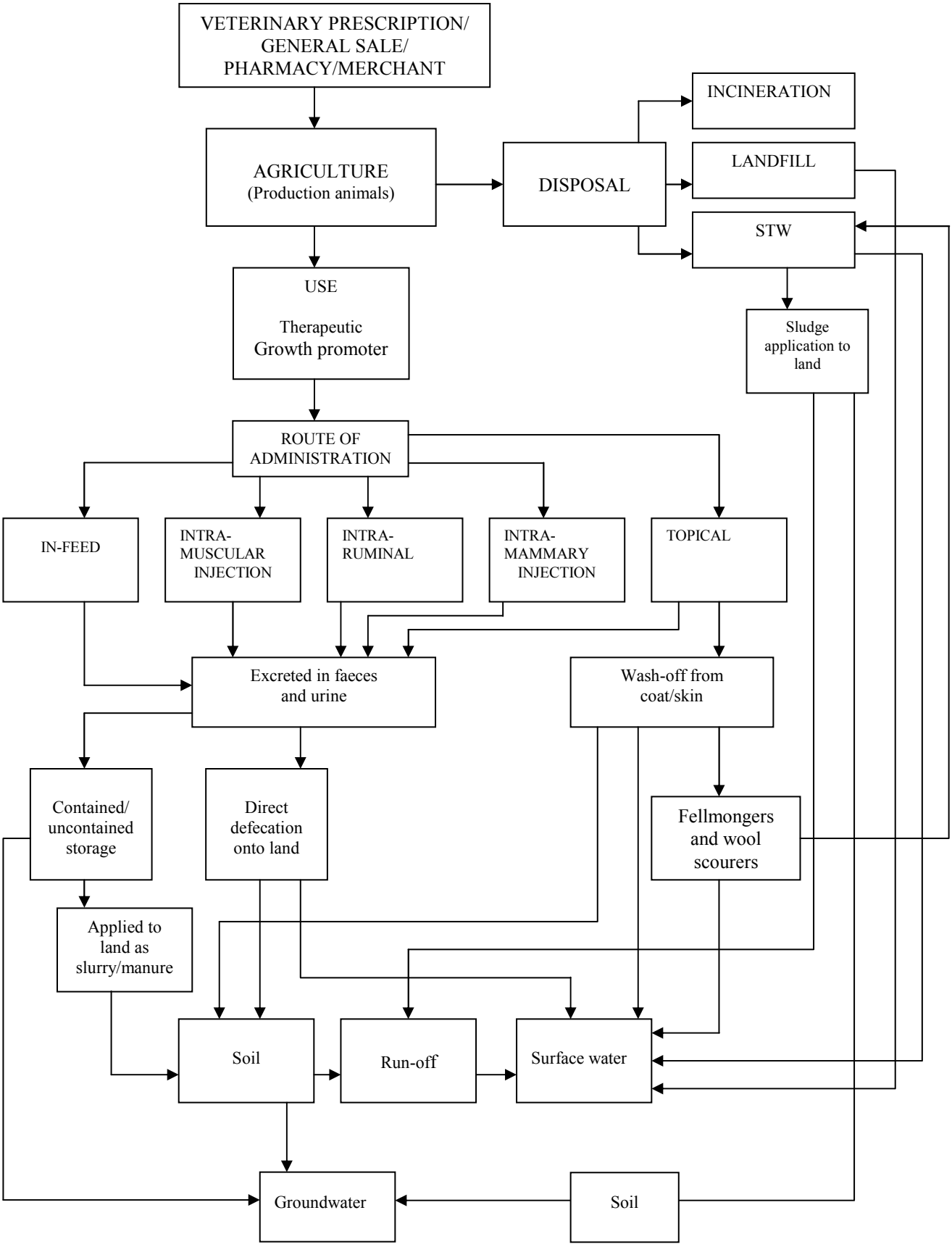


Figure 4-4 Pathways of veterinary medicines, used to treat livestock, to the environment

4.2.2 Aquaculture

Chemotherapeutic pharmaceuticals used in fish farming are limited to anti-infective agents for parasitic and microbial diseases, anaesthetic agents and medical disinfectants. Drugs are commonly administered as medicated feed, injection or in the case of topical applications as a bath formulation (Figure 4-3). Bacterial infections in fish are usually treated using medicated food pellets which are added directly to pens or cages (Hektoen *et al*., 1995; Samuelsen *et al*., 1992).

When infected, cultured fish show reduced appetite and thus feed intake. Consequently, a large proportion of medicated feed that is not eaten by the fish passes through the cages and is available for distribution to other compartments. Furthermore, the bioavailability of many antibacterial agents is relatively low and drugs may also enter the environment via faeces and urine (Björklund and Bylund, 1991; Hustvedt *et al*., 1991). In recent years improved husbandry practices have reduced the amount of waste feed generated and more recently authorised medicines have greater bioavailability (F>95%) (National Office of Animal Health and Veterinary Medicines Directorate, pers. comm.). Nevertheless, deposition of drugs from uneaten feed or faeces on or in under-cage sediment can be a major route of environmental contamination for pharmaceuticals used in aquaculture (Lunestad, 1992; Björklund *et al*., 1991; Jacobsen and Berglind, 1988). Once present on or in sediment, compounds may also leach back into the water column. During periods of treatment, some of the drugs entering the environment in waste feed and faeces are also taken up by exploitative wild fish, shellfish and crustacea (Capone *et al*., 1996; Ervik *et al*., 1994; Samuelsen *et al*., 1992; Björklund *et al*., 1990).

Where topical applications of chemotherapeutants are made, fish are usually crowded into a small water volume for treatment (Burka *et al*., 1997; Grave *et al*., 1991). Concentrated drugs are added directly to the water of open net-pens or ponds, net-pens enclosed by a tarpaulin or tanks. Waste effluent is then either released into the surrounding water column or subject to local wastewater treatment and recycling (filters, settlement basins and ponds) (Montforts, 1999; Burka *et al*., 1997; Grave *et al*., 1991). In addition, sludge recovered from waste water recycling activities may be applied directly to land or sold as fertiliser (Montforts, 1999).

4.2.3 Agriculture (livestock production)

Large quantities of animal health products are used in agriculture to improve animal care and increase production. These may be released to the environment in a number of ways, illustrated in Figure 4-4 and discussed in more detail below.

Some drugs used in livestock production are poorly absorbed by the gut and the parent compound or metabolites are known to be excreted in the faeces or urine, irrespective of the method of application (Beconi-Barker *et al*., 1996; Sommer *et al*., 1992; Magnussen *et al*., 1991; Stout *et al*., 1991; Chui *et al*., 1990; Donoho, 1987; Campbell *et al*., 1983). During livestock production, veterinary drugs enter the environment through removal and subsequent disposal of waste material (including manure/slurry and ‘dirty’ waters), via excretion of faeces

and urine by grazing animals, through spillage during external application or by direct exposure/discharge to the environment.

With all hormones, antibiotics and other pharmaceutical agents administered either orally or by injection to animals, the major route of entry of the product into the environment, is probably via excretion following use and the subsequent dispersal of contaminated manure onto land (Halling-Sørensen *et al.*, 2001). Many intensively reared farm animals are housed indoors for long periods at a time. Consequently, large quantities of farmyard manure, slurry or litter are produced which are then disposed of at relatively high application rates onto land (Montforts, 1999; ADAS, 1998; ADAS, 1997). Although each class of livestock production has different housing and manure production characteristics, the emission and distribution routes for veterinary medicines are essentially similar. As well as contaminating the soil column, it is possible for veterinary medicines to leach to shallow groundwater from manured fields or even reach surface water bodies through surface run-off (Hamscher *et al*., 2000, 2000a, 2000b; Meyer *et al*., 2000; Hirsch *et al*., 1999; Nessel *et al*., 1989). In addition, drugs administered to grazing animals or animals reared intensively outdoors are deposited directly to land or surface water in dung or urine, exposing soil organisms to high local concentrations (Halling-Sørensen, 2000; Montforts, 1999; Halling-Sørensen *et al*., 1998; Strong and Wall, 1994; Sommer *et al*., 1993; McCracken, 1993; Strong, 1993; Strong, 1992; Sommer and Overgaard Nielsen, 1992).

Another significant route for environmental contamination is the release of substances used in topical applications. Various substances are used externally on animals and poultry for the treatment of external or internal parasites and infection. Sheep in particular suffer from a number of external insect parasites for which treatment and protection is sometimes obligatory. The main methods of external treatment include plunge dipping, pour-on formulations, or the use of showers or jetters. With all externally applied veterinary medicines, both diffuse and point source pollution can occur. Sheep dipping activities provide several routes for environmental contamination. In dipping practice, chemicals may enter watercourses through inappropriate disposal of used dip, leakage of used dip from dipping installations or from excess dip draining from treated animals. Current disposal practices rely heavily on spreading used dip onto land (MAFF, 1998; HSE, 1997). Under the Groundwater Regulations 1998, from April 1999, disposal of spent dip to land requires authorisation from the Environment Agency or the Scottish Environment Protection Agency. Active substances in sheep dip may cause deleterious effects on terrestrial biota if applied to land at rates exceeding the recommended disposal rates. To date there is little detailed information regarding this potential area of concern. The Environment Agency is currently undertaking research to investigate the environmental fate and behaviour of used sheep dip disposed to land and its effects on terrestrial ecosystems.

Two other major sources of pollution arising from sheep dip chemicals include emissions from fellmongers and wool treatment plants and wash-off from the fleeces of treated animals (Armstrong and Philips, 1998). Monitoring data (Environment Agency, 2001; Environment Agency, 1998) has demonstrated high numbers of Environmental Quality Standard (EQS) failures in the Yorkshire area associated with the textile industry. Whilst effluent produced from the wool scouring process is normally treated for the removal of pollutants, this process

is not always effective and chemicals may be released in discharges from the treatment plants. In addition spills and leaks of untreated effluent directly to surface water drains from both fell-mongers and wool treatment plants often occur (Environment Agency, 1999).

Wash-off of chemicals from the fleeces of recently treated animals to soil, water and hard surfaces may occur on the farm, during transport or at stock markets. Some market authorities insist animals are dipped before entering the market to restrict the spread of disease, thus creating the potential for contaminated run-off from uncovered standing areas (Armstrong and Philips, 1998). The Environment Agency, working in partnership with representatives from the Scottish Environment Protection Agency, Veterinary Medicines Directorate, National Office of Animal Health, water companies, the textile industry and sheep farmers has produced a strategy for reducing sheep dip chemical pollution from the textile industry that provides detailed discussion, and makes recommendations for dealing with the problem (Environment Agency, 1999).

Other topically applied veterinary medicines likely to wash-off following use, include udder disinfectants from dairy units and endectocides for treating cattle parasites. Udder washings containing anti-infective agents and other such potentially contaminated dirty water produced by dairy units may enter the environment through soakaways, surface water drains or via its inclusion in stored slurry and subsequent application to land. Wash-off from the coats/skin of cattle treated with pour-on formulations can occur where the animals are exposed to rain shortly after dosing (Bloom and Matheson, 1993). Residues of drugs in wash-off may accumulate in localised high concentrations on land with high stocking densities. Contaminated surface run-off from open cattle yards is normally integrated with slurry and manure and thus would be subsequently spread onto land. In addition, residues may wash off the backs and coats of grazing animals such as cattle and sheep that have access to surface water bodies as drinking water.

4.2.4 Companion/domestic animals

To date, the environmental fate of veterinary medicines used in companion animals has not been extensively researched. This is probably because unlike production animals reared in agriculture, companion animals are kept on a small-scale basis and are therefore not subject to mass medication. Where used, drugs are likely to be dispersed into the environment via run-off or leaching from on-ground faecal material (Daughton and Ternes, 1999). In addition, ectoparasiticides applied externally to canine species may contaminate surface water through direct loss from the coat when the animal enters the water (Figure 4-2).

4.2.5 Disposal of unwanted drugs

Veterinary pharmaceutical drugs may be subject to disposal at any stage during their lifecycle. It is probably fair to assume that, as with human pharmaceuticals, a proportion of all prescribed or non-prescribed veterinary medicines will be unused and unwanted by the end user. The principal end users of veterinary medicines are veterinarians, livestock producers or domestic users.

In the UK, statutory controls exist for the disposal of 'controlled' waste (Environment Protection Act, 1990) and veterinary medicines that are 'special' wastes (Special Waste Regulations, 1996). Prescription only medicines are classed as special waste. Some merchant and general sale list veterinary medicines will also be covered by the Special Waste Regulations, but only if they can be classified as special waste by displaying one or more of the hazardous properties described in the Regulations.. Although the Regulations state that in the case of prescription only medicines, "householders are encouraged to return unused or life-expired medicines to their local pharmacist for safe disposal", veterinary medicinal waste generated by a household or from agricultural premises is not considered to be special waste under the Regulations. However, the law is set to change and it is anticipated that regulations bringing agricultural waste within the controlled waste regime will be introduced during 2001/2002. This is expected to place the same statutory controls on the movement and disposal of pharmaceutical and veterinary preparations from agricultural sources as for domestic, commercial and industrial sources. In addition, List I or II substances as defined by the Groundwater Regulations (1998), require authorisation for disposal.

Disposal of veterinary medicines by end users should be interpreted to include damaged, outdated or outmoded animal medicines, as well as used containers and packages, contaminated sharps, applicators and protective clothing (Cook, 1995). Users are advised to always follow advice on the label regarding disposal and never to dispose of such items with domestic rubbish or pour animal medicines down the drain or toilet (VMD, 2001b).

Where appropriate, product label and safety data sheets provided by manufacturers impart information relating to the safe disposal of veterinary medicines and packaging. Distributors, veterinary practices, farmers and feed compounders can also contact the manufacturer or local authority for advice, especially where large quantities of animal medicines require disposal and collection services are operated by some county councils for the periodic disposal of special waste (Cook, 1995). Users of companion animal products may return unwanted or unused product to the veterinary surgery or local pharmacist.

In practice, normal methods for disposal include flushing down the toilet, incineration and local domestic waste collection. Domestic users will undoubtedly flush unwanted medicines down toilets or place them with the domestic refuse (Daughton and Ternes, 1999). For ectoparasiticides, in particular sheep dips, containers should be returned to suppliers for correct disposal to high temperature incineration or licensed landfill. If on farm disposal is planned, containers (water soluble preparations) should be triple rinsed before burial away from water courses or any land drains as specified by the Code of Good Agricultural Practice for the Protection of Water, 1998. Inappropriate disposal of empty containers and unwanted product by careless operators may lead to contamination of soil and waters.

Unwanted or expired products that are returned to the manufacturer are usually disposed of through incineration or landfilling at suitable sites (Velagaleti and Gill, in press). Where drugs are disposed of in sufficient quantities to unlined landfill sites, residues present in uncontained leachate may reach shallow groundwater and surface waters (Holm *et al*., 1995).

4.3 Discussion

Table 4-1 ranks veterinary medicines by product type and administration route in order to identify which products have the greatest potential to enter the environment. The available information indicates that veterinary products used in aquaculture and the treatment of livestock, especially when whole herds are treated in one instance, have the highest potential to be released to the environment. Inputs from the manufacturing process are low, since manufacture and formulation are subject to tight regulatory controls. The significance of release of veterinary medicines as a consequence of the treatment of companion animals is unknown, but is anticipated to be low because animals tend to be treated individually.

Environmental exposure will also be determined by the route of administration of a product. For example, substances that are applied topically such as in sheep dip preparations will have a high potential for release to the environment, whereas substances administered by injection may be extensively metabolised and hence have low potential to enter the environment.

4.4 Summary

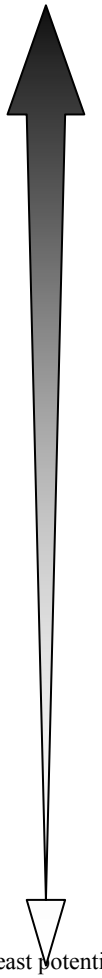
- The major routes of entry of veterinary medicines to the environment are likely to be from aquaculture facilities and the treatment of groups of livestock animals. Emissions during the manufacturing process and from the treatment of companion animals are likely to be less significant.

- The importance of individual routes into the environment for different types of veterinary medicines will vary according to the type of treatment and livestock category (Table 4-1).

- The disposal of waste medicines is subject to a range of controls and guidelines are available for the safe disposal of unused medicines and associated packaging. However, it is possible that products are inappropriately discharged to surface waters and disposed of in refuse.

Table 4-1 Significance of emissions from a range of treatment types, in terms of potential to enter the environment

Route of administration	Livestock category	Main type of compounds used	Emission pathway into the environment	Potential to enter environment
Topical	Fish	Antiparasitic agents, medical disinfectants, anaesthetics	Direct entry into the aquatic environment	Most potential
Oral (medicated feed)	Fish	Antimicrobials, antibiotics, ectoparasiticides	Direct entry into the aquatic environment	
Topical	Grazing/outdoor reared: sheep, cattle, pigs and poultry	Sheep dip chemicals, ectoparasiticides, endoparasiticides and endectocides as pour-on formulations	Wash-off from skin, hair or feathers to land and water. Contamination of soil, surface water and groundwater through the disposal of spent dip to land and seepage from sheep dip facilities.	
Topical	Indoor/intensively reared: cattle, sheep, pigs and poultry	Sheep dip chemicals, ectoparasiticides, endoparasiticides and endectocides as pour-on formulations, udder treatments	Wash-off from skin, hair or feathers to slurry, manure or litter, subsequent disposal to land. Run-off from hard surfaces to surface water drains.	
Oral	Indoor/intensively reared: cattle, sheep, pigs and poultry	Antimicrobials, antibiotics, growth promoters, digestive enhancers, ectoparasiticides, endoparasiticides, endectocides, cocciodiostats, hormones	Application of slurry and manure to land from intensively reared animals.	
Intramuscular/ sub-cutaneous/ intramammary injection	Indoor/intensively reared: cattle, sheep, pigs and poultry	Ectoparasiticides, endoparasiticides, endectocides, antibiotics, antimicrobials	Application of slurry and manure to land from intensively reared animals.	
Oral	Grazing/outdoor reared: sheep, cattle, pigs and poultry	Antimicrobials, antibiotics, growth promoters, digestive enhancers, ectoparasiticides, endoparasiticides, endectocides, cocciodiostats, hormones	Direct excretion of parent compound or metabolites in faeces and urine to land and surface water by grazing animals.	
Intramuscular/sub-cutaneous/ intramammary injection	Grazing/outdoor reared: sheep, cattle, pigs and poultry	Ectoparasiticides, endoparasiticides, endectocides, antibiotics, antimicrobials	Direct excretion of parent compound or metabolites in faeces and urine to land and surface water by grazing animals.	
Topical	Dogs, cats, horses	Ectoparasiticides, endectocides, antimicrobials	Wash-off from skin or hair to land and water.	
Oral	Dogs, cats, horses	Ectoparasiticides, endoparasiticides, endectocides, antibiotics, anti inflammatories	Direct excretion of parent compound or metabolites in faeces and urine to land and surface water.	Least potential



Footnote: Although not a treatment, the inappropriate disposal of containers/packaging (particularly sheep dip) can be a significant source of contamination to the environment (SEPA, pers. comm.)

5 OCCURRENCE IN THE ENVIRONMENT

5.1 Introduction

Veterinary medicines have been measured in surface waters, groundwaters, sediments, slurry/manure and biota. In the UK, monitoring studies have focused on veterinary products used in sheep dips and aquaculture. Data on concentrations arising from the treatment of livestock were available from studies performed in Germany.

This chapter reviews these monitoring studies and provides a brief summary of analytical methods (detailed information is provided in Appendices D, E and F).

Summaries of monitoring data and the availability of analytical methods are provided in Table 5-1 and Table 5-2.

5.2 Overview of analytical methods

5.2.1 Sampling

Although a substance may be detected in a single sample, it is important to assess the nature of the sampling programme in order to assess the relevance of the results in the wider context.

For substances applied to land, ideally event based monitoring should be performed in response to rainfall, of surface waters, groundwaters and soil waters in order to determine concentrations of veterinary medicines. For products used non-continuously in aquaculture, a periodic sampling strategy would be more appropriate where grab samples are taken at fixed intervals following treatment. A similar monitoring strategy would be required for substances being continuously discharged during the manufacturing process.

5.2.2 Extraction

Methods are available in the scientific literature for the extraction of a number of chemicals used in veterinary products (including macrolides, tetracyclines, anthelmintics, pyrethroids, organophosphorous compounds and 2,4-diaminopyrimidines) from a number of environmental media, including sediment, surface waters and soil. Methods are also available for a number of other chemical classes that have been applied to foodstuffs. A summary of extraction techniques used to extract veterinary medicines from environmental media and selected foodstuffs is given in Appendix D. Very few, if any of these methods have been through validation and ring-testing procedures.

Samples of sediment and soil are generally extracted (often after pH adjustment with a buffer) using an appropriate organic solvent. The resulting extracts are typically ‘cleaned up’ and fractionated to isolate analytes of interest using solid phase extraction cartridges. Many veterinary medicines are highly substituted with ionizable groups consequently the extraction methodology can be very pH sensitive. Buffers are therefore often used in both the extraction and determination processes.

Table 5-1 Summary of measured environmental concentrations of veterinary medicines detected in surface and groundwater, soil and sediment

	Range of concentrations detected			
Compound	Surface Water (ng l^{-1} unless otherwise stated)	Groundwater (ng l^{-1} unless otherwise stated)	Soil (µg kg^{-1} unless otherwise stated)	Sediment (µg kg^{-1} unless otherwise stated)
Chlorfenvinphos	up to 30800	up to 70	-	-
Chloramphenicol	0.06 µg l^{-1}	-	-	-
Chlortetracycline	0.5 µg l^{-1}	0.17-0.22 µg l^{-1}	0.7±0.2-41.8	-
Coumaphos	30	-	-	-
Cypermethrin	1-85100	-	-	-
Desmethylamino metabolite	-	-	-	>0.5
Diazinon	3-0.58 x 10^6	up to 216	-	-
Emamectin benzoate	nd	-	-	0.25-2.73
Fenchlorphos	<10-777	-	-	-
Flumethrin	1-2190	-	-	-
Ivermectin		-	0.1-2	trace-6.8 ng g^{-1}
Monensin	-	-	0.8-1.08 mg kg^{-1}	
Oxolinic acid	-	-	-	<0.05-0.2 µg g^{-1}
Oxytetracycline	-	0.15-0.19 µg l^{-1}	0.9±0.1-8.6±4.5	0.1-285 µg g^{-1}
Propetamphos	up to 19.2 x 10^6	up to 489	-	-
Sulphamethazine	-	0.08-0.16 µg l^{-1}	-	-
Tetracycline	-	0.11-0.27 µg l^{-1}	<1-39.6±33.6	-
Tylosin	-	0.13-0.42±0.47 µg l^{-1}	Trace (LOD 0.2 µg kg^{-1})	-

Table 5-2 Available analytical methodologies and monitoring data for major classes of veterinary medicine

Therapeutic class	Chemical group	Analytical methods	Monitoring data
Antimicrobials	tetracyclines	√√	W,G,Se,S,F,Fa
Antimicrobials	potentiated sulphonamides	√√	G,F
Endoparasiticides - coccidiostats	-	√	F
Antimicrobials	β-lactams	√√	-
Ectoparasiticides- sheep dips	organophosphates	√√	W,G
Antimicrobials	macrolides	√√	G,S
Growth promoters	-	√	S,F
Antimicrobials	aminoglycosides	√√	-
Neurological preparations – general anaesthetics	-	√	-
Endoparasiticides - wormers	pyrimidines	-	-
Ectoparasiticides – sheep dips	pyrethroids	√√	W
Endoparasiticides - wormers	azoles	√	-
Endoparasiticides - wormers	macrolide endectins	√√	R,Se,S,F
Antimicrobials	others	√√	W,Se,F,Fa
Neurological preparations – euthanasia products	-	-	-
Neurological preparations – local anaesthetics	-	-	-
Antimicrobials	pleuromutilin derivatives	√	-
Antimicrobials	lincosamides	-	-
Antimicrobials - antifungals	azoles	-	-
Endoparasiticides - wormers	others	-	-
Antimicrobials	fluoroquinolones	√	-
Antimicrobials - antifungals	others	-	-
Antimicrobials - antifungals	biguanide/gluconate	-	-
Neurological preparations - tranquilisers	-	-	-
Anti-inflammatory preparations (NSAIDS)	-	-	-
Neurological preparations -analgesics	-	-	-
Hormones	-	√√	-
Enteric preparations	-	-	-
Endoparasiticides - antiprotozoals	-	-	-
Endectocides	macrocyclic lactones	√√	R,Se,S,F
Ectoparasiticides	others	-	-
Ectoparasiticides	amidines	-	-
Ectoparasiticides – spray and pour-ons for sheep	-	√√	W
Ectoparasiticides – aquaculture treatments	-	-	W,Se,Fa
Antiseptics	?	-	-
Anti-inflammatory preparations	steroids	-	-
Diuretics	?	-	-
Cardiovascular treatments	?	-	-
Locomotor treatments	?	-	-
Immunological products	?	-	-

√ - method available; √√ - method available for environmental media; W-surface waters; G-groundwater; R-runoff water; Se-sediment; S-soil; F-Faeces, Fa-fauna

5.2.3 Analytical techniques

Various analytical techniques have been used to determine concentrations of veterinary medicines in a variety of matrices and a number of reviews are available that detail the methodologies available (Oka *et al*., 2000; Stead, 2000; Belal *et al*., 1999; Carlucci, 1998; Levêque *et al*., 1998; Schenck and Callery 1998; Niessen, 1998; Kanfer *et al*., 1998). A wide range of techniques have been used including X-ray crystallography; nuclear magnetic resonance spectroscopy (NMR); microbiological assay; radiochemical assay; radioimmunoassay; enzyme immunoassay; fluoroimmunoassay; chemiluminescence immunoassay; nephelometric and turbidimetric immunoassay; immunohistochemical techniques; mass spectrometry (MS); gas chromatography (GC); thin layer chromatography (TLC); high-performance liquid chromatography (HPLC); and capillary electrophoresis (CE). Most of the methods developed to date have been aimed at the determination of veterinary products in food stuff although some work has been performed to develop methods for environmental matrices (e.g. Hamscher *et al*., 2000; Floate *et al*., 1997; Sams, 1993), a summary of techniques used for both foodstuffs and environmental matrices is given in Appendix E.

Specific analytical methods and extraction techniques concentrating on environmental and waste media are given in Appendix E. Chromatographic techniques predominate, with HPLC coupled to UV, fluorescence or MS detection the most common. Fluorescence detection is more sensitive than UV detection and is useful for compounds with natural fluorophores, such as the quinolones, or compounds that can be derivatised to produce a fluorescent compound, such as sulfonamides using fluorescamine or by chelating tetracyclines with metal ions

5.3 Aquaculture

In the UK, six antimicrobials currently have marketing authorisation for use in aquaculture; oxytetracycline, oxolinic acid, amoxycillin, florfenicol, sarafloxacin and co-trimazine (trimethoprim-sulphadiazine). In addition, ectoparasiticides such as emamectin benzoate, cypermethrin, teflubenzuron, azamethiphos and hydrogen peroxide are used as sea-lice treatments. In Norway a slightly larger range of antimicrobials and ectoparasiticides are permitted. The range in both countries is representative of those products permitted for use in Europe and North America, whereas in other countries, such as Japan, a much larger range of products have approval for specific purposes (Alderman and Hastings, 1998).

During the past two decades, a number of studies have investigated the environmental impact of chemotherapeutic drugs used in aquaculture. Antibacterial drugs are mostly given as medicated food pellets. It is well documented that the majority of orally administered chemotherapeutics ultimately leave the treated cages/lagoons as surplus food and enter the environment (Lunestad, 1992; Samuelsen *et al*., 1992a; Thorpe *et al*., 1990 cited in Capone *et al*., 1996). To ensure cost-effective treatment, aquaculture facilities endeavour to ensure that most of an administered medicine is taken up by the target stock (National Office of Animal Health, pers. comm.).

A discussion of monitoring studies that have been conducted, including measured environmental concentrations is presented below.

5.3.1 Emamectin benzoate and its major metabolite (4"-epiaminoavermectin B_{1a})

Emamectin benzoate is a premix therapeutic agent, effective against all parasite life stages of sea-lice, and is the only avermectin currently authorised for use in aquaculture in the UK.

As part of an environmental risk assessment of emamectin benzoate, field monitoring studies were carried out at a fish farm sited on a Scottish loch to determine chemical residues in sediment, flocculent material retrieved from the loch bed, water, particulate matter and deployed and indigenous fauna (SEPA, 1999). Most samples collected and analysed contained no concentrations of either the parent compound or its major desmethylamino metabolite (LOD water 0.2 $\mu g\ l^{-1}$; LOD sediment, flocculent material, particulate matter, deployed and indigenous fauna 0.25 $\mu g\ kg^{-1}$). However, a maximum concentration of 5.0 $\mu g\ kg^{-1}$ of emamectin benzoate was recorded one week post treatment in hermit crabs, and at 1.23 and 1.99 $\mu g\ kg^{-1}$ in dogfish and the crab species *Munida rugosa*, respectively at the same time interval.

5.3.2 Oxolinic acid

At least two monitoring studies have shown residues of oxolinic acid to be present in the surrounding wild fish population and other marine animals during and after the medication of cultivated fish (Ervik *et al*., 1994; Samuelsen *et al*., 1992). In both studies, wild fauna were captured and monitored within the vicinity of aquaculture facilities off the west coast of Norway, following treatment with oxolinic acid. In a previous study conducted at five fish farms located in the Baltic Sea (Björkland *et al.*, 1991), oxolinic acid was not detected in any of the 24 specimens of wild bleak captured close to pens of treated rainbow trout.

Samuelsen *et al.* (1992) reported oxolinic acid residues in 11 different species of fish, crab and mussel collected from two separate fish farms. On day 0 (the day medication was terminated), the average concentrations of oxolinic acid detected in fish muscle was 4.38 $\mu g\ g^{-1}$ at Farm 1 and 0.42 $\mu g\ g^{-1}$ at Farm 2. The maximum concentration was observed in the muscle of coalfish (12.51 $\mu g\ g^{-1}$) at Farm 1 on the fourth day after medication had ceased. Maximum concentrations of oxolinic acid detected in samples of crab muscle ranged from 0.09 to 3.77 $\mu g\ g^{-1}$ at Farm 1 and 0.02 to 0.87 $\mu g\ g^{-1}$ at Farm 2. Homogenised tissue from mussels generally contained much lower concentrations (0.05 to 1.48 $\mu g\ g^{-1}$). Twelve days after medication had ceased, only minor concentrations were detected in the tissues of all of the species examined.

A later study of six farms (Ervik *et al.* 1994) produced similar results. The majority of wild fish (72 to 100% of the catch) contained measurable residues of oxolinic acid in muscle tissue. The mean muscle concentration varied from 0.58 $\mu g\ g^{-1}$ at Farm 1 to 4.89 $\mu g\ g^{-1}$ at Farm 2. The highest concentration of 15.74 $\mu g\ g^{-1}$ was detected in the fish species saithe.

Little information exists regarding residues of oxolinic acid in sediments from fish farms. In a study conducted off the south-west coast of Finland (Björkland *et al.*, 1991), residues of oxolinic acid were detected in anoxic sediments collected below three out of five fish farms where fish had been treated. Maximum concentrations of 0.05-0.2 μg g^{-1} were measured in sediments for five days after treatment of the fish.

5.3.3 Oxytetracycline

The environmental fate of oxytetracycline following its use in aquaculture has been extensively researched (Kerry *et al*., 1996; Capone *et al*., 1996; Coyne *et al*., 1994; Samuelsen *et al*., 1992; Björklund *et al*., 1991; Björklund *et al*., 1990; Jacobsen and Berglind, 1988).

There are only a limited number of studies that have investigated residues of oxytetracycline in wild fauna (Capone *et al*., 1996; Björklund *et al*., 1990). In a study carried out off the south-west coast of Finland in 1987, samples of roach and bleak were collected close to treated pens at two separate fish farms (Björklund *et al*., 1990). Concentrations of oxytetracycline ranged from 0.06-1.3 μg g^{-1} in the muscle tissue of bleak samples collected from Farm A on the last day of medication. One day after medication ceased oxtetracycline was detected in one fish (n=8) at a concentration of 0.06 μg g^{-1}. At Farm B, roach specimens collected on days 1 and 2 after medication contained very low levels of oxytetracycline (0.05-0.1 μg g^{-1}). Thereafter, trace residues of oxytetracycline were observed in some fish samples up to seven and 13 days after treatment at farms A and B, respectively.

Similar, low concentrations of oxytetracycline in wild fauna were obtained in a more recent study conducted in Puget Sound, Washington (USA) (Capone *et al*., 1996). Crabs and oysters were collected from the area around a salmon mariculture facility that historically used high amounts of antibacterials. Only trace oxytetracycline residues (about 0.1 μg g^{-1}) were found in oysters or Dungeness crab. However, the authors report drug residues of between 0.8-3.8 μg g^{-1} in the edible crabmeat of approximately half of the red rock crabs sampled during treatment and 12 days after treatment. Some months after oxytetracycline use at the farm, isolated trace concentrations were detected in two red rock crabs collected at 41 and 75 days.

There is considerable evidence to show that the enriched sediments, often present under fish farm cages, contain residues of oxytetracycline (Kerry *et al*., 1996; Capone *et al*., 1996; Coyne *et al*., 1994; Samuelsen *et al*., 1992; Björklund *et al*., 1991; Björklund *et al*., 1990; Jacobsen and Berglind, 1988).

Rapid sedimentation is a process characteristic of many aquaculture facilities, due to debris (mainly faeces and uneaten food) leaving the cages and accumulating underneath. Consequently, sediments containing oxytetracycline may be quickly buried and the drug may persist indefinitely. In Norway, residues of oxytetracycline were found in bottom sediments sampled below four different fish farms at 1, 4, 10 and 12 weeks after medication (Jacobsen and Berglind, 1988). The drug was found at concentrations ranging from 0.1-4.9 mg kg^{-1} dry matter, which may cause antimicrobial effects (Jacobsen and Berglind, 1988).

Many other studies report concentrations of less than 10 mg kg-1 under salmonid net-cages. In a study located in the Baltic Sea off the south-west coast of Finland, sediment samples collected on the last day of medication from two separate fish farms were shown to contain oxytetracycline at concentrations ranging from 0.05-3.8 μg g^{-1} (Björklund *et al*., 1990). Eight days after medication had ceased, drug levels at one farm had decreased to below the detection limit (0.05 μg g^{-1}). In contrast, up to 16 μg g^{-1} was measured in sediments taken at the other farm on day 8, and at 308 days the bottom deposits still contained between 1.0 and 4.4 μg oxytetracycline per g sediment. The half-lives for oxytetracycline in fish farm sediments were calculated to be 9 and 419 days for these farms. The authors indicate that lower temperature and stagnant, anoxic conditions were probably responsible for the increased half-life for the drug at Farm B.

In a separate study conducted off the south-west coast of Finland, five separate fish farms were monitored during and up to 12 days after treatment (Björklund *et al*., 1991). The maximum concentrations of oxytetracycline detected in the sediments were between 2.0 and 6.3 μg g^{-1}. Twelve days after the end of medication, levels of the drug had decreased to between 0.8 and 2.5 μg g^{-1}.

Similarly, low concentrations are reported in an investigation conducted at a marine salmon farm situated in Galway Bay, Ireland (Coyne *et al*., 1994). Oxytetracycline was detected in the top 2 cm of sediment samples collected from under two adjacent cage blocks following the therapeutic use of the drug. Peak concentrations of 10.9 ± 6.5 μg g^{-1} and 9.9 ± 2.9 μg g^{-1} were detected on the tenth day of treatment and 3 days after its last use, from under cage blocks 6 and 7, respectively. Approximately one month after treatment, mean concentrations had decreased to between 1.6 ± 0.4 and 2.3 ± 0.5 μg g^{-1}. At 66 and 71 days after the end of therapy, concentrations were below the limit of detection.

In a later cage block study at the same site in Galway Bay, oxytetracycline was detected at concentrations ranging from 1.3-4.5 μg g^{-1} in the top 2 cm of four of the eleven sediment cores collected 5 days after the last administration of medicated feed (Kerry *et al*., 1996). The authors note that the lower concentrations are probably as a result of the reduced treatment rate, 20 kg of the agent was used in this study as opposed to the 175 kg used previously.

Capone *et al*. (1996) presented an extensive study consisting of field investigations at three salmon mariculture facilities in Puget Sound, Washington (USA). The farms studied were chosen to represent a gradient in the magnitude of antibacterial usage. The frequency of detection of oxytetracycline was shown to parallel drug use. Residues were rarely detected beneath a farm that used very little oxytetracycline (3 kg), however, concentrations of between 0.5 and 4 μg g^{-1} were commonly detected at a farm that used 186 kg in a single prophylactic treatment period. Significantly, oxytetracycline residues (0.2-2 μg g^{-1}) were measured in surficial and subsurface sediments prior to treatment. The authors believe that these persistent residues are probably due to drug usage during the previous summer or earlier.

In contrast to the above investigations, much larger concentrations of oxytetracycline were detected by Norwegian researchers under a salmon farm situated off the west coast of Norway (Samuelsen *et al*., 1992a). Following a single 10-day therapeutic use of the drug, peak

concentrations of 189 and 285 μg g^{-1} were detected in under-cage sediment cores collected over a period of 18 months, following medication. The disparity in results obtained in this study with previous studies is considered an artefact of gross overfeeding at the farm (Smith, 1996; Kerry *et al*., 1996; Coyne *et al*., 1994).

5.3.4 Flumequine

In Europe, flumequine is only permitted for use in Norway (Alderman and Hastings, 1998). To date, only a single study has sought to quantify environmental concentrations following use of the compound in aquaculture. Researchers in Norway recorded mean muscle concentrations of between 0.06 and 1.12 mg kg^{-1} in the muscle of wild fish caught in the vicinity of a farm one day following termination of treatment (Ervik *et al*., 1994).

5.3.5 Ivermectin

The potential of ivermectin to be used as an effective feed treatment to control lice infestation of salmon has long since been recognised. Currently, ivermectin is not authorised in the UK for use in aquaculture. However, it is given consideration here as a result of its historical usage. During the mid-1990's Discharge Consents were issued by SEPA to approximately 30-35 of the 260-280 active marine salmon sites in Scotland (Davies and Rodger, 2000).

Following oral administration, ivermectin is mainly excreted in an unchanged form (Høy *et al*., 1990). Given this, a variety of modelling approaches have attempted to estimate the extent to which orally administered ivermectin will accumulate in sediments under fish farms (Davies *et al*., 1998). The presence of ivermectin in sediments has also been investigated at a small number of commercial fish farms. Unpublished work from two studies (for which a limit of quantitation of 10 and 50 ng g^{-1} was achieved), failed to detect any ivermectin residues in sediments (Kwok, unpublished; Nixon, E., unpublished, cited in Cannavan *et al*., 2000). In a third monitoring study, quantifiable residues of ivermectin (measured as H_2B_{1a}, the secondary butyl compound of ivermectin) were detected in sediments under and adjacent to salmon cages situated approximately 1 km off-shore on the west coast of Ireland (Cannavan *et al*., 2000). Sediment cores were collected on the final day of a four-month period in which the drug was administered twice weekly. Ivermectin was detected at concentrations of between 1.4 and 6.8 ng g^{-1} to a depth of up to 12 cm in cores collected from under cages and up to 31 m away from the edge of the cage block. In addition, analysis of the top 2 cm of three sediment samples that had previously been collected from the same farm but stored for 4-5 years revealed H_2B_{1a} concentrations of between 1.4 and 5.6 ng g^{-1}.

5.4 Agriculture

5.4.1 Sheep-dipping chemicals

In the UK, the following active substances are currently approved for use in sheep dips: diazinon, cypermethrin, flumethrin and amitraz (VMD, 2001). Previously, propetamphos and chlorfenvinphos have also been used. Following the introduction of the 1980 Directive of the European Communities (EC) relating to the quality of water intended for human consumption

(87/778/EEC), several extensive monitoring studies have been undertaken to determine the extent to which sheep-dips are present in freshwaters.

In a preliminary water quality survey conducted by the Tweed River Purification Board, diazinon was detected in 17 out of 20 catchments sampled during 1989, at concentrations in the range of 8-200 ng l^{-1} (Virtue, 1992). These results prompted a more extensive programme of monitoring to be carried out during 1990, 1991and 1992, involving 1302 farms (Virtue and Church, 1993), later extended to cover the autumn dipping periods of 1993 and 1994 (Virtue and Clayton, 1997). During October 1990, diazinon and propetamphos were detected in surface waters throughout the area as a whole at concentrations ranging from 14-124 ng l^{-1} and 72-366 ng l^{-1}, respectively (Virtue and Church, 1993). Apart from one anomalous high result (1.06×10^3 ng l^{-1}), samples collected from 1991 onwards showed a significant reduction in both compounds (Virtue and Clayton, 1997). In addition, stream samples were collected downstream of dippers previously identified as 'high risk'. During 1990/91, eight serious pollution incidents were observed with dip active ingredient concentrations in stream water recorded above 1 µg l^{-1} and in one sample the concentration of propetamphos exceeded 1 mg l^{-1} (Virtue and Clayton, 1997).

Similarly, during 1984-1986 a programme of sampling and analysis was undertaken in the Grampian region to determine the level of pollution attributable to sheep dipping activities (Littlejohn and Melvin, 1991). Certain organophosphorous insecticides and phenolic compounds were monitored in surface water samples collected from the River Ugie and its tributaries as well as sewage treatment works water. Residues of diazinon, propetamphos and fenchlorphos were detected in relatively few catchment samples (<2.5%) at levels greater than 100 ng l^{-1}. Maximum concentrations detected for each of the three compounds ranged from 108-2173 ng l^{-1}. Chlorfenvinphos, however, was found in over a quarter of samples collected throughout the catchment at concentrations greater than 100 ng l^{-1}, and in a few samples levels exceeded 3000 ng l^{-1}. During 1984, γ-hexachlorocylochexane (lindane), an organochlorine insecticide, was also detected on several occasions in both surface and treated water at concentrations exceeding 100 ng l^{-1}, although no further residues were detected after this time due to its withdrawal as a sheep dip at the end of 1984. The authors report that there was little evidence of contamination by phenolic compounds (Phenol, p-Cresol), used to assist emulsification and dispersal of the active compounds and for their bactericidal properties, despite their content far exceeding that of the organophosphorous insecticides in sheep-dips used in the catchment.

In Grampian region, long-term biological monitoring has been carried out at twenty sites on the Tay and its major tributaries since 1988 by the Scottish Environment Protection Agency (SEPA, 2000). Data that has been collected to date shows statistically significant declines in fauna since approximately 1996. Whilst SEPA recognises that natural environmental change will influence fauna abundance and biomass, it considers that the increased use of synthetic pyrethroid sheep dips since 1995 is responsible for the decline of fauna in a number of rivers and implicated in the decline in others. Investigations showed that particularly poor results obtained at a number of sites were traced directly to known sheep dip pollution incidents involving synthetic pyrethroid dips and dippers using synthetic pyrethroid dips.

In England and Wales, the majority of monitoring data relating to sheep-dip chemicals in controlled waters and discharges has been produced by the Environment Agency (formerly National Rivers Authority). Sheep-dip chemicals are among the 180 pesticides monitored in fresh surface waters, groundwaters, and marine waters as well as trade effluents in England and Wales.

Since 1997 the Environment Agency has conducted a programme of targeted monitoring and pollution prevention visits in Wales and areas of the Midlands with the aim of establishing whether farmer awareness of risks associated with sheep dipping would result in environmental improvements. The programme has continued on an annual basis and is targeted particularly at catchments within intensive sheep rearing areas. Both chemical and biological monitoring are performed. In 1998, biological monitoring carried out in the sheep dipping regions of Wales indicated that some 1200 km of river may be affected by sheep dip in Wales as a whole (Environment Agency, 1998). In 1999, the presence of sheep dip was found to be widespread with 67 % of 111 river sites monitored showing levels above the limit of detection. Sixteen sites (14 %) of the 111 monitored failed the Maximum Allowable Concentration (MAC) Environmental Quality Standard (EQS)[1] for one or more sheep dip chemical (Environment Agency, 2000). Extensive biological surveys were also conducted with a total of 827 km covered between a network of sites. The results showed that at least 66 km (8%) were known to be or suspected of being affected by sheep dip (Environment Agency, 2000).

Other biological monitoring carried out by the Agency included biological assessments at 300 sites in a number of catchments as part of the Cumbrian Sheep Dip Campaign conducted in 1998. Fourteen sites showed a slow recovery after severe depletion of fauna from previous sheep dip contamination and a further twelve sites showed significant insecticidal impact and were subsequently targeted for special campaigns and visits (Environment Agency, 1998).

Chemical monitoring data for England and Wales for 2000 obtained by the Environment Agency and is summarised in Table 5-3. The data show that the number of samples with concentrations above the limit of detection (LOD) as a proportion of the number of samples collected is greatest for surface freshwaters. Of these, the majority of positive detections (82%) are associated with the two organophosphate dips, diazinon and propetamphos. From a total of 4186 samples analysed, diazinon was detected above the limit of detection (LOD: 1-12500 ng l^{-1}) in 498 samples at concentrations ranging from 1-550 ng l^{-1}. Residues of propetamphos were detected in 168 out of a total of 3763 samples, at concentrations ranging from 1-11738000 ng l^{-1} (LOD: 1-10000 ng l^{-1}). Chlorfenvinphos, cypermethrin and flumethrin were detected in fewer samples (56, 81 and 13, respectively) at concentrations ranging from 1-242 ng l^{-1}, 1-85100 ng l^{-1} and 1-2190 ng l^{-1}, respectively. The number of groundwater and

[1] Environmental Quality Standards (EQS) for sheep dip chemicals (freshwater and marine water):

	Maximum Allowable Concentration (MAC) ($\mu g\ l^{-1}$)	Average Annual Concentration (AA) ($\mu g\ l^{-1}$)
Cypermethrin	0.001	0.0001
Diazinon	0.01	0.01
Propetamphos	0.1	0.01
Flumethrin	No EQS (insufficient data)	

marine water samples containing concentrations of sheep dip chemicals above the LOD was very much smaller. Chlorfenvinphos, diazinon and propetamphos were detected infrequently in groundwater and marine water at maximum concentrations of 20, 140 and 58 ng l^{-1}, respectively.

Table 5-3 Summary of concentrations of sheep dip chemicals detected in surface freshwater, groundwater and marine water in England and Wales, 2000 (data taken from Environment Agency, 2001)

Compound	Sample type	Total no of samples	No. samples >LOD	Range of concentrations detected (ng l^{-1})	LOD range (ng l^{-1})	No. sites failing an EQS
Chlorfenvinphos	FW GW MW	3634 727 253	56 2 3	1-242 15-20 5-18	5-20000 1-20000 5-40	4
Cypermethrin	FW GW MW	2513 16 98	81 0 0	1-85100 - -	1-100 1-1 1-100	47
Diazinon	FW GW MW	4186 767 258	498 3 13	1-550 26-140 5-60	1-12500 5-10000 5-40	17 1
Flumethrin	FW GW MW	2043 8 -	13 0 -	1-2190 - -	1-45000 1-1 -	No EQS for flumethrin
Propetamphos	FW GW MW	3763 767 97	168 3 4	1-11738000 29-58 5-10	1-10000 1-10000 1-40	13

FW – Surface freshwater
GW – Groundwater
MW – Marine water

Since 1998, the Agency's monitoring programme for England and Wales has shown a decrease in the number of EQS failures for sheep dip chemicals. In England and Wales in 1998, there were 209 sites where the concentration of diazinon, cypermethrin, propetamphos or chlorfenvinphos exceeded the EQS (Environment Agency, 1998). The majority of these failures occurred in Wales, Northumbria and Cumbria and are associated with sheep farming enterprises. A cluster of failures in Yorkshire is associated with discharges from the textile industry. In 1999 and 2000, the number of sites, in England and Wales where the concentration of sheep dip chemical exceeded the EQS was 86 and 82, respectively (Environment Agency, 2001). The majority of failures occurred in the textile region of Yorkshire and in the sheep farming areas of Wales, whereas in 1998 a large number of the

sheep dip EQS failures also occurred in Northumbria and Cumbria. Figure 5-1 shows the distribution of failures for 2000.

Overall, the results for 1999 and 2000 indicate a downward trend in the overall number of EQS failures from 1998. This is considered to be attributable at least in part, to a reduction in high risk dipping practises brought about by increased awareness and pollution prevention campaigns. The sharp decline in the number of failures for the organophosphate sheep dip chemicals may be a result of the temporary ban introduced during 2000 although since during this period synthetic pyrethroid dips were the only sheep dip available for use, the number of failures for cypermethrin increased slightly.

Activities by the Environment Agency to reduce the impact of sheep dip chemicals on aquatic life by encouraging best practice include, the publication of pollution prevention guidelines (Sheep dipping PPG 12), the publication of a sheep dip strategy (A strategic review of sheep dipping, R & D technical report P170) and a sheep flock management review which followed on from the sheep dip strategy and looked at the extent to which the use of chemicals can be reduced by flock management practises that limit or control sheep ectoparasites (Sheep Flock Management, R & D Technical report P170).

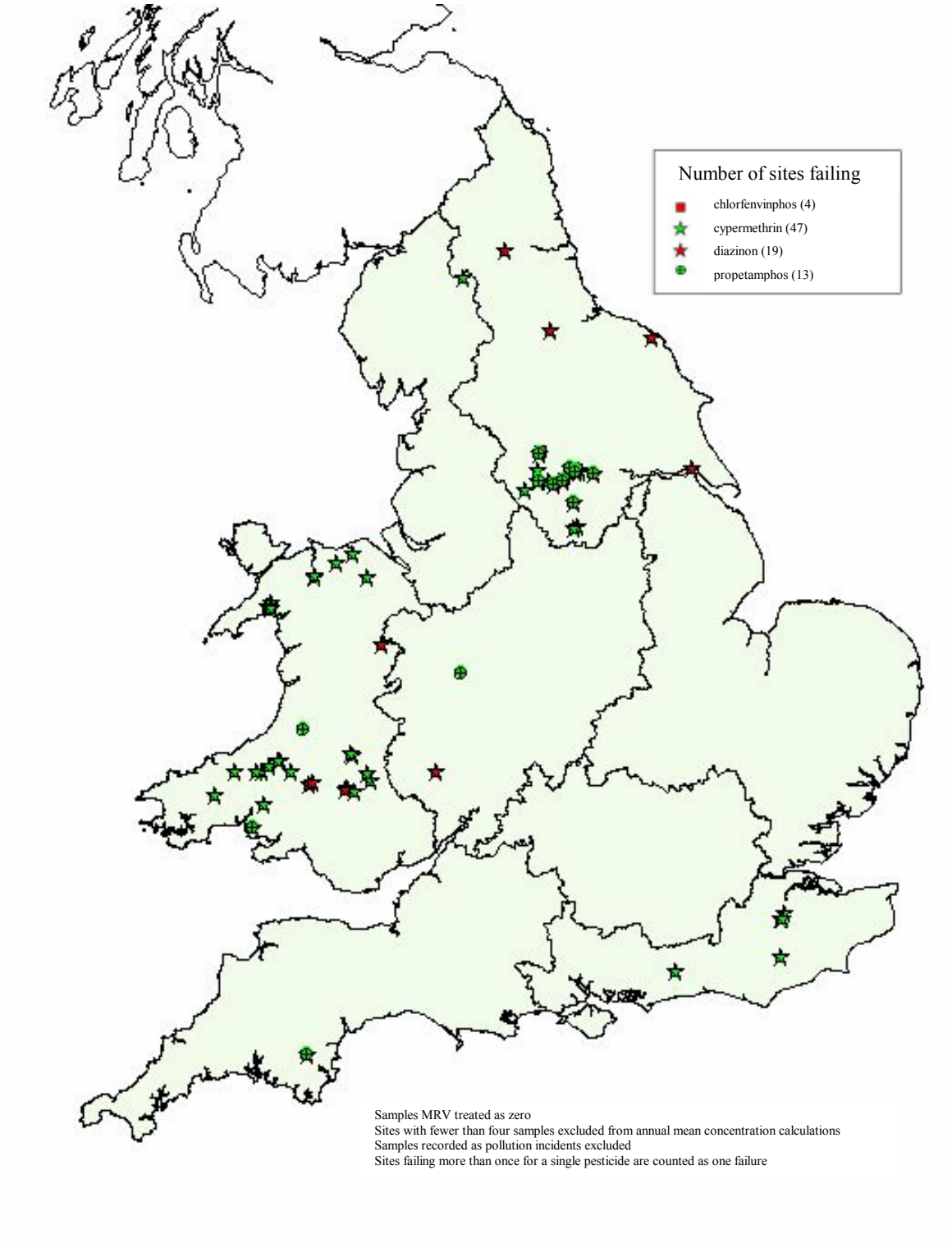


Figure 5-1 Environmental Quality Standards (EQS) failures for sheep dip chemicals in England and Wales, 2000 (Environment Agency, 2001)

5.4.2 Antibacterials and anthelmintics

5.4.2.1 Soil

Several veterinary drugs have been detected in soil that has been amended with animal manure. To date, the majority of data has been produced by a group of researchers in Germany. In three separate investigations, soil samples collected from regions with intensive livestock production were analysed for frequently used drugs (Hamscher *et al.*, 2000; Hamscher *et al.*, 2000a; Hamscher *et al.*, 2000b). In the first study, soil samples were collected at various depths from eight fields in the Lower Saxony region, that had been manured with slurry two days prior to sampling (Hamscher *et al.*, 2000). In the upper 10 cm of the soil samples, 9-12 $\mu g\ kg^{-1}$ of chlortetracycline, oxytetracycline and tetracycline were detected whereas only trace concentrations of tylosin could be found. Concentrations of the three tetracycline compounds decreased with depth to around 1 $\mu g\ kg^{-1}$ below 60 cm.

In a subsequent study conducted in Northern Germany, soil samples were collected and analysed from twelve different agricultural fields, 4-5 months after being treated with animal slurry (Hamscher *et al.*, 2000a). Tetracycline and chlortetracycline were detected in the top 30 cm of nearly all samples at concentrations of between 1-32.2 and 1.2-26.4 $\mu g\ kg^{-1}$, respectively. In a follow-on study, conducted by the same researchers, the average distribution of tetracycline in the top 30 cm of soil amended with animal slurry, was between 20 and 40 $\mu g\ kg^{-1}$ (Hamscher *et al.*, 2000b). Levels of chlortetracycline were generally below 5 $\mu g\ kg^{-1}$, although a peak concentration of 41.8 $\mu g\ kg^{-1}$ was detected at a depth of 0-10 cm in one soil sample.

Elsewhere, information on residues of veterinary medicines in soil is particularly scarce. American researchers detected trace amounts (approximately 0.1-2 $\mu g\ kg^{-1}$) of ivermectin in the top (0-3 inches) of soil in a cattle feedlot housing animals treated 28 days previously (200 $\mu g\ kg^{-1}$ body weight) (Nessel *et al.*, 1989). The authors suggest the concentrations detected in the soil is probably as a result of the faeces being trampled into the mud and subsequently being protected from light thus retarding degradation.

5.4.2.2 Surface water

Monitoring drug residues in the aquatic environment has gained much interest in recent years, owing to the regular detection of many pharmaceutical compounds in sewage effluents and surface water bodies (Ayscough, 2000; Stumpf *et al.*, 1999; Hartig *et al.*, 1999; Halling-Sørensen *et al.*, 1998; Heberer *et al.*, 1998; Ternes, 1998). Whilst many of the chemicals that have been detected can be attributed to human pharmaceutical use, there are few incidences of drugs used in animal medicine being found in surface water bodies. Whilst screening sewage treatment work effluents and associated receiving surface waters for 18 different antibiotic substances, residues of chloramphenicol were detected by German researchers at concentrations of 0.06 and 0.56 $\mu g\ l^{-1}$ (Hirsch *et al.*, 1999). The authors point out that as its use in human medicine is extremely limited, the two positive detections are more likely to result from its sporadic veterinary use in fattening farms. Chloramphenicol is no longer

authorised in the UK for use as a veterinary medicine (Fort Dodge Animal Health, pers. comm.).

In studies for the Centers of Disease Control (CDC), the US Environmental Protection Agency (USEPA) and US Geological Survey (USGS) sampled and analysed liquid waste from hog lagoons (13 in three states) and surface and groundwater from areas associated with intensive swine and poultry production (52 from seven states) (Meyer *et al*., 2000). All samples were analysed for chlortetracycline. Whilst the compound was detected at up to several hundred parts per billion in lagoon samples, it was only found in one surface water sample at a concentration of 0.5 $\mu g\ l^{-1}$ (limit of detection).

5.4.2.3 Groundwater

There are few reports of veterinary medicines being detected in groundwater (Hamscher *et al*., 2000; Hirsch *et al*., 1999). In an extensive monitoring study conducted in Germany, a large number of groundwater samples were collected from agricultural areas in order to determine the extent of contamination by antibiotics (Hirsch *et al*., 1999). The data show that in most areas with intensive livestock breeding, no antibiotics were present above the limit of detection (0.02-0.05 $\mu g\ l^{-1}$). Sulfonamide residues were however detected in four samples. Whilst the source of contamination of two of these is considered to be attributable to irrigation with sewage, the authors conclude that sulfamethazine, detected at concentrations of 0.08 and 0.16 $\mu g\ l^{-1}$, could possibly have derived from veterinary applications, since it is not used in human medicine.

In the investigations of Hamscher *et al*. (2000) soil water was collected and analysed from four separate areas of agricultural land: two belonging to livestock farms and treated with animal slurry and two where no animal manure had been applied for approximately five years. Chlortetracycline, oxtetracycline, tetracycline and tylosin were all found at the limit of detection (0.1-0.3 $\mu g\ l^{-1}$) in water samples collected at 80 and 120 cm depth, independent of soil treatment. In addition, no biologically active residues could be detected with microbiological assays that had approximately five-fold higher detection limits.

Veterinary medicines are also known to leach from landfill sites. In Denmark, high concentrations (ppm) of numerous sulfonamides were found in leachates close to a landfill site where a pharmaceutical manufacturer had previously disposed of large amounts of these drugs over a 45 year period (Holm *et al*., 1995). Concentrations dropped off significantly tens of metres down gradient, most probably due to microbial attenuation. Although this is recognised as a specific problem, in the UK the disposal of smaller quantities of veterinary medicines to landfill should nevertheless be considered a potential route for environmental contamination.

5.4.2.4 Surface/sub-surface run-off

So far, only one study has investigated the occurrence of veterinary drugs in surface/sub-surface run-off. In a post approval study carried out for Merck & Co., the run-off from a cattle feedlot following injection of five steers with ivermectin at 200 $\mu g\ kg^{-1}$ body weight was

collected and analysed for six separate time periods (Nessel *et al*., 1989). Samples were collected during the seven days prior to treatment (to establish baseline data) and during four consecutive seven-day periods following injection. The authors report trace amounts of ivermectin (1.1-1.2 ng l^{-1}) detected in two surface water samples collected, 0-6 and 14-20 days post treatment and 2 ng l^{-1} of ivermectin in the surface water of a pen flood irrigated on day 28 after the treated animals had been removed. In the seven day period prior to treatment ivermectin was detected at concentrations of 3.2-4.4 ng l^{-1} and 0.8-1.5 ng l^{-1} in surface and sub-surface water, respectively.

5.4.2.5 Faeces and urine

Some drugs used in livestock production are poorly absorbed by the gut and thus are excreted in the faeces, irrespective of the method of application (Sommer *et al*., 1992; Chui *et al*., 1990; Campbell *et al*., 1983). It is common practice for animal waste (faeces and urine) to be spread onto land as organic fertiliser. Furthermore, faeces are deposited directly onto pasture by grazing animals such as cattle, sheep and horses and by animals reared semi-intensively on outdoor systems such as pigs and poultry. Consequently, residues of drugs in animal faeces are an important consideration when assessing the potential environmental effects following the use of veterinary medicines in agriculture. To date, the majority of published information regarding concentrations of drug residues in animal excreta relates to the use of avermectins.

In metabolism studies, the majority of ivermectin has been shown to be excreted during the first seven days after standard therapeutic injection (200 µg kg^{-1} body weight) (Merck, Sharpe & Dohme, 1983 cited in Strong, 1992; Chiu *et al*., 1990). The manufacturers of ivermectin estimate the maximum concentration of the drug in cattle faeces during this period as 0.353 mg kg^{-1} (wet weight) (Merck, Sharpe & Dohme, 1983 cited in Strong, 1992). In a pour-on formulation study, peak concentrations of approximately 80 µg kg^{-1} were observed in manure between days 3 and 7 post-dose and levels decreased to 13 µg kg^{-1} by day 42 (Halley *et al*., 1986 cited in Bloom and Matheson, 1993). In other metabolism studies, ivermectin was found in the faeces of cattle, sheep and pigs at concentrations of 0.24-0.27 mg kg^{-1} (2.5 days), 0.63-0.71 mg kg^{-1} (1-3 days) and 0.22-0.24 mg kg^{-1} (1-7 days), respectively (Halley *et al*., 1989).

In field experiments, residues of ivermectin were detected in cattle dung at concentrations of between 3-4 mg kg^{-1} and 6-9 mg kg^{-1} (dry weight of dung), one to two days after subcutaneous injection and pour-on treatments, respectively (Sommer and Steffansen, 1993). By day 14, levels fell to around the limit of detection (0.03 µg g^{-1}) or below. Similar results are reported in an earlier investigation, where average concentrations of 3.8, 1.6 and 0.3 mg kg^{-1} (dry weight of dung) were found in the dung of 15 treated cattle at 2, 7 and 17 days after treatment (Sommer and Overgaard Nielsen, 1992).

In a cattle feedlot study, researchers in Missouri, USA, detected ivermectin at concentrations ranging from 55-75µg kg^{-1} in faecal samples three days after standard therapeutic injection of the drug (Nessel *et al*., 1989). In an investigation comparing levels of ivermectin excreted in faeces from grain-fed and pasture-fed cattle, concentrations of between 0.07 and 0.36 mg kg^{-1} (wet wt) were detected in the first nine days post treatment (Cook *et al*., 1996). Residues of

excreted ivermectin have also been investigated in horse faeces following a single oral dose of 200 µg ivermectin per kg of body weight (Jernigan *et al*., 1990 cited in Sams, 1993). Peak concentrations (1.9-8.47 µg g^{-1}) were detected one day after treatment and by day 3 levels had mostly declined to below the LOD (0.05 µg g^{-1}). Studies assessing the off-target effects of ivermectin also report the presence of residues in the dung of treated cattle up to 10 days post-treatment), although levels are not quantified (Floate, 1998; Floate *et al*., 1997).

Reports of residues of other veterinary medicines detected in animal faeces, notably antibiotics, are much less readily available in open literature. In Canada, manure from poultry fed a ration containing 11 µg g^{-1} chlortetracycline, was found to contain residues of the antibiotic at concentrations 22.5 µg g^{-1} (Warman and Thomas, 1981).

In a metabolism study, narasin, a polyether antibiotic used as an anticoccidial agent in poultry farming, was detected in the excreta of chickens and quail up to two weeks post-treatment (Catherman *et al*., 1991). Narasin equivalent peak concentrations of 725 µg kg^{-1} (chickens) and 371 µg kg^{-1} (quail) were observed 24 h after [^{14}C]narasin injection. By day 14, both species were excreting only trace amounts.

In a study of the environmental fate of ceftiofur sodium, [^{14}C]ceftiofur equivalent concentrations of up to 216 mg l^{-1} and 5.4 mg kg^{-1} were detected in samples of urine and faeces collected from animals injected 24 hours previously with 2.2 mg of [^{14}C]ceftiofur free acid equivalent per kg body weight (Gilbertson *et al*., 1990).

In extensive biochemical studies on the fate of monensin in animals and the environment, the compound was detected in fresh faeces from monensin-fed cattle at concentrations of 4.5 mg kg^{-1} (Donoho, 1984). In addition, in a manure pile prepared from collections from cattle fed monensin at 40g/U.S. ton of feed, the drug was measured 2, 5 and 11 weeks after establishing the pile at concentrations of 4.7, 2.8 and 0.7 mg kg^{-1}. More recently, sulphadimethoxine concentrations ranging from 300 to 900 mg kg^{-1} were found in the fresh faeces of treated calves (Brambilla, unpublished data, 1995, cited in Migliore *et al*., 1995).

5.4.2.6 Run-off from topical application

Veterinary drugs in topically applied formulations have the potential to be washed off the backs of treated animals exposed to rain shortly after dosing. In a wash-off study conducted by Merck & Co., animals were treated with a topical dose of ivermectin (500 µg kg^{-1} body weight) and then 6 hours later subjected to 12.5 mm artificial rainfall over a 10 minute period (Bloom and Matheson, 1993). Approximately 0.6% (714 µg) of the applied dose was recovered in the wash-off water (5.4 l). The average concentration of ivermectin was determined to be 1.32 µg l^{-1}. In the UK such intensive rainfall is considered to occur approximately once every 15 to 20 years (Meteorological Office, pers.comm.).

5.5 Summary

- Analytical methods are available for a wide range of veterinary medicines. These have generally been developed for the determination of the concentrations of veterinary medicines in food. However, methods are available for selected compounds in surface waters, sediments, manure/slurry, soils and groundwater.

- A number of studies in the literature have reported concentrations of veterinary medicines (and some metabolites) in surface waters, groundwaters, soil, sediment and biota. These have generally concentrated on substances used in aquaculture and in sheep dips. (Table 5-1).

- Reported concentrations for sheep dip chemicals were as high as 19.2 x 10^6 ng l^{-1} in surface waters and 489 ng l^{-1} in groundwaters (Virtue and Clayton, 1997; Environment Agency, 1997) and often exceed the Environmental Quality Standard (EQS). However, monitoring undertaken by the Environment Agency indicates a significant downward trend in the number of EQS failures detected in 1999 and 2000 compared with 1998 (Environment Agency, 2001).

- Reported concentrations of veterinary products used in aquaculture were as high as 1.06 μg l^{-1} in water (emamectin benzoate) and concentrations in sediment were as high as 285 μg g^{-1} (oxytetracycline) (SEPA, 1999; Samuelsen *et al*., 1992).

- A limited amount of data was available on concentrations of antibacterial agents and anthelmintics used to treat livestock. Reported concentrations of chlortetracyline, ivermectin and monensin in soil reached 42 μg kg^{-1}, 2 μg kg^{-1} and 1 mg kg^{-1}, respectively (Hamscher *et al*., 2000b; Nessel *et al*., 1989; Donoho, 1984). Concentrations of oxytetracycline, tetracycline, chlortetracycline and tylosin were also detected in groundwater (Hamscher *et al*., 2000).

- With the exception of a metabolite of emamectin benzoate, information regarding analysis for metabolites and transformation products of veterinary medicines is not publicly available.

6 METABOLISM AND ENVIRONMENTAL FATE

6.1 Introduction

Once administered to an animal, veterinary products may be metabolised and the resulting metabolites will be excreted, with any remaining parent compound, in urine and faeces. The resulting excreta may be released directly to land or stored and applied to land at a later stage.

Once released into the environment, veterinary medicines will be transported and distributed between the major environmental compartments (i.e. soil, air, surface waters, sediment and biota). The resulting concentrations in these compartments will be determined by a number of factors and processes, including:

- dosage of compound
- the physico-chemical properties of the substance
- degradation in manure and slurry
- partitioning to soil and sediment
- abiotic and biotic degradation
- environmental characteristics (including soil type, climatic conditions)

A number of studies have investigated the metabolism and environmental behaviour of veterinary medicines. A detailed discussion of some of these factors and processes is given below.

Data on the metabolism, persistence and degradation of veterinary medicines available in the scientific literature are given in Appendices G to I. The persistence and degradation data were reviewed for their reliability and quality scores were assigned to each study using the criteria described in Appendix H.

6.2 Metabolism of veterinary medicines

For compounds that are administered by injection, some of the dose may remain at the injection site for some time and therefore may not be absorbed (VMD, pers.comm). For compounds that are administered orally, the amount absorbed can range from a small proportion to around 100%. Once absorbed the product may undergo phase I metabolism followed by phase II metabolism. These reactions may produce polar metabolites that are excreted in the urine or faeces. If the compound is not metabolised, then it may be excreted unchanged. Consequently, animal faeces may well contain a mixture of the parent compound and metabolites. The environmental impact of the parent and major metabolites should therefore be considered in any assessment of risk.

A summary of the metabolism of the major therapeutic classes of veterinary medicinal products is given in Table 6-1.

Table 6-1 Metabolism of major therapeutic classes of veterinary medicines

Therapeutic class	Chemical group	Metabolism
Antimicrobials	tetracyclines	minimal
Antimicrobials	potentiated sulphonamides	high
Endoparasiticides - coccidiostats	-	moderate-high
Antimicrobials	β-lactams	?
Ectoparasiticides- sheep dips	organophosphates	?
Antimicrobials	macrolides	minimal
Growth promoters	-	?
Antimicrobials	aminoglycosides	minimal-high
Neurological preparations – general anaesthetics	-	?
Endoparasiticides - wormers	pyrimidines	?
Ectoparasiticides – sheep dips	pyrethroids	?
Endoparasiticides - wormers	azoles	moderate
Endoparasiticides - wormers	macrolide endectins	minimal-moderate
Antimicrobials	others	moderate-high
Neurological preparations – euthanasia products	-	?
Neurological preparations – local anaesthetics	-	?
Antimicrobials	pleuromutilin derivatives	?
Antimicrobials	lincosamides	moderate
Antimicrobials - antifungals	azoles	?
Endoparasiticides - wormers	others	?
Antimicrobials	fluoroquinolones	minimal-high
Antimicrobials - antifungals	others	?
Antimicrobials - antifungals	biguanide/gluconate	?
Neurological preparations - tranquilisers	-	?
Anti-inflammatory preparations (NSAIDS)	-	?
Neurological preparations -analgesics	-	?
Hormones	-	?
Enteric preparations	-	?
Endoparasiticides - antiprotozoals	-	minimal-high
Endectocides	macrocyclic lactones	minimal-high
Ectoparasiticides	others	?
Ectoparasiticides	amidines	?
Ectoparasiticides – spray and pour-ons for sheep	-	?
Ectoparasiticides – aquaculture treatments	-	?
Antiseptics	?	?
Anti-inflammatory preparations	steroids	?
Diuretics	?	?
Cardiovascular treatments	?	?
Locomotor treatments	?	?
Immunological products	?	?

minimal (<20%)
moderate (20-80%)
high (>80%)
- unknown

6.3 Fate in manure and slurry

On livestock farms where animals are housed, large quantities of farmyard manure (animal urine and faeces along with fouled bedding material) and/or slurry (urine, faeces and washing-down water) are produced. Both can be either stored in manure pits for subsequent application or applied immediately to land as an organic matter supplement and fertiliser (Velagaleti, in press). In the UK, the storage time for slurry varies from 0 to 50 months, with an average of 9 months and for manure from 0 to 48 months with an average of about 6 months (WRc-NSF, 2000). Consequently there is the potential for veterinary medicines to be degraded during a period of storage.

Data are available on the persistence in manure of a range of commonly used classes of antibiotic veterinary medicines (Table 6-2). Sulphonamides, aminoglycosides, beta-lactams and macrolides have half-lives of 30 d or lower, and are therefore likely to be significantly degraded during manure/slurry storage (although no data is available on the fate of the degradation products). In contrast, the macrolide endectin ivermectin, tetracyclines and quinolones have longer half-lives and are therefore likely to be more persistent.

Table 6-2 Persistence of major classes of veterinary medicines in manure

Chemical group	Compound	t½ (d)	Persistence class
aminoglycosides	unspecified*	30	moderately persistent
beta-lactams	unspecified*	5	slightly persistent
macrolides	tylosin	<2	impersistent
	unspecified*	21	slightly persistent
macrolide endectins	ivermectin	>45	moderately persistent
quinolones	unspecified*	100	very persistent
sulphonamides	sulfachloropyridazine	<8	slightly persistent
	unspecified*	30	moderately persistent
tetracyclines	unspecified*	100	very persistent
others	amprolium	>8	slightly persistent
	meticlorpindol	>8	slightly persistent
	nicarbazin	>8	slightly persistent

Classification of persistence taken from Hollis (1991):
impersistent: DT_{50} < 5 d
slightly persistent: DT_{50} 5-21 d
moderately persistent: DT_{50} 22-60 d
very persistent: DT_{50} > 60 d
Halling-Sørensen *et al.,* (unpublished)

6.4 Fate in soil

When a veterinary medicine reaches the soil, it may partition to the soil particles, leach to groundwater and/or be degraded.

Data are available on the sorption behaviour of antibiotics, sheep dip chemicals and avermectins in soils (Appendix H). A summary of the mobility of the major classes of veterinary medicines is also provided in Table 6-3.

The degree to which veterinary medicines may adsorb to particulates varies widely. Consequently, the mobility of different veterinary medicinal products also varies widely. Partition co-efficients (K_D) range from low (0.6 l kg^{-1}) to high (6000 l kg^{-1}) adsorption (K_{OC}, the organic normalised partition co-efficient from 40-163 x 10^5 l kg^{-1}). In addition, the variation in partitioning for a given compound in different soils can be significant (up to a factor of 30 for efrotomycin). This variation does not appear to be reduced by normalization to the organic carbon content of the soils for most of the compounds.

Table 6-3 Mobility of major classes of veterinary medicines in soil

Chemical group	Compound	Koc	Mobility class
azoles	metronidazole	38-56	mobile
fluoroquinolones/quinolones	ciprofloxacin	61000	immobile
	enrofloxacin	16506-768740	immobile
	flurochloquinolone carboxylic acid	40714	immobile
	ofloxacin	44143	immobile
	olaquindox	46-116	moderately mobile-mobile
macrolides	tylosin	553-7988	immobile-slightly mobile
macrolide endectins	avermectin B_{1a}	5300-30000	immobile
	ivermectin	12600-15700	immobile
organophosphorous compounds	chlorfenvinphos	295	moderately mobile
	coumaphos	5778-21120	immobile
	diazinon	229-1549	slightly-moderately mobile
sulphonamides	sulfamethazine	60	mobile
synthetic pyrethroids	deltamethrin	46 x 10^4-163 x 10^5	
tetracyclines	oxytetracycline	27792-93317	immobile
	tetracycline	40 x 10^3	
others	efrotomycin	580-11000	immobile-slightly mobile

Classification of mobility taken from Hollis (1991):
immobile: Koc >4000 moderately mobile: Koc 75-499 very mobile: Koc <15
slightly mobile: Koc 500-4000 mobile: Koc 15-74

The range of partitioning values can be explained by studies addressing the sorption of tetracycline and enrofloxacin. The results suggest that surface interactions of these compounds with clay minerals are responsible for the strong sorption to soils. The underlying processes are cation-exchange (tetracycline at low pH) and surface complexation with divalent cations sorbed at the clay surfaces (tetracycline at intermediate pH and enrofloxacin). This indicates that, in order to arrive at a realistic assessment of the availability of these compounds for transport through the soil and uptake into soil organisms, soil chemistry may not be reduced to the organic carbon content but that the clay content, pH of the soil solution and the coverage of the ion-exchange sites need to be accounted for.

The main route for degradation of veterinary medicines in soils is via aerobic soil biodegradation. Degradation rates in soil vary with half-lives ranging from days to years. Available data are provided in Appendix I and summarised below in Table 6-4.

Degradation of veterinary medicines is affected by environmental conditions such as temperature and pH and the presence of specific degrading bacteria that have developed to degrade groups of medicines (Ingerslev and Halling-Sørensen, 2001; Gilbertson *et al*., 1990). The summary data show that as well as varying significantly between chemical classes degradation rates for veterinary medicines also vary within a chemical class. For instance, of the quinolones, olaquindox can be considered to be only slightly persistent (half-life 6-9 days) whilst danofloxacin is very persistent (half-life 87-143 days). In addition, published data for some individual compounds show persistence varies according to soil type and conditions. In particular, diazinon was shown to be relatively impersistent (half-life 1.7 d) in a flooded soil that had been previously treated with the compound, but was reported to be very persistent in sandy soils (half-life 88-112 d) (reported in Lewis *et al*., 1993). Of the available data, coumaphos and emamectin benzoate were the most persistent compounds in soil with maximum reported half-lives of 300 and 427 days, respectively, whilst tylosin and dichlorvos were the least persistent with half-lives of 3 to 8 and <1 day, respectively.

Degradation rates in manure are generally faster than degradation in soil. For example under methanogenic conditions the degradation of tylosin A was less then two days and was enhanced by increasing concentrations of manure particles in the incubation medium under aerobic conditions (Loke *et al*., 2000). Moreover, when manure is combined with soil, degradation may be enhanced. When manure or slurry is combined with soil, temperature has been shown to significantly affect the rate of degradation of a compound. For example, a half-life of 91 to 217 days was recorded for ivermectin in a soil/faeces mixture during winter weather conditions (Halley *et al*., 1993). In contrast, the compound was shown to degrade much more rapidly in a soil/faeces mixture during the summer period with a half-life of 7 to 14 days being measured (Halley *et al*., 1989). The timing of application of manure/slurry to land may therefore be a significant factor in determining the subsequent degradation rate of a compound.

Depending on the nature of the chemical, other degradation and depletion mechanisms may occur, including soil photolysis and hydrolysis. The degradation products of both photolytic and hydrolytic degradation processes may undergo aerobic biodegradation in upper soil layers or anaerobic degradation in deeper soil layers.

Table 6-4 Persistence of major classes of veterinary medicines in soil

Chemical group	Compound	t½ (d)	Persistence class
azoles	metronidazole	9.7-26.9	slightly-moderately persistent
bambermycins	flavomycin	<30*	-
cephalosporin derivatives	ceftiofur	22.2-49	moderately persistent
fluoroquinolones/quinolones	danofloxacin	87-143	very persistent
	olaquindox	5.8-8.8	slightly persistent
	sarafloxacin	>65 <80	very persistent
macrolides	tylosin	<5*	impersistent
		3.3-8.1	impersistent-slightly impersistent
macrolide endectins	emamectin benzoate	174-427	very persistent
	ivermectin	7-217*	slightly-very persistent
		14-56	slightly-moderately
organophosphorous compounds	chlorfenvinphos	4-30 weeks	moderately-very persistent
	coumaphos	200-300	very persistent
	diazinon	1.7-112	impersistent-very persistent
	dichlorvos	<1	impersistent
penicillins	procaine benzyl penicillin	<3 h*	impersistent
synthetic pyrethroids	deltamethrin	<23	-
tetracyclines	chlortetracycline	>30*	-
others	bacitracin	12-22.5*	slightly-moderately persistent
	virginamycim	>64	very persistent

Classification of persistence taken from Hollis (1991):
impersistent: DT_{50} < 5 d
slightly persistent: DT_{50} 5-21 d
moderately persistent: DT_{50} 22-60 d
very persistent: DT_{50} > 60 d

* mixture of soil and manure/faeces

The mobility of veterinary medicines in soils will be very influential in determining the concentrations of veterinary medicines in the environment. Laboratory studies have quantified the sorption and mobility of four antibiotics in different soil types (Rabølle and Spliid, 2000). Distribution coefficients (K_d values) determined by a batch equilibrium method varied between 0.5 and 0.7 for metronidazole, 0.7 and 1.7 for olaquindox and 8 and 128 for tylosin. Tylosin sorption correlated positively with soil clay content and oxytetracycline was particularly strongly sorbed in all soils investigated with K_d values between 417 in a sandy soil, 1026 in a sandy loam and no significant desorption. The mobility of the four antibiotics

corresponded to their respective sorption capabilities. For the weakly sorbed substances, metronidazole and olaquindox, all of the applied substance was recovered in the leachate from both sandy loam and sandy soils, whereas the strongly sorbed compounds, oxytetracycline and tylosin were not detected in any leachate samples.

Whilst some veterinary medicines sorb strongly to soil or surface particulate matter, following their disposal to land there is the potential for transportation to surface waters via particles carried in surface water run-off, or to sub-surface drains and channels through cracks and fissures during rapid bypass flow. In England and Wales up to a third of soils possess the potential to crack and in a further third bypass flow through macropores may be a dominant process (Hollis and Carter, 1990). In a drainage study conducted in the UK, oxtetracycline (K_{OC} 28000-93000) was detected in drainflow from a clay loam soil at concentrations up to 500 $\mu g\ l^{-1}$, within 36 hours of application in slurry to the soil surface (Cranfield Centre for EcoChemistry, unpublished). Current risk assessment models for veterinary medicinal products do not consider this potential route of exposure.

6.5 Fate in surface waters

A number of studies have investigated the persistence of veterinary medicines in surface waters and freshwater and marine sediment (Appendix I). Substances may be degraded abiotically via photodegradation (although this is unlikely to be a significant degradation route in the UK climate) and/or hydrolysis or biotically by aerobic or anaerobic organisms. Table 6-5 provides a summary of the persistence of major classes of veterinary medicines in water.

The quinolones, tetracyclines, ivermectin and furazolidone are all rapidly photodegraded with half-lives ranging from < 1 h to 22 d (Lunestad *et al*., 1995; Halley *et al*., 1993; Davis *et al*., 1993; Oka *et al*., 1989). In contrast trimethoprim, ormethoprim and the sulphonamides are not readily photodegradable (Lunestad *et al*., 1995).

Of the compounds studied in terms of potential to hydrolyse, ceftiofur is the only compound to be rapidly hydrolysed with a half-life of 8 d at pH 7 (Gilbertson *et al*., 1990). Whilst propetamphos was rapidly hydrolysed at pH 3(11 days), hydrolysis at pH 6 and 9 was slower (1 year and 41 days) (Lewis, 1998).

Of the organophosphorous compounds that have previously been authorised for use in ectoparasitic sheep dip preparations, chlorfenvinphos, coumaphos and dichlorvos are all relatively impersistent in biologically active water with half-lives ranging from <1 to <25 days (Lewis, 1998; Tomlin, 1997; Lewis *et al*., 1993). Flumethrin, a synthetic pyrethroid also used as a sheep dip ectoparasiticide, was much more persistent in water, with a half-life greater than 3 months.

Table 6-5 Half-lives of major classes of veterinary medicines in water

Chemical group	Compound	t½ (d)
cephalosporin derivatives	ceftiofur	4.2-100
2,4-diaminopyrimidines	ormethroprim	>42
	trimethoprim	>42
fluoroquinolones/quinolones	flumequine	<9
	oxolinic acid	<9
	sarafloxacin	<1 h
macrolide endectins	ivermectin	<0.5
organophosphorous compounds	chlorfenvinphos	<25
	coumaphos	<7
	dichlorvos	<1
	propetamphos	5 d- 1 year
sulphonamides	sulfadiazine	>21
	sulfadimethoxine	>21
synthetic pyrethroids	cypermethrin	5
	flumethrin	>3 months
tetracyclines	oxytetracycline	<9
	tetracycline	3 h
others	furazolidone	<9

6.5.1 Fate in sediment

A large body of data exists on the degradability of veterinary medicines, used for aquaculture, in both marine and freshwater sediments (Chien *et al*., 1999; Marengo *et al*., 1997; Bohm, 1996; Hektoen *et al*., 1995; Lai *et al*., 1995; Lunestad *et al*., 1995; Coyne *et al*., 1994; Samuelsen *et al*., 1994; Hansen *et al*., 1993; Samuelsen *et al*., 1992a; Pouliquen *et al*., 1992; Samuelsen *et al*., 1991; Bjorklund *et al*., 1990; Samuelsen, 1989; Jacobsen and Berglind, 1988).

Of the compounds studied to date, florfenicol, chloramphenicol and furazolidone were the least persistent with half-lives of between 0.4 and 18.4 days (Table 6-6). The other substances studied (flumequine, ormethoprim, oxytetracycline, oxolinic acid, sarafloxacin, sulfadiazine, sulfadimethoxine and trimethoprim) persisted in sediments with half-lives being generally greater than 30 days.

Table 6-6 Persistence of major classes of veterinary medicines in sediment

Chemical group	Compound	t½ (d)	Persistence class
phenicols	chloramphenicol	0.4-18.4	impersistent to slightly persistent
	florfenicol	1.7-7.3	impersistent to slightly persistent
2,4-diaminopyrimidines	ormethoprim	<30	-
	trimethoprim	<60-100	up to very persistent
fluoroquinolones/quinolones	flumequine	60 to >300	moderately to very persistent
	oxolinic acid	48 to >300	moderately to very persistent
	sarafloxacin	>83>300	very persistent
sulphonamides	sulfadiazine	50-180	moderately to very persistent
	sulfadimethoxine	>180	very persistent
tetracyclines	oxytetracycline	9-414	slightly-very persistent
others	furazolidone	0.75	impersistent

Classification of persistence taken from Hollis (1991):
impersistent: DT_{50} < 5 d
slightly persistent: DT_{50} 5-21 d
moderately persistent: DT_{50} 22-60 d
very persistent: DT_{50} > 60 d

6.6 Summary

- A number of studies have investigated the fate of veterinary medicines in a range of media, including manure, slurry, water, soil and sediment. Data are available on the mobility and persistence of a number of the major product classes (particularly antibiotics and anthelmintics) but there are significant data gaps.

- The persistence of major groups of veterinary medicines in manure and slurry varies. Sulphonamides, beta-lactams, macrolides and aminoglycosides are all likely to be significantly degraded during typical UK manure/slurry storage regimes. In contrast, quinolones and tetracyclines are likely to persist.

- A number of studies have investigated the sorption behaviour and persistence of veterinary medicines in soils. Sorption coefficients range over 4 orders of magnitude and there is significant variation between coefficients for the same compound in different soil types. Unlike many industrial compounds and pesticides, this variation cannot be explained by hydrophobicity and soil organic carbon content, although tylosin sorption has been shown to correlate positively with soil clay content.

- Veterinary medicines can persist in soils for days to years and studies have demonstrated that half-lives are influenced by a range of factors including temperature, pH and the presence of manure.

- In sediments, the phenicols (chloramphenicol and florfenicol) as well as furazolidone have been shown to rapidly degrade whilst the 2, 4-diaminopyrimidine, quinolone, tetracycline and sulphonamide classes all persist.

- Generally, published tests have investigated the degradation of the parent compound. Information relating to the degradation of transformation products was unavailable.

- Whilst the fate of a range of veterinary products has been extensively investigated, few studies have assessed the fate of metabolites and transformation products.

7 ENVIRONMENTAL HAZARD

7.1 Introduction

Data on the aquatic and terrestrial toxicity of veterinary medicines published in the scientific literature are given in Appendices J and K. The data for each study were reviewed in terms of reliability and assigned a quality score as described in Appendix J.

With the exception of coccidiostats, pyrimidine wormers, growth promoters, barbiturates, cephalosporin derivatives, biguanide/gluconates, NSAIDs, hormones, antiprotozoals and enteric preparations, data were available on the ecotoxicity of the major product classes to aquatic organisms. The data indicates that most groups can be considered very toxic on the basis of at least one test result.

Slightly less data were available on the effects of the substances on terrestrial organisms and compounds were classified as non-hazardous to very toxic.

A summary of both aquatic and terrestrial toxicity data is provided in Table 7-1.

7.2 Aquatic Toxicity

Data on the aquatic toxicity of 63 veterinary medicines covering a range of species and endpoints were identified. Generally data were available for three main therapeutic groups, sheep dip chemicals, antibacterial agents and endectocides. Data was also available on the effects of the hormone treatment, ethinyl estradiol.

7.2.1 Antiparasitics

7.2.1.1 Sheep dip chemicals

The effects of currently and previously approved sheep dip chemicals (including chlorfenvinphos, coumaphos, cypermethrin, deltamethrin, diazinon, fenchlorphos, flumethrin and propetamphos) on aquatic organisms has been extensively investigated and Environmental Quality Standards are available. Acute toxicity values for the compounds to insects, crustaceans and fish are generally in the low ng l^{-1} to the low μg l^{-1} range, indicating a very high acute toxicity.

7.2.1.2 Others

To date, there is little available data on the toxicity of other ectoparasiticides to aquatic species. However, the aquatic toxicities of emamectin benzoate, hydrogen peroxide and ivermectin have been extensively investigated (summarised in Appendix J), because of their potential use in aquaculture.

Table 7-1 Effect concentrations of veterinary compounds to aquatic and terrestrial organisms

Veterinary medicine class	Compound	Aquatic toxicity effect concentration (mg l^{-1})	Terrestrial toxicity effect concentration (mg kg^{-1})
amidine	amitraz	1->1000	
azoles	benzimidazole		>10->1000
	dimetridazole	200	
	fenbendazole	1-10	
	metronidazole	2.03-1000	
	triclabendazole	45-133	
aminoglycosides	neomycin	2829	
	streptomycin	0.007-487	
2,4-diaminopyrimidine	trimethoprim	16-130	
fluoroquinolones/quinolones	cinoxacin	0.117-73	
	ciprofloxacin	0.005-0.08	
	enoxacin	0.049-19.7	
	flumequine	0.019-477	
	lomefloxacin	0.022-170	
	naladixic acid	0.2-22.9	
	norfloxacin	0.022-69.6	
	ofloxacin	0.01-82.8	
	olaquindox	5.1-1000	
	oxolinic acid	0.023->26	
	pipemidic acid	1.019->151	
	pirimidic acid	0.121	
	sarafloxacin	0.015-24	
halogenated hydrocarbons	halothane	0.5%	0.5-2%
imidazothiazole	levamisole	10	
lincosamides	lincomycin	5-379	
macrolides	erythromycin	<10-388	
	spiramycin	0.005-2.3	
	tylosin	0.034-680	2520->5000
macrolide endectins	abamectin	0.022-430	11-2000
	doramectin	5.1-11	3-38.3
	emamectin benzoate	0.000043-1.73	570-1318 (dietary LD50)
	ivermectin	0.025->10000	0.0005-100
organophosphorous compounds	chlorfenvinphos	0.0001-100	
	coumaphos	0.000074-22	
	diazinon	0.000026-29.22	0.0258-74.15
	dichlorvos	0.00019	0.29 µg/organism
	fenchlorphos	0.005-2.5	
	propetamphos	0.00878-21.4	

Table 7-1 continued

Veterinary medicine class	Compound	Aquatic toxicity Effect concentration (mg l^{-1})	Terrestrial toxicity effect concentration (mg kg^{-1})
penicillins	amoxillin	0.0037-3108	
	ampicillin	163	
	benzyl penicillin	0.006	
pleuromutilin derivatives	tiamulin	0.003-67	
	valnemulin	>2-44.7	
polypeptide antibiotics	bacitracin	6.3-126.4	
sulfonamides	sulfadiazine	0.135-403	100
	sulfachlorpyridazine	250->1000	
	sulfadimethoxine	19.5-1866	
synthetic pyrethroids	cypermethrin	0.00015	0.035 µg/organism-0.02
	deltamethrin	0.0000014-8600	0.051 µg/organism-28.6
tetracyclines	chlortetracycline	0.05-3.1	
	oxytetracycline	0.0611-<200	>2000>5620
	tetracycline	0.0251-579	
others	aminosidine	10-2220	
	benzyl alcohol	5-2600	
	chloramphenicol	0.0643-2074	
	cypromazine	0.037->300	>25 µg/organism->5620
	ethinyl estradiol	0.0000001->20	
	furazolidone	40-250	
	griseofulvin	<0.25->1000	
	hydrogen peroxide	2.3-224	
	phosmet	0.0016-0.07	
	procaine hydrochloride	10-101	
	teflubenzuron	>500	non-low toxicity

None of the compounds tested to date have been shown to have significant antibacterial or anti-fungal properties (CORDAH, 1999). However, avermectins are particularly toxic to crustaceans with effect levels to mysid shrimps ranging from 26 µg l^{-1} (ivermectin) to 22 µg l^{-1} (abamectin). In addition, data for enamactin benzoate shows that the compound has a very high acute toxicity to several species of freshwater fish (96 h LC50; 174-1340 µg l^{-1}) (CORDAH, 1999). In acute toxicity tests, hydrogen peroxide is shown to be non-hazardous to toxic to various species of fish and aquatic invertebrates (US EPA, 2001).

Chronic and acute toxicity data for phosmet, an ectoparasiticide used for the treatment of mange and louse infestations in pigs, shows the compound to be very hazardous to daphnids (EC50; 0.0056 mg l^{-1}) and fish (LC50; 0.07 mg l^{-1}) (Lewis and Bardon, 1998).

Small amounts of data are also available on the aquatic toxicity of the endoparasitic wormers, abamectin, triclabendazole, fenbendazole and levamisole, the coccidiostat dimetridazole and the endectocide doramectin.

7.2.2 Antibacterial compounds

A number of studies have investigated the effects of antibacterial veterinary medicines (Wollenberger *et al*., 2000; Holten Lützhøft *et al*., 1999; Lanzkey and Halling-Sørensen, 1997).

The toxic effect data for antibacterial agents on most aquatic species is generally in the mg l^{-1} range (e.g. Lanzky and Halling-Sørensen, 1997; Migliore *et al*., 1997a). The exception to this are algae where certain species (e.g. *Microcystis aruginosa*) are particularly sensitive with reported EC50 values ranging from 0.0037 (amoxicillin) to 112 mg l^{-1} (trimethoprim) and the marine bacterium *Vibrio fischeri*, where the toxicity ranged from 0.014 (ofloxacin) – 8.21 (streptomycin) mg l^{-1} (Backhaus and Grimme, 1999).

A limited amount of data was also available on the chronic toxicity of antibacterial compounds to daphnids (Wollenberger *et al*., 2000). Ratios of acute EC50s or LOECs to chronic EC50s or NOECS range from 2.2 to 16 (Table 7-2). In current risk assessment approaches (e.g. biocides, pesticides and industrial chemicals) a factor of 10 is typically used to account for differences between acute and chronic endpoints and the data given below supports its use for veterinary medicines.

Table 7-2 Acute and chronic toxicity values for a range of antibacterial agents to Daphnia magna (data taken from Wollenberger *et al*., 2000)

	Acute		Chronic		Ratio
	LOEC (mg l^{-1})	EC50 (mg l^{-1})	EC50 (mg l^{-1})	NOEC (mg l^{-1})	
Metronidazole	1000			250	4
Oxolinic acid		4.6		0.75	6
Oxytetracycline	100		46.2		2.2
Streptomycin		487		32	15
Sulfadiazine		221	13.7		16
Tetracycline	340		44.8		7.6
Tiamulin		32	5.4		5.9
Tylosin		483		90	5.4

7.2.3 Ethinyl oestradiol

Both long-term and short-term toxicity studies have been performed on ethinyl oestradiol (Schweinfurth *et al*., 1996; Kopf, 1995). These studies indicate that ethinyl oestradiol is non-toxic to microbes and that toxicity to daphnids and algae is generally in the low mg l^{-1} range. However, long-term studies into the toxicity of ethinyl oestradiol to fish indicated that fish growth is reduced in larvae at concentrations exceeding 100 ng l^{-1}. Moreover, histological changes in the kidney and livers of larvae and juvenile fish have been reported at concentrations as low as 10 ng l^{-1}.

7.3 Terrestrial effects

Data were available on the toxicity of 45 chemicals used in veterinary medicines to terrestrial organisms (summarised in Appendix K). These tests covered a range of species, including microbes, plants, earthworms and insects, and a range of endpoints. Five main classes of product have been studied, the endectocides, sheep dip chemicals, antibacterial agents, anticoccidials and performance enhancers.

7.3.1 Antiparasitics

7.3.1.1 Sheep dip chemicals

For chemicals used in sheep dip formulations, the practice of applying spent sheep dip to land as a means of disposal may have implications with regards to toxicity to sensitive terrestrial ecosystems. Acute toxicity studies have shown diazinon to be highly toxic to earthworms (48 hr LC_{50} 25.8 µg l^{-1} (aqueous exposure route))(Larkin and Tjeerdema, 2000). In addition, the toxicity of diazinon to saprophytic isopods has been shown to be dependent on the route of exposure. In studies where substrate exposure was assessed using contaminated sand and dietary exposure was evaluated by feeding organisms contaminated leaves, the former was found to be far more lethal (Vink *et al*., 1995).

In laboratory studies, cypermethrin and diazinon are shown to strongly affect honeybees, with lethal topical doses of 0.02 and 0.45 µg per bee reported, respectively (Larkin and Tjeerdema, 2000; Tomlin, 1997).

Apart from diazinon, very little data are available on the toxicity to terrestrial invertebrates of chemicals used in sheep dip preparations. However, the Environment Agency is currently funding research being conducted by the University of Durham in which the overall objective is to quantify the impact of sheep dip chemicals on terrestrial invertebrates and assess the potential secondary effects on upland birds.

7.3.1.2 Others

The avermectins are powerful insecticides that are thought to exhibit their effect on the γ-aminobutyric acid mediated neuromuscular synapse with chloride channels appearing to be particularly sensitive (Turner and Schaeffer, 1989). Exposure to avermectins can elicit a number of responses, including adult and larval mortality, an effect on feeding, disruption of

water balance, a reduction in growth rate, interference with moulting, inhibition of metamorphosis and/or pupation, prevention of adult emergence, disruption of mating and interference with egg production and oviposition (Strong, 1993; Strong and Brown, 1987). As a consequence, dung from animals treated with avermectins may not support the development of either target (e.g. *Haemotobia irritans*, *Musca autumnnalis*, *Musca domestica* and *Musca vetustissimia*) or non-target (e.g. sphaerocerids, muscids, sepsids and coleopterans) insects (Strong and James, 1993; Sommer *et al*., 1993; Sommer *et al*., 1992; Madsen *et al*., 1990; Ridsdill- Smith, 1988; Strong and Brown, 1987; Wall and Strong, 1987; Schmidt, 1983; Miller *et al*., 1981). The toxicity of avermectins to dung insect populations is associated with a retardation in the rate of breakdown of pats. For example pats containing ivermectin have been shown to be intact after 340 d, whereas, untreated pats were largely degraded within 80 d (e.g. Floate, 1998).

The effects on other invertebrates have not been extensively investigated although investigations with annelids demonstrated no effect on population density (Wall and Strong, 1987). The possible indirect effects of avermectin contaminated dung on vertebrate populations has also been highlighted (e.g. McCracken, 1993), their use may result in a depletion in the quantity and quality of vertebrate food resources, this may be particularly critical during the breeding season or when young animals are foraging and fending for themselves.

Moxidectin is less toxic to dung-inhabiting insects than ivermectin, for example, it is 64 times less toxic than ivermectin against *Onthophagus gazella* and *Haemotobia irritans* (Doherty *et al*., 1994; Strong and Wall, 1994).

Doramectin, used in the UK to treat sheep scab, is cited as having a low inhibitory effect on soil organisms, and only in concentrations that exceed the levels that are likely to be excreted by treated sheep (Taylor, 1999). The potential toxic effects of doramectin have also been studied in species that typically breed or feed on cattle dung. Researchers reported that mating and oviposition were unaffected by the presence of doramectin at up to 250 μg kg^{-1} in dung, although larval development was affected at concentrations of between 64 and 250 μg kg^{-1} (Taylor, 1999).

7.3.2 Antibacterial agents, anticoccidials and growth promoters

Summary data is available on the toxicity of antibacterial agents, anticoccidials and performance enhancers to earthworms, microbes and plants (VICH, 2000). For the antibacterial agents, microbes are the most sensitive test species with minimum inhibitory concentrations (MICs) or no observed effect concentrations (NOECs) ranging from 100 (apramycin) to 500,000 (tiamulin) μg kg^{-1}. For the anticoccidials, plants and microbes were the most sensitive with microbial inhibition concentrations or NOECs ranging from 100 (narasin) to 200,000 (halofuginone) μg kg^{-1}. For the growth promoters, plants are shown to be sensitive to monensin (NOEC; 150 μg kg^{-1}) and microbes to lasalocid sodium (NOEC; 2000 μg kg^{-1}).

7.4 Oestrogenic activity

A number of compounds and environmental effluents have been associated with potential reproductive and developmental abnormalities in fish. For example, hermaphrodite fish have been observed in rivers below sewage treatment plants (Harries *et al*., 1997; Purdom *et al*., 1994). Consequently, UK government agencies have been highly active in researching the effects of oestrogenic compounds on aquatic life (e.g. Environment Agency, 1998).

Four chemicals used in veterinary products have been identified as exhibiting endocrine disrupting properties, namely oestradiol, ethinyl oestradiol, diazinon and permethrin (Environment Agency, 1998). For example, ethinyl oestradiol has been shown to reduce egg deposition in adult fish at concentrations of 10 ng l^{-1} and a nine month study with fish resulted in a NOEC for reproduction of 1 ng l^{-1} (Schweinfurth *et al*., 1996).

Limited data are available on the fate of oestradiol and ethinyl oestradiol used as veterinary medicines (Arcand-Hoy *et al*., 1998), consequently it is difficult to assess the importance of their use in veterinary products in terms of oestrogenic effects on the aquatic environment. Data are however available on endogenous oestrogens (Shore *et al*., 1988) which demonstrate that these compounds can be transported from poultry farms, via agricultural run-off to rivers and streams. The reported concentrations of the endogenous oestrogens in manure were 66 ng g^{-1}, with concentrations in water collected from four streams ranging from 0.8 to 10.4 ng l^{-1}.

It is possible that other veterinary medicines may cause endocrine disruption in ecosystems. However, because of the lack of appropriate screening methods, ecologically significant changes in reproductive function resulting from endocrine-disruptive effects of chemicals are not routinely detected.

7.5 Summary

- The effects of avermectins, sheep dip chemicals and ethinyl oestradiol on aquatic organisms are well documented and these substances are known to be toxic to various organisms at low concentrations (ng l^{-1} - µg l^{-1}).

- Data are also available on the aquatic toxicity of other veterinary products, in particular antibacterial agents. These data indicate that toxicity values are generally in the mg l^{-1} range. Toxicity is greater for certain species of algae and marine bacteria.

- A large body of data was available on the toxicity of avermectins to terrestrial organisms. Exposure of insects to low concentrations of avermectins can elicit a number of responses including mortality, reduction in growth rate and interference with moulting. Avermectins can effect the micro-ecology of dung and may also affect the ecology of other surrounding terrestrial populations.

- Data were available on the toxicity of antibacterial compounds, anticoccidials and performance enhancers to terrestrial organisms. The lowest reported effect concentrations for any of the species tested and products tested was 100 µg kg^{-1}.

- Data were available on both the acute and chronic effects of antibacterial agents to aquatic and terrestrial organisms. Acute to chronic ratios for the aquatic environment ranged from 2.2 to 16.

- Four chemicals used in veterinary medicines have been shown to exhibit oestrogenic activity. Limited field monitoring studies of endogenous oestrogens from livestock indicate that oestrogens can be transported from livestock facilities to the aquatic environment.

- Whilst data from the public domain were available for a number of the major product classes, there are significant data gaps.

8 PRIORITISATION OF VETERINARY MEDICINES OF CONCERN FOR THE ENVIRONMENT

To gain a greater understanding of the potential risks to the environment, arising from the use of veterinary medicinal products, an initial identification and prioritisation of those veterinary medicines of most significant environmental concern has been performed. The outcome of the prioritisation work will be used to:

- guide Agency policy direction
- ensure that the Agency's monitoring programme is effectively targeted and,
- where necessary, enable appropriate pollution prevention tools or control measures to be applied.

The prioritisation exercise has considered data on usage, exposure routes and environmental effects of all generic groups of veterinary medicines. The work has been constrained by the fact that for many veterinary medicines there are little or no data in the public domain. The work described herein is therefore an initial prioritisation exercise based on available data.

The impact of a veterinary medicine on the environment is dependent on a number of factors which include:

- amount used
- usage pattern/route of administration
- degree of metabolism
- potential for degradation during storage
- persistence in soil and water
- mobility
- toxicity to terrestrial and aquatic organisms
- bioaccumulation potential

The large number and wide variety of veterinary medicines available has led to the development of a prioritisation scheme that employs a two phased approach. Phase 1, which is described in this Chapter, is essentially an initial broad screen, using only those factors considered most influential in determining risk to the environment. The aim of phase 1 is to identify those veterinary medicines considered to have the greatest potential to impact the environment, and hence the highest priority in terms of considering their risk to the environment.

An overview of the prioritisation process used for phase 1 is illustrated in Figure 8-1. The prioritisation process was performed in two stages. The first stage identified those compounds with the greatest potential to reach the environment in significant amounts. For these compounds, a simple assessment of hazard was then conducted by classifying compounds as very high, high, medium or low hazard on the basis of their ecotoxicity (both aquatic and terrestrial).

On the basis of a combination of potential to reach the environment and intrinsic hazard, compounds were classified according to their relative risk to the environment. Those compounds deemed potentially high risk to the environment (e.g. high potential to reach the environment and high toxicity) are considered to be the highest priority compounds for further action. The risk posed by compounds identified through this process will be considered in greater detail in further work (phase two). Following further assessment in phase two, targeted environmental monitoring may be carried out to ascertain if environmental concentrations are ecologically significant and where necessary, pollution prevention tools can be developed or control measures applied.

For many compounds data was either unavailable or considered to be of poor quality. For these chemicals the worst case score appropriate to the criteria being assessed was assigned.

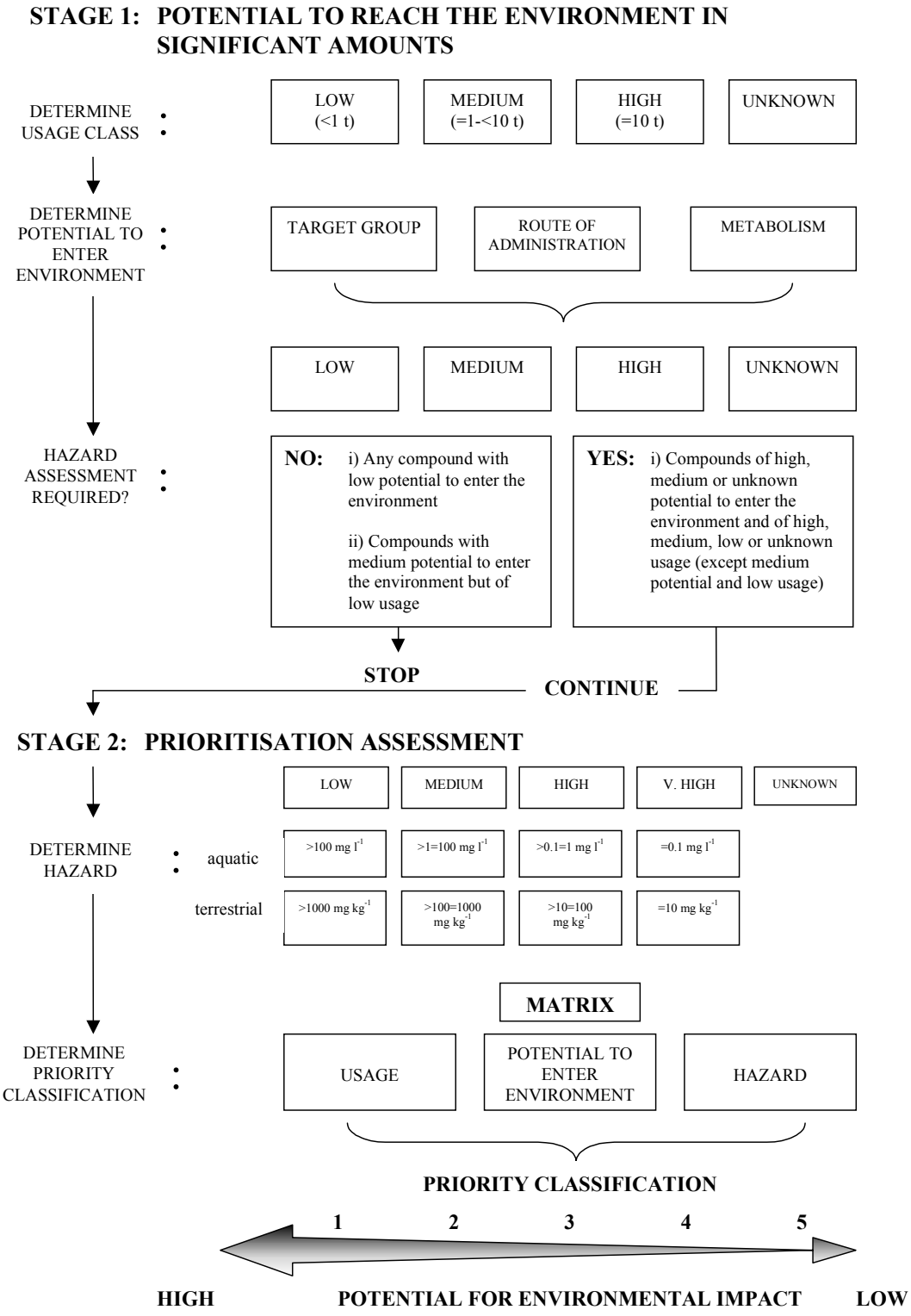


Figure 8-1 Schematic presentation of the prioritisation process used

8.1 Stage 1. Potential to reach the environment in significant amounts

Using the data on usage, pathways of entry to the environment and metabolism presented in Chapters 3, 4 and 6 respectively, those veterinary medicines considered to reach the environment in potentially significant amounts were identified.

Groups of substances were initially ranked as high (≥ 10 tonnes per annum (tpa)), medium (≥ 1 - < 10 tpa), low (< 1 tpa) or unknown usage, using data compiled in Chapter 3. The potential for the substance to enter the environment was then assessed. As discussed in Chapter 4, the potential for each of the individual substances to enter the environment is dependent on a number of variables, including:

1. the target treatment group
2. route of administration
3. metabolism
4. the potential for the substance to be degraded in slurry or manure during storage.

For example, a compound used for the simultaneous treatment of an entire herd of animals is likely to have a higher potential to reach the environment than a substance used to treat individual animals. In addition, a distinction is made between companion animals and individual animals, the latter referring to food production animals, since the scenarios in which compounds will be used on these two treatment groups will differ. The route of administration will also affect the potential for a compound to enter the environment. Substances applied topically are more likely to enter the environment than substances administered by other routes, such as orally or by injection. By the very nature of the route of administration, compounds that are used in aquaculture have a high potential to enter the environment because in many instances they are added directly into the aquatic environment.

Substances applied orally or by injection may be extensively metabolised and therefore may not be excreted as the parent compound. There may also be the potential for compounds to degrade during storage of manure and slurry, prior to spreading onto land, further reducing the amounts released to the environment. For compounds that are metabolised by the animal or degraded during storage, consideration of the environmental impact of metabolites may be more relevant.

Factors 1 – 3 (as listed above) were considered when determining the potential for a particular substance to enter the environment. The potential for degradation in slurry or manure during storage was not considered as it is dependent on the storage time prior to land spreading and hence was not an appropriate criteria for the initial broad screen. Degradation of a compound in slurry or manure during storage, prior to land spreading, should be considered, when appropriate, in the second phase of this work.

Substances were classified as having high, medium, low or unknown potential to enter the environment using the criteria detailed in Table 8-1.

Table 8-1 Criteria used to assess the potential for the environment to be exposed to an individual veterinary medicine

Classification	Target group	Route of administration	Metabolism	Rationale
High	Aquaculture	Topical/other	na	Substances typically applied directly into the aquatic environment.
	Herd	Topical	na	As the substances are applied topically, there is the potential for wash-off from the animal. Topical treatments used in herds are likely to enter the environment in higher amounts than topical treatments used to treat individual or companion animals because of the quantities used.
	Herd	Other	L	Potential impact from substances used as herd treatments that are not significantly metabolised.
Medium	Herd	Other	M	Potential impact from substances used as herd treatments that are moderately metabolised.
	Companion/ Individual	Topical	na	Potential for direct entry to the environment in excreta. However since only individuals are treated the environmental impact is considered to be lower than for herd treatments. Topical treatments have a higher potential to reach the environment than 'other' routes of administration.
Low	Herd	Other	H	Low potential for substances used as herd treatments to enter the environment because of significant metabolism.
	Companion/ Individual	Other	na	Negligible environmental impact on the basis that it is individuals that are treated rather than herds, therefore metabolism is not considered.
Unknown	Herd	Other	U	Unknown potential to enter environment because of insufficient data on metabolism.

Metabolism: H = >80%; M = 20-80%; L = < 20%; U = unknown
na = not applicable
Other = orally or by injection
Individual = individual food production animals

Using the classifications determined for usage and potential to enter the environment, those substances considered to have the greatest potential to enter the environment and therefore requiring hazard assessment, were identified using the matrix detailed in Table 8-2. Compounds identified as both high usage and having a high potential to enter the environment were considered to potentially represent the highest risk to the environment and hence were deemed to be the highest priority for further assessment.

For those compounds regarded as having low potential to enter the environment it was considered unnecessary to assess their intrinsic hazard in this prioritisation exercise, as relative to the other veterinary medicines, they are likely to represent a low risk to the environment. This included those compounds administered either orally or by injection as herd treatments that are significantly metabolised, as well as compounds used to treat companion or individual food production animals by non-topical routes. In addition, compounds with a medium potential to enter the environment, for example those used as herd treatments that are moderately metabolised as well as those used to treat companion or individual animals topically were excluded from hazard assessment when usage was less than one tonne per annum.

The results of stage one of the prioritisation exercise are presented in Appendix L, Table L- 1. Compounds identified as having a high potential to enter the environment and of high usage included a number of antimicrobial compounds (the tetracyclines, sulphadiazine, trimethoprim, amoxicillin, tylosin, dihydrostreptomycin, neomycin and apramycin) and diazinon, an ectoparasiticide commonly used in sheep dip preparations.

A total of 15 individual compounds and substances belonging to four therapeutic groups where individual compounds were not identified were considered to have sufficiently low potential to enter the environment that they did not require a hazard assessment. These included some compounds that were considered to be high usage, but with a high potential for metabolism (including sulphadimidine, dimetridazole and narasin and avilamycin). However, it should be noted that although these compounds have not been taken forward for a hazard assessment in this initial prioritisation process, the potential environmental impacts of any metabolites excreted should not be ignored. It is therefore recommended that the environmental impact of metabolites of these compounds are considered further in Phase two of this project.

Therapeutic groups identified as relatively low priority and hence not requiring a hazard assessment at this stage included general anaesthetics for companion animals, which because of the manner in which they are used and the fact they are gaseous are unlikely to reach water or land in significant quantities. Furthermore, the release of gaseous compounds to the atmosphere will be subject to significant dissipation in air. Therapeutic groups where usage was less than one tonne per annum and which are considered to have low potential to reach the environment included some antifungals, neurological preparations and anti-inflammatory preparations. Several other therapeutic groups were also considered as low priority despite usage being unknown because they are used to treat individual animals (companion or food production). These include anti-inflammatory steroids, diuretics, cardiovascular and respiratory treatments and locomotor treatments.

Table 8-2 Matrix used to identify substances requiring hazard assessment

Usage	Potential to enter environment	Hazard assessment required?
H	H	✔
H	M	✔
H	L	x
H	U	✔
M	H	✔
M	M	✔
M	**L**	x
M	U	✔
L	H	✔
L	M	x
L	L	x
L	U	✔
U	H	✔
U	M	✔
U	L	x
U	U	✔

H = high M = medium
L = low U = unknown

For compounds that are used on more than one target treatment group, the potential to reach the environment has been assessed separately for each target group, as this may affect the potential for environmental impact. For example, for compounds that are used to treat all three target groups, i.e. companion/individuals, herds and aquaculture, the potential to reach the environment in significant amounts is considered high when used in aquaculture but negligible when used to treat individuals. Likewise, compounds are classified as having a higher potential to enter the environment when used as topical herd treatments than when used topically to treat companion animals or individuals.

8.2 Stage 2. Hazard assessment

For those compounds that were identified as having the potential to enter the environment in significant quantities, a simple assessment of hazard was conducted using the toxicity data provided in Appendices J and K and discussed in Chapter 7. This enabled identification of those compounds having a high potential to enter the environment and which were also highly toxic (and thus represented potentially the highest risk to the environment). These compounds are considered to be the highest priority for further consideration of their impact on the environment and the possible need for control measures such as pollution reduction programmes.

Substances were classified as having very high, high, medium or low aquatic and/or terrestrial ecotoxicity using the criteria detailed in Table 8-3.

Mobility, persistence in the environment and bioaccumulation potential were not considered in stage 2 because, as described above, phase 1 is an initial prioritisation employing a broad

screening approach. The results of the current prioritisation exercise will be refined, if necessary, in phase two of this work, to take into account additional factors such as mobility and persistence. Such additional work is beyond the scope of the current project.

Table 8-3 Classification criteria for ecotoxicity

Hazard classification	Aquatic toxicity[a] ($mg\ l^{-1}$)	Terrestrial toxicity[b] ($mg\ kg^{-1}$)
VH	≤ 0.1	≤ 10
H	> 0.1 ≤ 1	>10 ≤ 100
M	>1 ≤ 100	>100 ≤ 1000
L	> 100	> 1000

[a] based on harmonised system for the classification of chemicals which are hazardous for the aquatic environment; OECD (1998)
[b] based on a proposed EU hazard assessment scheme for the terrestrial environment
VH = very high H = high
M = medium L = low

The hazard classification 'unknown' was assigned to those compounds where no data for aquatic toxicity or terrestrial toxicity was available. In addition, as an indication of the relative completeness of the available data on which the hazard classification was determined, a score (denoted by subscript number) was assigned. The criteria used to assign scores are summarised in Appendix L, Table L- 2. This score took into account the number and types of tests (e.g. acute and chronic) that had been performed on a particular substance. A score of one denotes a hazard classification based on a more comprehensive data set than those hazard classifications with a score of two, three or four. The system of scoring largely reflects the extent to which aquatic and terrestrial ecotoxicity data were available.

For aquatic hazard classifications, the score takes into account the number of trophic levels tested as well as the type of tests conducted. Chronic tests for three different trophic levels are regarded as being more comprehensive than a mixture of chronic tests for one or two trophic levels and several acute toxicity tests. For terrestrial hazard classifications, the score simply indicates the number of trophic levels tested. A score of one denoting three trophic levels and representing a hazard classification based on the most comprehensive data available. A simpler system was adopted for the terrestrial data than for aquatic toxicity data because there are comparably fewer toxicity data available for terrestrial species. The results of the hazard assessment are presented in Appendix L, Table L- 3.

Considering both the potential to reach the environment (stage one) and hazard classification (stage two) substances were then assigned to one of five groups using the matrix detailed in Appendix L, Table L- 4. Compounds assigned to group one are considered to have the greatest potential for environmental impact and thus are the highest priority for further work. These are compounds that have a combination of high or medium usage, together with high or

medium potential to enter the environment and very high or high toxicity to either aquatic or terrestrial organisms. Compounds that were considered to have low potential to enter the environment in significant amounts and thus did not require a hazard assessment, for the purposes of this work, were assigned to the lowest group (five).

Where there was uncertainty in any one of the three criteria used, such as unknown data (U) or in the case of usage, incomplete data (suffixed [b]), the worst case classification was assumed for the criteria (unknown potential to enter the environment and usage assumed to be high; unknown hazard assumed to be very high). Usage data that is incomplete, for example where the available information indicates low, medium or high usage but where it is known that this may be an underestimate of the total usage, is assumed to be high.

The results of the prioritisation exercise are summarised in Appendix L, Table L- 5 and Table L-6. Table L- 5 lists those compounds considered to have the greatest potential for environmental impact (group one compounds). Compounds are ranked in descending order of annual tonnage, with the compound used in the greatest quantities assumed to present potentially the greatest risk to the environment placed at the top of the list. Those substances where, in the absence of data, it was necessary to assume a worst case classification for one or more criteria, are identified with an asterisk. The same procedure has been followed for compounds assigned to groups two and five (Appendix L, Table L-6). No compounds were allocated to groups three or four using the prioritisation procedure and available data.

A total of 56 compounds were assigned to the 'high priority' category (group one). However, there was only sufficient data available to fully characterise the potential risk for eleven of these compounds. These compounds are, in order of priority:

- oxytetracycline (herd and aquaculture scenarios/aquatic compartment)
- chlortetracycline (herd scenario/aquatic and terrestrial compartments)
- tetracycline (herd scenario/aquatic compartment)
- sulphadiazine (aquaculture scenario/aquatic and terrestrial compartments)
- amoxicillin (herd and aquaculture scenarios/aquatic compartment)
- diazinon (herd scenario/aquatic and terrestrial compartments)
- tylosin (herd scenario/aquatic compartment)
- dihydrostreptomycin (herd scenarion/aquatic compartment)
- apramycin (herd scenario/terrestrial compartment)
- cypermethrin (herd scenario/aquatic compartment)
- sarafloxacin (aquaculture scenario/aquatic and terrestrial compartments)

An indication as to which target treatment group(s) presents the greatest potential for the compound to enter the environment, and the environmental compartment of concern on which the current prioritisation has been based, is provided in brackets. It should be noted that whilst for the purpose of this review there was sufficient data to enable these compounds to be assigned a priority classification of one, further data will be required for some compounds in the event of more detailed risk assessment being carried out. These 'additional' data are highlighted in Appendix L, Table L- 5.

For the remaining 45 compounds some of the data required for the prioritisation exercise was either unavailable or incomplete and so the prioritisation exercise has incorporated one or more worst-case assumptions. Compounds identified as potentially high risk (group one), but requiring further data were (ranked on the basis of annual usage):

1. trimethoprim
2. baquiloprim
3. amprolium
4. clopidol
5. lasalocid sodium
6. maduramicin
7. nicarbazin
8. robenidine hydrochloride
9. procaine penicillin
10. procaine benzylpenicillin
11. clavulanic acid
12. monensin
13. salinomycin sodium
14. flavophospolipol
15. neomycin
16. flavomycin
17. morantel
18. flumethrin
19. triclabendazole
20. fenbendazole
21. levamisole
22. ivermectin
23. cephalexin
24. florfenicol
25. tilmicosin
26. oxolinic acid
27. lido/ligocaine hydrochloride
28. tiamulin
29. lincomycin
30. clindamycin
31. nitroxynil
32. enrofloxacin
33. dimethicone
34. poloxalene
35. toltrazuril
36. decoquinate
37. diclazuril
38. phosmet
39. piperonyl butoxide
40. amitraz
41. deltamethrin
42. cypromazine
43. emamectin benzoate
44. antiseptics
45. immunological products

Six compounds were assigned to group two in the first phase of the prioritisation process. These compounds, which are listed below, are considered to potentially represent a risk to the environment, but are of less concern than the group one compounds discussed above. None of these compounds had a complete data set for the purposes of the prioritisation exercise.

Group two compounds:

- procaine hydrochloride
- miconazole
- altrenogest
- progesterone
- medroxyprogesterone
- moxidectin

8.3 Discussion

A pragmatic and scientific approach has been adopted and developed in order to enable an initial identification and prioritisation of those veterinary medicines of environmental concern to be made, using available data. The exercise has identified those compounds considered to have the greatest potential to cause environmental impacts as a consequence of their use. However, it is important to recognise that many compounds identified as high priority in this exercise may not actually cause adverse impacts on the environment. The prioritisation exercise is simply a way of assessing the relative potential for veterinary medicines to cause harm, thus enabling those compounds likely to be of greatest concern to be identified.

The value of the approach employed is two-fold. Firstly, for those compounds where sufficient data was available, the list provides a system of relative ranking on the basis of potential environmental impact. Eleven substances were assigned to group one, on the basis of a 'complete' data set (for the purposes of this exercise) and thus considered to be the highest priority. These substances include a number of antimicrobials widely used as herd treatments and/or in aquaculture (oxytetracycline, chlortetracycline, tetracycline, sulphadiazine, amoxicillin, tylosin, dihyrostreptomycin and apramycin). A further antimicrobial compound, sarafloxacin, used exclusively in aquaculture treatments, was also identified as a high priority as were diazinon and cypermethrin, two compounds used extensively in sheep dips.

Further consideration should now be given to the risk posed to the environment for those chemicals identified as high priority in the current exercise. This should take into account, different uses of the same compound and consideration and identification of which environmental compartments are at risk. The assessments should focus on the UK situation and take into account different treatment scenarios, degree of metabolism, bioaccumulation potential and further data on environmental fate, behaviour and ecotoxicity.

Both cypermethrin and diazinon are known to cause environmental pollution and a significant body of data on their environmental fate, behaviour and ecotoxicity is available. Pollution incidents caused by poor sheep dipping practises can result in ecological damage over several kilometres of watercourse. Sheep dip chemicals are routinely monitored for by the Agency and each year there are a relatively high number of sites failing the Environmental Quality Standards (EQS) for both cypermethrin and diazinon. However, no routine monitoring is conducted by the Environment Agency for any of the chemicals (other than cypermethrin and diazinon) identified as a high priority and it is generally not known what, if any, environmental impact these chemicals may be causing. It is recommended that, following further assessment of potential environmental risks, as described above, limited targeted monitoring is conducted to ascertain whether these chemicals are present in the environment at ecologically significant levels. Ideally, this would involve an integrated chemical and biological monitoring programme.

The current review and prioritisation exercise highlight that there are many veterinary medicines for which little or no data are available in the public domain. Classification of many of the compounds was based on limited data and worst case assumptions. Forty-five substances were provisionally ranked as a high priority, including many other antimicrobial,

coccidiostat, endo- and ectoparasiticide, antifungal, antiprotozoal and growth promoting substances. However, for many of these compounds either accurate usage information was unavailable or their potential to enter the environment or intrinsic hazard was unknown.

It is considered a priority for any future work that data should be obtained for these compounds in order to refine and extend the current work. This is required in order to ascertain whether such chemicals are correctly classified in terms of their potential risk to the environment in the current exercise. Those that have been correctly classified will be added to the list of 11 substances described above for further consideration of their environmental impact. It is recommended that the Veterinary Medicines Directorate, National Office of Animal Health and the Animal Health Distributors Association are contacted to ascertain what additional data are available which could be made available and used, but are not in the public domain (i.e. data generated for product registration).

It should be recognised that the work has focused exclusively on the parent compound. However, following injection or oral administration to an animal, compounds may be metabolised and subsequently excreted, in part or completely, as transformation products. In addition, if excreted as the unaltered parent compound they may degrade on reaching the environment. The potential environmental impact of any metabolites or degradation products should be assessed, especially for those compounds considered to be low priority on the basis of this prioritisation exercise because they are extensively metabolised following administration. Data on metabolism and environmental degradation was very limited, and consequently detailed consideration in this review was not possible.

8.4 Summary

- In order to gain an understanding of the potential risks to the environment arising from the use of veterinary products, an initial assessment of those veterinary medicines of most significant environmental concern has been made. This will be used to guide Agency policy direction; ensure that the Agency's monitoring programme is effectively targeted; and where necessary enable appropriate pollution prevention tools to be applied.

- The large number and wide variety of veterinary medicines available has led to the prioritisation exercise employing a two phased approach. Phase 1 is essentially an initial broad screen, using only those factors considered most influential in determining risk to the environment. Phase 2 will aim to refine the prioritisation process by conducting detailed assessments of the risk to the environment from the 'highest priority' veterinary medicines as well as targeted environmental monitoring to ascertain if environmental concentrations are ecologically significant and whether pollution prevention measures are required.

- Phase 1 of the prioritisation exercise comprised of two stages. In the first stage, information on usage, target treatment groups, route of administration and metabolism were used to ascertain which substances had the potential to enter the environment in significant amounts. A simple assessment of hazard was then conducted at stage 2, and on

the basis of a combination of potential to reach the environment and intrinsic hazard, compounds were classified according to their relative risk to the environment.

- A total of 56 compounds were assigned to the 'high risk' category (group 1). However, there was sufficient data available to fully characterise the risks of only 11 of these compounds for the purposes of the prioritisation exercise. These included all three tetracyclines (i.e. oxytetracycline, chlortetracycline and tetracycline), sulphadiazine, amoxicillin, diazinon, tylosin, dihydrostreptomycin, apramycin, cypermethrin and sarafloxacin. It is recommended that further assessment of the environmental impact of these chemicals is conducted and that targeted environmental monitoring performed to ascertain their presence in the environment.

- Forty-five other compounds were identified as potentially high risk, although for these substances the prioritisation exercise has incorporated one or more worst-case assumptions. A high priority for future work will be to try and obtain additional data in order to ascertain whether these chemicals are correctly classified in terms of their potential risk to the environment in the current exercise.

9 CONCLUSIONS

Releases of veterinary medicines to the environment occur both directly, for example the use of medicines in fish farms, and indirectly, via the application of animal manure (containing excreted products) to land. Because of historic, measurable impacts in the environment, a number of groups of veterinary medicines have been well studied, including sheep dip chemicals, anthelmintics and fish farm medicines. However, the potential environmental impacts of other generic groups of veterinary medicines are less well understood. With the exception of sheep dip chemicals, the Agency does not currently monitor for veterinary medicines in the environment.

In order to gain a greater understanding of the potential risks to the environment arising from veterinary medicines, available data on usage, exposure routes, environmental fate, behaviour and effects of all generic groups of veterinary medicines have been collated and critically reviewed. Information was drawn predominantly from sources in the public domain. Contacts were also made with a number of organisations, including the Veterinary Medicines Directorate (VMD) and the National Office for Animal Health (NOAH). For many veterinary medicines, little or no data were available from the open scientific literature. The main conclusions from this work are detailed below:

1. A wide range of substances are used as veterinary medicines in the UK. The concentration in the environment, and hence its potential impact will be determined by a number of factors, not least the amount that is used per year. In order to identify substances of concern, information was obtained from a range of sources on the amounts of substances used or sold. Data varied in completeness of coverage of the market as a whole and included data from the Veterinary Medicines Directorate, IMS Health and the published literature.

2. Data obtained on the usage of antibiotic substances and organophosphates used in sheep dips were considered to represent the complete market for these products. The data indicated that around 50 tonnes of organophosphates are used in sheep dips annually in the UK and that over 400 tonnes of antibiotics are distributed annually. The major classes of antibiotics in terms of usage were tetracyclines, sulphonamides, β-lactams, macrolides, aminoglycosides and fluoroquinolones. Using the organophosphate sheep dip data, together with information on usage of sheep ectoparasiticide products it was possible to estimate the usage of synthetic pyrethroids in sheep dips and macrocyclic lactones administered by injection.

3. On the basis of the data collected during this review, overall antimicrobial compounds are sold in the largest amounts, followed by coccidiostats, organophosphate sheep dip chemicals and growth promoters.

4. Insufficient data were available to assess the major substances and amounts used of the following product types: endoparasitic wormers, biguande/gluconate antifungals, antiprotozoals, local anaesthetics, enteric preparations, antiseptics, steroids, diuretics, cardiovascular and respiratory treatments, immunological products and several

antimicrobial therapeutic groups (pleuormutilins, lincosamides and 'others'. Moreover, with the exception of antimicrobial compounds, no data were available on the amounts of veterinary medicines used in aquaculture.

5. The quantities of veterinary medicines released to the environment during use will depend on a number of factors including: usage, animal husbandry practices, treatment type and dose, metabolism within the animal and degradation rates in manure and slurry.

6. The importance of individual routes into the environment for different types of veterinary medicines will vary according to the type of treatment and livestock category. Treatments used in aquaculture have a very high potential to reach the aquatic environment, primarily because many are added directly to the environment. The main routes of entry to the terrestrial environment will be from the use of veterinary medicines in intensively reared livestock, via the application of slurry and manure to land, and the use of veterinary medicines in pasture reared animals where pharmaceutical residues will be excreted directly into the environment. Veterinary medicines applied to land via land spreading of slurry may also enter the aquatic environment indirectly via surface run-off and/or leaching to groundwater. It is likely that topical treatments will have a greater potential to be released to the environment than treatments administered orally or by injection. Inputs from the manufacturing process and companion animal treatments are likely to be minimal in comparison.

7. The disposal of waste medicines is subject to a range of controls and guidelines are available for the safe disposal of unused medicines and associated packaging. However, it is possible that products are inappropriately discharged to surface waters and disposed of in refuse. Currently there is insufficient information available to assess the significance of disposal as a potential source of veterinary medicines in soils, groundwaters and surface waters.

8. A number of studies have investigated the sorption behaviour and persistence of veterinary medicines in soils. However these data only covered organophosphate compounds, pyrethroids and antibacterial substances. Data were available on the sorption behaviour of a number of veterinary medicines in soils. The degree to which veterinary medicines may adsorb to particulates varied widely. Consequently, the mobilities of different veterinary medicinal products are also likely to vary widely. Partition coefficients (K_d) range from low (0.61 l kg^{-1}) to high (6000 l kg^{-1}) adsorption (K_{oc}, the organic carbon normalised partition co-efficient from 40 – 163 x 10^5 l kg^{-1}).

9. The variation in partitioning for many of the compounds in different soils was significant (up to a factor of 30 for efrotomycin). These differences could be not be explained by normalisation to the organic carbon content of the soils for many of these compounds. The differences may be explained by surface interactions of these compounds with clay minerals. This indicates that in order to arrive at a realistic assessment of the availability of veterinary medicines for transport through the soil and uptake into soil organisms, the K_{oc} (which is used in many of the exposure models) may not be an appropriate measure.

10. Veterinary medicines can persist in soils for days to years and half-lives are influenced by a range of factors including temperature, pH and the presence of manure. In surface waters, a range of veterinary medicines (tetracyclines, quinolones, ivermectin and furazolidone) may be photodegraded. However, this route of degradation is likely to be of little significance in the UK. The organophosphorous compounds chlorfenvinphos, coumaphos and dichlorvos all degrade relatively rapidly in biologically active waters; however, the synthetic pyrethroid, flumethrin is persistent. In sediments, the phenicols (chloramphenicol and florfenicol) as well as furazolidone have been shown to rapidly degrade whilst the 2, 4-diaminopyrimidine, quinolone, tetracycline and sulphonamide classes all persist. Limited information was available for other groups although, as with sorption data, this information may have been generated by industry as part of the product registration process.

11. The persistence of major groups of veterinary medicines in manure and slurry varies. Sulphonamides, beta-lactams, macrolides and aminoglycosides are all likely to be significantly degraded during typical UK manure/slurry storage regimes. In contrast, quinolones and tetracyclines are likely to persist. Limited data was publicly available on the persistence of other groups of substances in manure and slurry.

12. Whilst some veterinary medicines will sorb strongly to soil or surface particulate matter, following their disposal to land in slurry or manure, there is the potential for movement to surface waters via particles carried in surface water run-off, or to sub-surface drains and channels through cracks and fissures during rapid bypass flow.

13. With the exception of a few substances (e.g. emamectin benzoate), the occurrence and effects of metabolites and other transformation products in the environment have received little attention. The environmental impacts of degradation products may be of more relevance than the parent compound, especially if the parent compound is metabolised or degrades rapidly in the environment. Further information on the environmental impacts of transformation products is required.

14. Analytical methods are available in the scientific literature for a wide range of veterinary medicines. These have generally been developed for the determination of the concentrations of veterinary medicines in food. However, a limited number of methods are available for selected compounds in surface waters, sediments, manure/slurry, soils and groundwater. It is likely that additional methods will be required and existing methods validated and ring tested before any Environment Agency monitoring programme can be performed.

15. Whilst there has been no systematic monitoring of veterinary medicines in the UK environment, a number of veterinary medicines have been detected in surface waters, groundwaters, soil, sediment and biota. Concentrations for sheep dip chemicals were as high as 19.2×10^6 ng l^{-1} in surface waters and 489 ng l^{-1} in groundwaters and often exceed the Environmental Quality standard (EQS). Monitoring undertaken by the Environment Agency indicates a downward trend in the number of EQS failures detected in 2000 compared with 1998.

16. Reported concentrations of veterinary products used in aquaculture were as high as 1 $\mu g\ l^{-1}$ in water (emamectin benzoate) and concentrations in sediment were as high as 285 $\mu g\ g^{-1}$ (oxytetracycline). A limited amount of data was available on concentrations of antibacterial agents and anthelmintics used to treat livestock. Maximum reported concentrations of chlortetracyline, ivermectin and monensin in soil were 42 $\mu g\ kg^{-1}$, 2 $\mu g\ kg^{-1}$ and 1 $mg\ kg^{-1}$ respectively. Oxytetracycline, tetracycline, chlortetracycline and tylosin have also been detected in groundwater.

17. Data were available on the ecotoxicity of a wide range of veterinary medicines to aquatic and terrestrial organisms. For organophosphates, macrocyclic endectins and synthetic pyrethroids, data were available for a range of species and a range of endpoints (including both acute and chronic toxicity).

18. The acute and chronic effects of avermectins and sheep dip chemicals on aquatic organisms are well documented and these substances are known to be toxic to various organisms at low concentrations (ng l^{-1} to $\mu g\ l^{-1}$). Concerns have been raised about the possibility of indirect effects of these substances on predatory species (e.g. birds and bats) although limited information was available on these potential effects.

19. Data were also available on the aquatic and terrestrial toxicity of other veterinary products, in particular antibacterial agents. These data indicate that toxicity values are generally in the $mg\ l^{-1}$ range. Toxicity is greater for certain species of algae and marine bacteria. Generally, toxicity values for antibacterial agents were significantly higher than reported environmental concentrations. However, because of a lack of appropriate toxicity data, it is difficult to assess the environmental significance of these observations with regard to subtle long-term effects.

20. For a large number of substances, including tetracyclines, thiamphenicols, fluoroquinolones, macrolides and sulphonamides, the data available was limited. It is therefore difficult to fully assess the effects of these substances as in many instances no chronic data are available and the relative sensitivity of different species is unknown.

21. The presence of oestrogenic activity in sewage effluents and to a lesser extent surface waters has been recently documented. However, little attention has been paid to veterinary medicines as potential endocrine disrupting substances. Four chemicals used in veterinary medicines, namely oestradiol, ethinyl oestradiol, diazinon and permethrin have been shown to exhibit oestrogenic activity (Environment Agency, 1998). Limited field monitoring studies of endogenous oestrogens from livestock indicate that oestrogens can be transported from livestock facilities to the aquatic environment.

22. Using the data compiled in this report, an assessment of the trigger value (100 $\mu g\ kg^{-1}$) used in Phase I of the regulatory risk assessment procedures (VICH, 2000) required under Directive 81/852/EEC has been conducted. The work has demonstrated that the current trigger value may not be sufficiently protective of the terrestrial environment.

23. A number of risk assessment models are available. The models are currently not validated. Validation of these models should be viewed as a high priority. In addition, currently available risk assessment models do not consider a number of pathways to the environment such as run off from the farm yard and wash off of topical treatments to soil and surface waters.

24. An initial identification and prioritisation of those veterinary medicines likely to be of most significant environmental concern has been made using available data. The approach is simple, pragmatic and scientific. It considered both potential to reach the environment (in terms of annual tonnage of substance used, environmental exposure routes and degree of metabolism) and intrinsic hazard of a compound. Those compounds with a high potential to reach the environment and high toxicity were considered to be of most concern.

25. For many compounds there are little or no data on either usage, potential to enter the environment or intrinsic hazard. Where data was unavailable, a precautionary approach was applied and worst case assumptions were made for the purposes of the exercise.

26. A total of 56 compounds were assigned to the 'highest risk' category. However, only 11 of these had sufficient data available for the purposes of the exercise. These compounds are: oxytetracycline, chlortetracycline, tetracycline, sulphadiazine, amoxicillin, diazinon, tylosin, dihydrostreptomycin, cypermethrin, apramycin and sarafloxacin.

27. For the remaining 45 compounds a classification of 'high risk' on the basis of available data and worst case assumptions was made. Substances in this category included many antimicrobial compounds, coccidiostats, endo- and ectoparasiticides, antifungal treatments, antiprotozoals and growth promoters.

28. It is important to note that the substances identified as a high priority in the prioritisation exercise may not actually be causing impacts on the environment as a consequence of their use. The exercise has simply assessed the relative potential for veterinary medicines to cause harm.

10 RECOMMENDATIONS FOR FURTHER WORK

The review and prioritisation exercise described in this report have highlighted that for many veterinary medicines, little or no data are available in the public domain. In addition, it is important to note that compounds identified as a high priority through this work may not actually cause adverse impacts on the environment. The prioritisation exercise has simply produced a relative ranking of veterinary medicines on the basis of their potential impact.

In order to gain a better understanding of the environmental impacts of veterinary medicines and ensure appropriate risk mitigation measures are in place further work is now required for those veterinary medicines identified as high priority. Specific recommendations for further work are described below;

(i) Data Gaps

- For many veterinary medicines little or no data were available for the purposes of the current prioritisation exercise. Where possible further data should be obtained to address these data gaps and refine the current prioritisation exercise.

- It is recommended that industry organisations such as the National Office of Animal Health (NOAH) and Animal Health Distributors Association (AHDA) are contacted to determine the availability of missing usage data.

- The Veterinary Medicines Directorate should make widely available annual usage data for all groups of veterinary medicines supplied by approval holders as part of the Periodic Safety Updates.

- For many of the veterinary medicines considered in this prioritisation exercise, information on toxicity to aquatic and terrestrial organisms and metabolism were not available. It is likely that some of this data has been generated by industry in support of product registration but is not available in the public domain. Industry and regulatory bodies should make this data available to the Environment Agency, for identified potentially high priority compounds.

- Industry and regulatory bodies should make available to the Environment Agency data not currently available in the open scientific literature, on the environmental fate and behaviour of high priority compounds for the purposes of further assessment.

- Although not anticipated to be a major issue for target organisms, bioaccumulation data for those veterinary medicines identified as being of most concern should be obtained from industry and regulatory bodies and the bioaccumulation potential explored further within the context of the current prioritisation scheme, especially for non-target organisms. It may be possible to assess the potential for a substance to be bioaccumulated using data on target animals obtained in pharmacodynamic/pharmacokinetic studies performed by manufacturers as part of the current regulatory process.

- Industry and regulatory bodies should make available to the Environment Agency data on the amounts, properties and ecotoxicity of major metabolites for those compounds which are significantly metabolised.

(ii) Further assessment of those compounds identified as high priority

- In order to gain a greater understanding of the actual risk they pose to the environment, those compounds identified as a high priority should be studied further by the Environment Agency.

- The assessments should take into account different treatment scenarios, metabolism, the relative importance of different exposure routes and additional data not considered in the current prioritisation exercise (i.e. persistence, bioaccumulation potential and mobility).

- The likely environmental risks posed by metabolites of veterinary medicines that are significantly metabolised following administration should be investigated further by the Environment Agency, within the current prioritisation scheme.

- The main focus of this review has been on contamination of soil and surface waters and on potential impacts of soil-dwelling and aquatic organisms. In any further assessment conducted consideration should be given to the possible impacts of veterinary medicines on groundwater.

- The significance of exposure to the environment from the disposal of used containers, unused medicines or from discharges from manufacturing sites should be investigated further. In addition, substances may be released to the environment as a result of off-label use and poor slurry management practice. The significance of these exposure routes is currently unknown and should also be investigated further.

(iii) Conduct targeted environmental monitoring

- On the basis of the outcome of further assessment, targeted environmental monitoring should be performed to ascertain whether those compounds identified as high priority are present in the environment at ecologically significant levels.

- In order to perform environmental monitoring, analytical methods will be required. For many compounds, current analytical methods focus on non-environmental media, i.e. animal tissue and foodstuffs. For compounds that require environmental monitoring, industry should take responsibility to ensure that appropriate methods are developed for their products and made available to the Environment Agency. Validation of existing methods may also be required.

(iv) Identification of control measures and development of appropriate pollution prevention tools

- If a substance is identified as being a concern following further assessment and targeted monitoring, appropriate pollution prevention tools or other control measures should be implemented. Appropriate pollution prevention measures will depend on the substance and the type of use and could include: changes in animal husbandry, changes in slurry/manure handling practices, user awareness campaigns or re-evaluation of existing product approvals. Pollution prevention measures should be developed in consultation with all relevant stakeholders.

In addition to the recommendations described above to build on the prioritisation work conducted in this project, a number of more general recommendations can be made on the basis of the findings of the review. These are provided below:

(v) Regulatory approvals process

- The 'trigger concept' used for regulatory risk assessment of veterinary medicines under Directive 81/852/EEC has a number of shortcomings and its use should be reconsidered, especially the current soil trigger of 100 μg kg^{-1}. The regulatory risk assessment regime for veterinary medicines should be brought in line with regulatory risk assessment regimes for other chemicals such as industrial chemicals, pesticides and biocides which compare exposure with effects to make an assessment of risk.

- Regulatory authorities should work with industry to validate existing risk assessment exposure models. The relative significance of routes of entry to the environment such as wash off following topical treatment and farm yard run-off, which are not currently considered, should be assessed and incorporated into the models if appropriate.

- A number of veterinary medicines have been identified as having endocrine disrupting potential. However, limited information is available. Once an appropriate, internationally harmonised (e.g. OECD) testing procedure becomes available, it should be incorporated into the data requirements for product approval for veterinary medicines and consideration given to the endocrine disrupting potential within the risk assessment.

- Consideration should be give by the regulatory authorities to a similar system to that for pesticide registration, whereby applicants are required to develop a suitable method for environmental analysis as part of the product registration data requirements.

(vi) Liaison

- A number of studies are being performed at the EU level that are generating information on the fate, behaviour, effects and treatment of veterinary and human medicines. These include: ERAVMIS (Environmental Risk Assessment of Veterinary Medicines in Slurry); POSEIDON (Assessment of Technologies for the Removal of Pharmaceuticals and Personal Care Products in Sewage and Drinking Water Facilities to Improve the Indirect

Potable Water Reuse); and REMPHARMAWATER (Ecotoxicological Assessments and Removal Technologies for Pharmaceuticals in Wastewaters). It is recommended that links be established between these projects and other relevant studies in order to provide a forum to exchange information and ideas. Results from these studies should be made available to decision makers.

(vii) Further research

- With the exception of a few well studied groups, e.g. anthelmintics and sheep dip chemicals, ecotoxicity studies have only been performed on a limited number of species (particularly terrestrial species). For veterinary medicines that are identified as potentially being of high environmental risk, there would be value in conducting more extensive studies to establish species sensitivity distributions and likely impacts at the landscape scale.

- Whilst information was available on the direct effects of a range of veterinary medicines on aquatic and terrestrial organisms, limited information was available on the indirect effects. The possible indirect effects of veterinary medicines should therefore be identified. For example, concern has been raised over the possible indirect effects of anthelmintics on higher trophic levels (such as bat or bird species) that result from direct toxic effects of the products on dung invertebrates.

11 REFERENCES

Abraham, I., Fawcett, P., Kennedy, J., Kumar, A. and Ledger, R. (1997) Simultaneous analysis of lignocaine and bupivacaine enantiomers in plasma by high-performance liquid chromatography. *Journal of Chromatography B*, **703**, 203-208.

ADAS (1997) Animal manure practices in the pig industry: Survey report. Prepared by ADAS Market Research Team. July 1997.

ADAS (1998) Animal manure practices in the dairy industry: Survey report. Prepared by ADAS Market Research Team. March 1998.

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

Al-Ahmad, A., Daschner, F.D. and Kummerer, K. (1999) Biodegradability of ceftiofam, ciprofloxacin, meropenem, penicillin G and sulfamethoxazole and inhibition of waste water bacteria. *Archives Environmental Contamination and Toxicology*, **37**, 158-163.

Alderman, D.J. and Hastings, T.S. (1998) Antibiotic use in aquaculture. *International Journal of Food Science and Technology*, **33**, 139-155.

Antonian, L., DeMontigny, P. and Wislocki, P.G. (1998) An automated method for the determination of subnanogram concentrations of eprinomectin in bovine plasma, *Journal of Pharmaceutical and Biomedical Analysis*, **16**, 1363-1371.

Arcand-Hoy, L.D., Nimrod, A.C. and Benson, W.H. (1998) Endocrine-modulating substances in the environment: estrogenic effects of pharmaceutical products. *International Journal of Toxicology*, **17,** 139-158.

Armstrong, A. and Philips, K. (1998) A strategic review of sheep dipping. Environment Agency R & D Technical Report P170.

Ayscough, N.J., Fawell, J., Franklin, G. and Young, W. (2000) Review of human pharmaceuticals in the environment. Environment Agency R & D Technical Report P390.

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

Backhaus, T., Scholze, M. and Grimme, L.H. (2000) The single substance and mixture toxicity of quinolones to the bioluminescent bacterium *Vibrio fischeri*. *Aquatic Toxicology*, **49**, 49-61.

Backhaus, T., Faust, M., Junghans, M., Scholze, M., Grimme, H. (2001) Low algal toxicities of quinolones confirm their specific molecular mechanism of action. Paper presented at the SETAC Europe 11th Annual Meeting, Madrid, May, 2001.

Baguer, A.J., Jensen, J. and Krogh, P.H. (2000) Effects of the antibiotics oxytetracycline and tylosin on soil fauna. *Chemosphere*, **40**(7), 751-758.

Beconi-Barker, M.G., Roof, R.D., Vidmar, T.J., Hornish, R.E., Smith, E.B., Gatchell, C.L. and Gilbertson, T.J. (1996) Ceftiofur sodium: absorption, distribution, metabolism, and excretion in target animals and its determination by high performance liquid chromatography. *Veterinary Drug Residues*, **636**, 70-84.

Belal, F., Al-Majed, A.A. and Al-Obaid, A.M. (1999) Methods of analysis of 4-quinolone antibacterials. *Talanta*, **50**, 765-786.

Belfroid, A.C., van Drunen, M., van Gestel, C.A.M and van Hattum, B. (1996) *Relative risks of transformation products of pesticides for aquatic ecosytems.* Institut voor Milieuvraagstukken, Report No. R-96/09.

Björklund, H.V., Bondestam, J. and Bylund, G. (1990) Residues of oxytetracycline in wild fish and sediments from fish farms. *Aquaculture*, **86**, 359-367.

Björklund, H.V. and Bylund, G. (1991) Comparative pharmacokinetics and bioavailability of oxolinic acid and oxytetracycline in rainbow trout (*Oncorhynchus mykiss*). *Xenobiotica*, **21**, 1511-1520.

Björklund, H.V., Råbergh, C.M.I. and Bylund, G. (1991) Residues of oxolinic acid and oxytetracycline in fish and sediments from fish farms. *Aquaculture*, **97**, 85-96.

Bloom, R.A. and Matheson, J.C. (1993) Environmental assessment of avermectins by the US Food and Drug Administration. *Veterinary Parasitology*, **48**, 281-294.

Bohm, V.R. (1996) Auswirkungen von ruckstanden von antiinfektiva in tierischen ausscheidungen auf die gullebehandlung und den boden. *Dtsch. Tierarztl. Wschr,* **103**, 237-284.

Bowen, P.D.G. (1995) Antiparastic products, In: Animal medicines a user's guide: transport, storage and disposal of animal medicines. National Office of Animal Health Ltd, Enfield UK.

Boxall, A.B.A., Oakes, D., Ripley, P. and Watts, C.D. (2000) The application of predictive models in the environmental risk assessment of ECONOR. *Chemosphere*, **40**(7), 775-782.

Boxall, A.B.A. and Renaud, F. (2001) Terrestrail Hazard Assessment. A report to the Environment Agency. Contract Reference Number: RC638B, July 2001.

Briggs, G.G. (1981) Theoretical and experimental relationships between soil adsorption, octanol-water partition coefficients, water solubilities, bioconcentration factors and the parachor. *J. Agric. Food Chem*., **29**, 1050-1059.

Bull, D.L., Ivie, G.W., MacConnell, J.G., Gruber, V.F., Ku, C.C., Arison, B.H., Stevenson, J.M. and VandenHeuve, W.J.A. (1984) Fate of avermectin B1a in soil and plants. *Journal of Agricultural and Food Chemistry*, **32**, 94-102.

Burka, J.F., Hammell, K.L., Horsberg, T.E., Johnson, G.R., Rainnie, D.J. and Speare, D.J. (1997) Drugs used in salmonid aquaculture – a review. *Journal of Veterinary Pharmacology and Therapeutics*, **20**, 333-349.

Burkepile, D.E., Moore, M.T. and Holland, M.M. (2000) Susceptibility of five non-target organisms to aqueous diazinon exposure. *Bulletin of Environmental Contamination Toxicology*, **64**, 114-121.

Burridge, L.E. and Haya, K. (1993) The lethality of ivermectin, a potential agent for treatment of salmonids against sea lice, to the shrimp, *Crangon septemspinosa*. *Aquaculture*, **117**, 9-14.

Campbell, W.C., Fisher, M.H., Stapley, E.O., Albers-Schonberg, G. and Jacob, T.A. (1983) Ivermectin: a potent new antiparasitic agent. *Science, New York*, **221**, 823-828.

Canavan, A., Coyne, R., Kennedy, D.G. and Smith, P. (2000) Concentration of 22,23-dihydroavermectim B_{1a} detected in the sediments at an Atlantic salmon farm using orally administered ivermectin to control sea-lice infestation. *Aquaculture*, **182**, 229-240.

Capone, D.G., Weston, D.P., Miller, V. and Shoemaker, C. (1996) Antibacterial residues in marine sediments and invertebrates following chemotherapy in aquaculture. *Aquaculture*, **145**, 55-75.

Carlucci, G. (1998) Analysis of fluoroquinolones in biological fluids by high-performance liquid chromatography. *Journal of Chromatography A*, **812**, 343-367.

Catherman, D.R., Szabo, J., Batson, D.B., Cantor, A.H., Tucker, R.E. and Mitchell, J.R. (1991) Metabolism of narasin in chickens and quail. *Poultry Science*, **70**, 120-125.

Chen, Y., Rosazza, J.P.N., Reese, C.P., Chang, H.Y., Nowakowski, M.A. and Kiplinger, J.P. (1997) Microbial models of soil metabolim: biotransformations of danofloxacin. *Journal of Industrial Microbiology and Biotechnology*, **19**, 378-384.

Cherlet, M., De Baere, S., Croubels, S. and De Backer, P., (2000) Quantitative analysis of levamisole in porcine tissues by high-performance liquid chromatography combined with atmospheric pressure chemical ionization mass spectrometry. *Journal of Chromatography B*, **742**, 283-293.

Chiavarino, B., Crestoni, M.E., Di Marzio, A. and Fornarini, S., (1998) Determination of sulfonamide antibiotics by gas chromatography coupled with atomic emission detection. *Journal of Chromatography B*, **706**, 269-277

Chien, Y.H., Lai, H.T. and Lui, S.M. (1999) Modeling the effects of sodium chloride on degradation of chloramphenicol in aquaculture pond sediment. *The Science of the Total Environment*, **239**, 81-87.

Chiu, S.H.L., Green, M.L., Baylis, F.P., Eline, D., Rosegay, A., Meriwether, H. and Jacob, T.A. (1990) Absorption, tissue distribution, and excretion of tritium-labelled ivermectin in cattle, sheep, and rat. *Journal of Agricultural and Food Chemistry*, **38**, 2072-2076.

Code of Good Agricultural Practice for the Protection of Water, 1998. MAFF Publication 0587.

Committee for Veterinary Medicinal Products (1992) Dimetridazole (1), EMEA, London.

Committee for Veterinary Medicinal Products (1995) Oxytetracycline, tetracycline, chlortetracycline: Summary report (3). EMEA/MRL/023/95, EMEA, London.

Committee for Veterinary Medicinal Products (1996) Diclazuril: Summary report. EMEA/MRL/086/96-FINAL, EMEA, London.

Committee for Veterinary Medicinal Products (1996a) Eprinomectin: Summary report (1). EMEA/MRL/114/96-FINAL, EMEA, London.

Committee for Veterinary Medicinal Products (1996b) Flumequine: Summary report (1). EMEA/MRL/104/96-FINAL. EMEA, London.

Committee for Veterinary Medicinal Products (1997) Note for guidance: environmental risk assessment for veterinary medicinal products other than GMO-containing and immunological products. EMEA/CVMP/055/96-FINAL, European Agency for the Evaluation of Medicinal Products, London.

Committee for Veterinary Medicinal Products (1997a) Doramectin: Summary report (1). EMEA, London.

Committee for Veterinary Medicinal Products (1997b) Flubendazole: Summary Report (2). EMEA/MRL/267/97-FINAL, EMEA, London.

Committee for Veterinary Medicinal Products (1997c) Trimethoprim: Summary report (2). EMEA/MRL/255/97-FINAL, EMEA, London.

Committee for Veterinary Medicinal Products (1997d) Tylosin: Summary report (3). EMEA/MRL/205/97-FINAL, EMEA, London.

Committee for Veterinary Medicinal Products (1998) Bacitracin: Summary report. EMEA/MRL/451/98-FINAL, EMEA, London.

Committee for Veterinary Medicinal Products (1998) Difloxacin (extension to swine and cattle): Summary Report. EMEA/MRL/525/98-FINAL, EMEA, London.

Committee for Veterinary Medicinal Products (1998b) Enrofloxacin (modification for bovine, porcine and poultry): Summary report (2). EMEA/MRL/388/98-FINAL, EMEA, London.

Committee for Veterinary Medicinal Products (1998c) Halofuginone: Summary report. EMEA/MRL/485/98-FINAL, EMEA, London.

Committee for Veterinary Medicinal Products (1998d) Ivermectin (extension to deer): Summary report (4). EMEA/MRL/487/98-FINAL. EMEA, London.
Committee for Veterinary Medicinal Products (1998e) Lincomycin: Sumary report. EMEA/MRL/497/98-FINAL. EMEA, London.

Committee for Veterinary Medicinal Products (1998f) Oxolinic acid: Summary report. EMEA/MRL/501/98-FINAL. EMEA, London.

Committee for Veterinary Medicinal Products (1998g) Toltrazuril: Summary report (1). EMEA/MRL/314/97-FINAL. EMEA, London.

Committee for Veterinary Medicinal Products (1999) Amprolium: Summary report. EMEA/MRL/721/99-FINAL, EMEA, London.

Committee for Veterinary Medicinal Products (1999a) Ceftiofur: Summary report (2). EMEA/MRL/498/98-FINAL, EMEA, London.

Committee for Veterinary Medicinal Products (1999b) Florfenicol (extension to chicken): Summary report. EMEA/MRL/589/99-FINAL, EMEA, London.

Committee for Veterinary Medicinal Products (1999c) Florfenicol (extension to pigs): Summary report. EMEA/MRL/591/99-FINAL, EMEA, London.

Committee for Veterinary Medicinal Products (1999d) Flubendazole (extension to turkeys): Summary Report. EMEA/MRL/576/99-FINAL. EMEA, London.

Committee for Veterinary Medicinal Products (1999e) Propetamphos: Summary report. EMEA/MRL/626/99-FINAL. EMEA, London.

Committee for Veterinary Medicinal Products (1999f) Tilimicosin: Summary report (1). EMEA, London.

Committee for Veterinary Medicinal Products (1999g) Toltrazuril (extension to pigs): summary report (2). EMEA/MRL/620/99-FINAL. EMEA, London.

Committee for Veterinary Medicinal Products (2000) Erythromycin: Summary report (2). EMEA/MRL/720/99-FINAL, EMEA, London.
Committee for Veterinary Medicinal Products (2000a) Neomycin: Summary report (2). EMEA/MRL/730/00-FINAL. EMEA, London.

Committee for Veterinary Medicinal Products (2000b) Pirlimycin: Summary report (2). EMEA/MRL/719/99-FINAL. EMEA, London.

Committee for Veterinary Medicinal Products (2000c) Streptomycin and dihydrostreptomycin: Summary report (2). EMEA/MRL/728/00-FINAL. EMEA, London.

Committee for Veterinary Medicinal Products (2000d) Toltrazuril (extension to pigs): Summary report (3). EMEA/MRL/743/00-FINAL. EMEA, London.

Control of Pollution Act 1974, ISBN 0105440744.

Cook, D.F., Dadour, I.R. and Ali, D.N. (1996) Effect of diet on the excretion profile of ivermectin in cattle faeces. *International Journal for Parasitology*, **26**, 291-295.

Cook, R.R. (1995) Disposal of animal medicines. In: Animal medicines a user's guide: transport, storage and disposal of animal medicines. National Office of Animal Health Ltd, Enfield UK.

CORDAH (1999) Potential environmental impacts of emamectin benzoate, formulated as Slice®, for salmonids. Report No. SCH001R6.

Council Directive 81/852/EEC of the Commission of September 28, 1981 as published in the Official Journal of the European Community of November 6, 1981, No. L317, page 16, amended by:- Directive 92/18/EEC of the Commission of March 20, 1992 as published in the Official Journal of the European Community of April 10, 1002, No. L97, page 1.

Council Directive 87/778/EEC relating to the quality of water intended for human consumption. *Official Journal of the Europen Communities,* 1980, No. L/229/11, Parameter 55.

Council Directive 96/61/EC of 24 September 1996 concerning integrated pollution prevention and control. *Official Journal of the European Communities,* No. L 257 , 10/10/1996, p. 0026 – 0040.

Coyne, R., Hiney, M., O'Connor, B., Kerry, J., Cazabon, D. and Smith, P. (1994) Concentration and persistence of oxytetracycline in sediments under a marine salmon farm. *Aquaculture*, **123**, 31-42.

Daughton, C.G. and Ternes, T.A. (1999) Pharmaceuticals and personal care products in the environment; Agents of subtle change? Special report. *Environmental Health Perspectives Supplements*, **107**, 907-938.

Davies, I.M., McHenry, J.G. and Rae, G.H. (1997) Environmental risk of dissolved ivermectin to marine organisms. *Aquaculture*, **158**, 63-275.

Davies, I.M., Gillibrand, P.A., McHenry, J.G. and Rae, G.H. (1998) Environmental risk of ivermectin to sediment-dwelling organisms. *Aquaculture*, **163**, 29-46.

Davies, I.M. and Rodger, G.K. (2000) A review of the use of ivermectin as a treatment for sea lice (*Lepeophtheirus salmonis* (Kroyer) and *Caligus elongatus* Nordmann) infestation in farmed Atlantic salmon (*Salmo salar* L.). *Aquaculture Research*, **31**: 869-883.

Davis, M.L., Lofthouse, T.J. and Stamm, J.M. (1993) Aquatic photodegradation of 14C-sarafloxicin hydrochloride. Poster presented at the American Chemical Society E-Fate meeting, 28th March, 1993.

Doherty, W.M., Stewart, N.P., Cobb, R.M. and Keiran, P.J. (1994) In-vitro comparison of the larvicidal activity of moxidectin and abamectin against Onthophagus gazella (F)(Coleoptera: Scarabaeidae) and Haematobia irritans exigua De Meijere (Diptera: Muscidae). *Journal of the Australian Entomological Society*, **33**, 71-74.

Donoho, A.L. (1984) Biochemical studies on monensin. *Journal of Animal Science*, **58**, 1528-1539.

Donoho, A.L. (1987) Metabolism and residue studies with actaplanin. *Drug Metabolism Reviews*, **18**(2&3), 163-176.

Dusi, G. and Gamba, V. (1999) Liquid chromatography with ultraviolet detection of lasalocid, monensin, salinomycin and narasin in poultry feeds using pre-column derivatization. *Journal of Chromatography A*, **835**, 243-246.

Dusi, G., Faggionato, E., Gamba, V. and Baiguera, A. (2000) Determination of nicarbazin and clopidol in poultry feeds by liquid chromatography. *Journal of Chromatography A*, **882**, 79-84.

Edder, P., Cominoli, A. and Corvi, C., (1999) Determination of streptomycin residues in food by solid-phase extraction and liquid chromatography with post-column derivatization and fluorimetric detection. *Journal of Chromatography A*, **830**, 345-351.

Environment Agency (1997) The occurrence of sheep-dip pesticides in environmental waters. National Centre for Toxic and Persistent Substances, Environment Agency, Peterborough.

Environment Agency (1998) Pesticides 1998: A summary of monitoring of the aquatic environment in England and Wales. National Centre for Ecotoxicology and Hazardous Substances, Environment Agency, Wallingford.

Environment Agency (1999) Sheep dip chemicals and textiles working group - A strategy for reducing sheep dip chemical pollution from the textile industry. National Centre for Ecotoxicology and Hazardous Substances, Environment Agency, Wallingford.

Environment Agency (2000) Welsh sheep dip monitoring programme 1999. Environment Agency Wales,Cardiff. Environment Agency Midland Region, Solihull. April 2001.

Environment Agency (2001) Pesticides 1999/2000: A summary of monitoring of the aquatic environment in England and Wales. National Centre for Ecotoxicology and Hazardous Substances, Environment Agency, Wallingford.

Environment Protection Act 1990, ISBN 0105443905.

Ervik, A., Thorsen, B., Eriksen, V., Lunestad, B.T. and Samuelsen, O.B. (1994) Impact of administering antibacterial agents on wild fish and blue mussels *Mytilus edulis* in the vicinity of fish farms. *Diseases of Aquatic Organisms*, **18**: 45-51.

Floate, K.D., Taylor, W.G. and Spooner, R.W. (1997) Thin layer chromatographic detection of ivermectin in cattle dung. *Journal of Chromatography B*, **694**, 246-251.

Floate, K.D. (1998) Off-target effects of ivermectin on insects and on dung degradationin southern Alberta, Canada. *Bulletin of Entomological Research*, **88**, 25-35.

Gavalchin, J. and Katz, S.E. (1994) The persistence of fecal-borne antibiotics in soil. *Journal of AOAC International*, **77**(2), 481-485.

Gilbertson, T.J., Hornish, R.E., Jaglan, P.S., Koshy, T., Nappier, J.L., Stahl, G.L., Cazers, A.R., Nappier, J.M., Kubicek, M.F., Hoffman, G.A. and Hamlow, P. (1990) Environmental fate of ceftiofur sodium, a cephalosporin antibiotic. Role of animal excreta in its decomposition. *Journal of Agricultural and Food Chemistry*, **38**, 890-894.

Gover, J. and Strong, L. (1995) The effects of ivermectin in ingested cow-dung on the mortality and oviposition of the dung fly Neomyia cornicina. *Bulletin of Entomological Research*, **85**, 53-57.

Gover, J. and Strong, L. (1996) Determination of the toxicity of faeces of cattle treated with an ivermectin sustained-release bolus and preference trials using a dung fly, Neomyia cornicina. *Entomologia Experimentalis et Applicata*, **81**, 133-139.

Gover, J. and Strong, L. (1996b) Effects of ingestion of dung containing ivermectin on aspects of behaviour in the fly Neomyia cornicina. *Physiological Entomology*, **21**, 51-58.

Grant, A. and Briggs, A.D. (1998) Toxicity of ivermectin to estuarine and marine invertebrates. *Marine Pollution Bulletin*, **36**, 540-541.

Grave, K., Engelstad, M., Søli, N.E., Toverud, E.L. (1991) Clinical use of dichlorvos (Nuvan®)and trichlorfon (Neguvon®) in the treatment of salmon louse, *lepeophtheirus salmonis.* Compliance with the recommended treatment procedures. *Acta Veterinaria Scandinavica*, **32**, 9-14.

Greiner, P., Ronnefarth, I. (2001) Environmental risk assessment of veterinary medicines from a regulatory perspective. Paper presented at the SETAC Europe 11th Annual Meeting, Madrid, May, 2001.

Groundwater Regulations 1998, Statutory Instrument 1998 No.2746, ISBN 011079799X.

Gruber, V.F., Halley, B.A., Hwang, S-C., Ku, C.C. (1990) Mobility of avermectin B1a in soil. *Journal of Agricultural and Food Chemistry*, **38**, 886-890.

Gustafson, R.H. and Bowen, R.E. (1997) Antibiotic use in animal agriculture. *Journal of Applied Microbiology* 83: 531-541.

Haasnoot, W., Korsrud, G.O., Cazemier, G., Maneval, F., Keukens, H. and Nouws, J., (1996) Application of an enzyme immunoassay for the determination of sulphamethazine (sulphadimidine) residues in swine urine and plasma and their use as predictors of the level in edible tissue. *Food Additives and Contaminants*, **13**(7), 811-822.

Halley, B.A., Green, M.L. and Chiu, S.H.L. (1986) Tissue depletion and metabolism of radiolabelled MK-0933 in cattle dosed percutaneously. Environmental Assessment for the Ivomec © Pour-On Formulation: March 22, 1990. Unpublished.

Halley, B.A., Jacob, T.A. and Lu, A.Y.H. (1989) The environmental impact of the use of ivermectin: environmental effects and fate. *Chemosphere*, **18**, (7-8), 1543-1563.

Halley, B.A., Nessel, R.J. and Lu, A.Y.H. (1989a) Environmental aspects of ivermectin usage in livestock: general considerations. In: Campbell, W.D. (Ed) ivermectin and abamectin . Springer-Verlag, New York.

Halley, B.A., VandenHeuvel, W.J.A. and Wislocki, P.G. (1993) Environmental effects of the usage of avemectins in livestock. *Veterinary Parasitology*, **48**, 109-125.

Halling-Sørenson, B., Nors Nielsen, S., Lanzky, P.F., Ingerslev, F., Holten Lützhøft and Jørgensen, S.E. (1998) Occurrence, fate and effect of pharmaceutical substances in the environment- a review. *Chemosphere*, **36**, 357-393.

Halling-Sørenson, B. (1999) Algal toxicity of antibacterial agents used in intensive farming. *Chemosphere*, **40**, 731-739.

Halling-Sørenson, B., Jensen, J., Tjørnelund, J. and Montforts, M.H.M.M (2001) Worst-case estimations of predicted environmental soil concentrations (PEC) of selected veterinary antibiotics and residues used in Danish agriculture. In: Kümmerer, K. (Ed.), Pharmaceuticals in the Environment - Sources, Fate, Effects and Risks. Springer-Verlag, Germany.

Hamamoto, K., Koike, R., Shirakura, A., Sasaki, N. and Machida, Y. (1997) Rapid and sensitive determination of amprolium in chicken plasma by high-performance liquid chromatography with post-column reaction. *Journal of Chromatography B*, **693**, 489-492.

Hamscher, G., Abu-Quare, A., Sczesny, S., Höper, H. and Nau, H. (2000) Determination of tetracyclines and tylosin in soil and water samples from agricultural areas in lower Saxony, in: eds: van Ginkel, L.A., Ruiter, A., Proceedings of the Euroresidue IV conference, Veldhoven, Netherlands, 8-10 May 2000, National Institute of Public Health and the Environment (RIVM), Bilthoven

Hamscher, G., Sczesny, S., Abu-Quare, A., Höper, H. and Nau, H. (2000a) Substances with pharmacological effects including hormonally active substances in the environment: Identification of tetracyclines in soil fertilised with animal slurry. *Dtsch. tierärztl. Wschr.* **107**, 293-348.

Hamscher, G., Sczesny, S., Höper, H. and Nau, H., (2000b) Tetracycline and chlortetracycline residues in soil fertilized with liquid manure, proceedings of Livestock Farming and the Environment, Hannover, 28-29 September 2000.

Hamscher, G., Sczesny, S., Abu-Quare, A. and Nau, H., (2000c) ESI-LC-MS-MS techniques and HPLC directly coupled to a microbiological assay for the analysis of tetracyclines and tylosin in environmental samples. In: Eds: van Ginkel, L.A., Ruiter, A., Proceedings of the Euroresidue IV conference, Veldhoven, Netherlands, 8-10 May 2000, National Institute of Public Health and the Environment (RIVM), Bilthoven.

Hansen, P.K., Lunestad, B.T., Samuelsen, O.B. (1993) Effects of oxytetracycline, oxolinic acid and flumequine on bacteria in an artificial marine fish farm sediment. *Canadian Journal of Microbiology*, **39**, 1307-1312.

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

Harrison, A.C. and Walker, D.K. (1998) Automated 96-well solid phase extraction for the determination of doramectin in cattle plasma. *Journal of Pharmaceutical and Biomedical Analysis*, **16**, 777-783.

Hartig, C., Storm, T. and Jekel, M. (1999) Detection and identification of sulphonamide drugs in municipal waste water by liquid chromatography coupled with electrospray ionisation tandem mass spectrometry. *Journal of Chromatography A*, **854**, 163-173.

Health and Safety Laboratories, Sheffield. (2001) *personal communication.*

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

Hektoen, H., Berge, J.A., Hormazabal, V. and Yndestad, M. (1995) Persistence of antibacterial agents in marine sediments. *Aquaculture*, **133**, 175-184.

Hefnawy, M., El-Shabrawy, Y. and Belal, F. (1999) Spectroflurometric determination of alpha-aminocephalosporins in biological fluids and pharmaceutical preparations. *Journal of Pharmaceutical and Biomedical Analysis*, **21**, 707-707.

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

Hollis, J.M. (1991) Mapping the vulnerability of aquifers and surface waters to pesticide contamination at the national/regional scale. In: Walker, A. (Ed.), Monograph No. 47. Pesticides in soils and water: current perspectives. Proceedings of a symposium organised by the British Crop Protection Council held at the University of Warwick, Coventry, UK on 25-27 March, 1991.

Hollis and Carter (1990) A comparison of laboratory, lysimeter and field study techniques to determine environmental fate of pesticides in the UK. Brighton Crop Protection Conference, Pests and Diseases 1990, pp1005-1010. BCPC, Farnham.

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

Holten Lützhøft, H.C., Halling-Soerensen, B. and Jørgensen, S.E. (1999) Algal toxicity of antibacterial agents applied in Danish fish farming. *Archives Environmental Contamination and Toxicology*, **36**, 1-6.

Hows, M.E.P., Perret, D. and Kay, J. (1997) Optimisation of a simultaneous separation of sulphoamides, dihydrofolate reductase inhibitors and ß-lactam antibiotics by capillary electrophoresis. *Journal of Chromatography A*, **768**, 97-104.

Høy, T., Horsberg, T.E. and Nafstad, I. (1990) The disposition of ivermectin in Atlantic salmon *(Salmo salar)*. *Pharmacology and Toxicology*, **67**, 307-312.

HSE (1997) Sheep dipping. *Booklet AS29 (rev.2),* December 1997.

Hurtaud-Pessel, D., Delépine, B. and Laurentie, M. (2000) Determination of four nitroimidazole residues in poultry meat by liquid chromatography-mass spectrometry. *Journal of Chromatography A*, **882**, 89-98.
Hustvedt, S.O., Salte, R., Kvendseth, O. and Vassvik, V. (1991) Bioavailability of oxolinic acid in Atlantic salmon (*Salmo salar* L) from medicated feed. *Aquaculture*, **97**, 305-310.

Illarionov, A.I. (1993) Toxicokinetics of insecticides in honey bees. *Agrokhimiya*, **5**, 90-95.

Ingerslev, F. and Halling-Sørensen, B. (2001) Biodegradability of metronidazole, olaquindox and tylosin and formation of tylosin degradation products in aerobic soil/manure slurries. *Chemosphere*, **48**, 311-320.

Jacobsen, P. and Berglind, L. (1988) Persistence of oxytetracycline in sediments from fish farms. *Aquaculture*, **70**, 365-370.

Jen, J-F., Lee, H-L. and Lee, B-N. (1998) Simultaneous determination of seven sulfonamide residues in swine wastewater by high-performance liquid chromatography. *Journal of Chromatography A*, **793**, 378-382.

Jernigan, A.P., Herd, R.P. and Sams, R. (1990) Determination of ivermectin in equine feces. *Fed. Am. Soc. Exp. Biol*., **4**(3): Abstr. No.2810.

Jørgensen, S.E. and Halling-Sørensen, B. (2000) Drugs in the environment. *Chemosphere*, **40**, 691-699.

Kanfer, I., Skinner, M.F. and Walker, R.B. (1998) Analysis of macrolide antibiotics. *Journal of Chromatography A*, **812**, 255-286.

Kerry, J., Coyne, R., Gilroy, D., Hiney, M. and Smith, P. (1996) Spatial distribution of oxytetracycline and elevated frequencies of oxytetracycline resistance in sediments beneath a marine salmon farm following oxytetracycline therapy. *Aquaculture*, **145**, 31-39.

Kopf, W. (1995) Wirkung endokriner stoffe in biotests mit wasserorganismen. Vortrag bei der 50. Fachtung des bay, LA fu wasserwirtschaft: stoffe mit endokriner. Wirkung im Wasser (abstract).

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

Lacorte, S. and Barceló, D. (1995) Determination of organophosphorus pesticides and their transformation products in river waters by automated on-line solid-phase extraction followed by liquid chromatography-mass spectrometry. *Journal of Chromatography A*, **712**, 103-112.

Lai, H.T., Liu, S.M. and Chien, Y.H. (1995) Transformation of chloramphenicol and oxytetracycline in aquaculture pond sediments. *Journal of Environmental Science and Health A,* **30** (9), 1897-1923.

Lanzky, P.F. and Halling-Sørensen, B. (1997) The toxic effect of the antibiotic metronidazole on aquatic organisms. *Chemosphere*, **35**, 2553-2561.

Larkin, D.J. and Tjeerdema, R.S. (2000) Fate and effects of diazinon. *Reviews of Environmental Contamination and Toxicology*, **166**, 49-82.

Levêque, D., Gallion-Renault, C., Monteil, H. and Jehl, F. (1998) Analysis of recent antimicrobial agents in human biological fluids by high-performance liquid chromatography. *Journal of Chromatography A*, **815**, 163-172.

Lewis, K.A and Bardon, K.S. (1998) A computer based informal environmental management system for agriculture. Environmental Modelling Software, **13**, 123-137.

Lewis, S., Watson, A. and Hedgecott, S. (1993) Propsed environmental quality standards for sheep dip chemicals in water. Chlorfenvinphos, Coumaphos, Diazinon, Fenchlorphos, Flumethrin and Propetamphos. WRc plc, R & D Note 216. Scotland and Northern Ireland Forum for Environmental Research and the National Rivers Authority.

Lewis, S. (1998) Proposed environmental quality standards for sheep dip chemicals in water. Chlorfenvinphos, Coumaphos, Diazinon, Fenchlorphos, Flumethrin and Propetamphos – an update. Environment Agency, Draft R & D Report P128.

Liddel, J.S. (2000) Sheep ectoparasiticide use in the UK: 1993, 1997 and 1999. Paper presented to the 5th International Sheep Veterinary Congress, Stellenbosch, South Africa

Littlejohn, J.W. and Melvin, A.A.L. (1991) Sheep-dips as a source of pollution of freshwaters – a study in Grampian Region. *Journal of the Chartered Institute of Water and Environmental Management*, **5**, 21-27.

Loke, M.L., Ingerslev, F., Halling-Sørensen, B. and Tjornelund, J. (2000) Stability of tylosin A in manure containing test systems determined by high performance liquid chromatography. *Chemosphere*, **40**, 759-765.

Lunestad, B.T. (1992) Fate and effects of antibacterial agents in aquatic environments. Proceedings of the Conference on Chemotherapy in Aquaculture: From Theory to Reality. Office International des Epizooties, Paris, France.

Lunestad, B.T., Samuelsen, O.B., Fjelde, S. and Ervik, A. (1995) Photostability of eight antibacterial agents in seawater. *Aquaculture*, **134**, 217-225.

Luo, Y., McNamara, B., Fennell, M.A., Teleis, D.C., May, L., Rudy, J., Watson, A.O., Uboh, C.E. and Soma, L.R., (1998) Quantification of penicillin-G and procaine in equine urine and plasma using high-performance liquid chromatography. *Journal of Chromatography B*, **714**, 269-276.

Lutnicka, H., Bogacka, T. and Wolska, L. (1999) Degradation of pyrethroids in an aquatic ecosystem model. *Water Research*, **33 (16)**, 3441-3446.

Madsden, M., Overgaard Nielsen, B., Holter, P., Pedersen, O.C., Brrochner Jespersen, J., Vagn Jensen, K.-M., Nansen, P. and Gronvold, J. (1990) Treating cattle with ivermectins: effects on the fauna and decomposition of dung pats. *Journal of Applied Ecology*, **27**, 1-15.

MAFF (1998) Code of Good Agricultural Practice for the Protection of Water. Ministry of Agriculture, Fisheries and Food. Welsh Office Agricultural Department. October 1998.

Magnussen, J.D., Dalidowicz, J.E., Thomson, T.D. and Donoho, A.L. (1991) Tissue residues and metabolism of avilamycin in swine and rats. *Journal of Agricultural and Food Chemistry*, **39**, 306-310.

Manceau, J., Gicquel, M., Laurentie, M. and Sanders, P. (1999) Simultaneous determination of enrofloxacin and ciprofloxacin in animal biological fluids by high-performance liquid chromatography, application in pharmacokinetic studies in pig and rabbit. *Journal of Chromatography B*, **726**, 175-184.

Marengo, J.R., Kok, R.A., O'Brien, K., Velagaleti, R. and Stamm, J.M. (1997) Aerobic biodegradation of (^{14}C)-sarafloxicin hydrochloride in soil. *Environmental Toxicology and Chemistry*, **16**(3): 462-471.

Martínez Galera, M., Martínez Vidal, A., Garrido Renich, A. and Gil García, M.D. (1996) Determination of cypermethrin, fenvalerate and *cis*- and *trans*-permethrin in soil and groundwater by high-performance liquid chromatography using partial least-squares regression. *Journal of Chromatography A*, **727**, 39-46.

Matha, V. and Weiser, J. (1988) The molluscicidal effect of ivermectin on *Biomphalaria glabrafa*. *Journal of Inveretebrate Pathology*, **52**, 354-355.

McCracken, D.I. (1993) The potential for avermectins to affect wildlife. *Veterinary Parasitology*, **48**, 273-280.

McKellar, Q.A. (1997) Ecotoxicology and residues of anthelmintic compounds. *Veterinary Parasitology*, **72**, 413-435.

Melancon, S.M., Pollard, J.E., Hern, S.C. (1986) Evaluation of SESOIL, PRZM and PESTAN in a laboratory column leaching experiment. *Environmental Toxicology and Chemistry*, 5, 865-878.

Merck, Sharp, & Dohme (1983) Environmental impact report on Ivomec injection. New Animal Drug Application no.128-409.

Meyer, M.T., Bumgarner, J.E., Varns, J.L., Daughtridge, J.V., Thurman, E.M. and Hostetler, K.A. (2000) Use of radioimmunoassay as a screen for antibiotics in confined animal feeding operations and confirmation by liquid chromatography/mass spectrometry. *The Science of the Total Environment*, **248**, 181-187.

Meyer, W., Backhaus, T., Froehner, K., Scholze, M., Grimme, H. (2001) Single substance and mixture toxicity of selected pharmaceuticals. Paper presented at the SETAC Europe 11th Annual Meeting, Madrid, May, 2001.

Migliore, L., Brambilla, G., Cozzolino, S. and Gaudio, L. (1995) Effect on plants of sulphadimethoxine used in intensive farming (*Panicum miliaceum, Pisum sativum* and *Zea mays*). *Agriculture, Ecosystems and Environment*, **52**, 103-110.

Migliore, L., Brambilla, G., Casoria, P., Civitareale, S.C. and Gaudio, L. (1996) Effect of sulphadimethoxine contamination on barley (*Hordeum disticum* L., Poaceae, liliopsida). *Agriculture, Ecosystems and Environment*, **60,** 121-128.

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

Migliore, L., Civitareale, C., Brambilla, S.C., Casoria, P. and Gaudio, L. (1997a) Effects of sulphadimethoxine on cosmopolitan weeds (*Ameranthus retroflexus* L., *Plantago major* L. and *Rumex acetosella* L.). *Agriculture, ecosystems and Environment,* **65**, 163-168.

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

Miller, J.A., Kunz, S.E., Oehlar, D.D. and Miller, RW. (1981) Larvicidal activity of Merck MK-933, an avermectin, against the horn fly, stable fly, face fly, and house fly. *J. Econ. Entomol*. **74**, 608-611.

Montforts, M.H.M.M. (1999) Environmental risk assessment for veterinary medicinal products Part1. Other than GMO-containing and immunological products. RIVM report 601300 001, April 1999. National Institute of Public Health and the Environment, Bilthoven, The Netherlands.

Nessel, R.J., Wallace, D.H., Wehner, T.A., Tait, W.E. and Gomez, L. (1989) Environmental fate of ivermectin in a cattle feedlot. *Chemosphere*, **18**, 1531-1541.

Niessen, W.M.A. (1998) Analysis of antibiotics by liquid chromatography-mass spectrometry. *Journal of Chromatography A*, **812**, 53-75.

NOAH (2000) Compendium of data sheets for veterinary products 2000-2001. National Office of Animal Health Ltd, Enfield, UK.

Novartis (1999) Safety Data Sheet: Sulfachloropyridazine-Na. Release date 18-Oct-1999.

Nowara, A., Burhenne, J. and Spiteller, M. (1997) Binding of fluoroquinolone carboxylic acid derivatives to clay minerals. *Journal of Agricultural and Food Chemistry*, **45**, 1459-1463.

Oka, H., Ikai, Y., Kawamura, N., Yamada, M., Harada, K-I, Ito, S. and Suzuki, M. (1989) Photodecomposition products of tetracycline in aqueous solution. *Journal of Agriculrural and Food Chemistry*, **37**, 226-231.

OECD (1998) Harmonized integrated hazard classification system for human health and environmental effects of chemical substances. As endorsed by the 28th Joint Meeting of the Chemicals Committee and the Working Party on Chemicals in November 1998. Sourced from OECD website: http://www.oecd.org/

Oka, H., Ikai, Y., Kawamura, N., Yamada, M., Harada, K., Ito, S. and Suzuki, M. (1989) Photodecomposition products of tetracycline in aqueous solution. *Journal of Agricultural and Food Chemistry*, **37**, 226-231.

Oka, H., Ito, Y. and Matsumoto, H. (2000) Chromatographic analysis of teteracycline antibiotics in foods. *Journal of Chromatography A*, **882**, 109-133.

Pang, G-F., Cao, Y-Z., Fan, C-L., Zhang, J-J., Li, X-M. and Wang, C. (2000) Determination of clopidol residues in chicken tissues by high-performance liquid chromatography-mass spectrometry. *Journal of Chromatography A*, **882**, 85-88.

Pepper, T. and Carter, A. (2000) Monitoring of pesticides in the environment. Report prepared for the Pesticides in the Environment Working Group. R & D Project E1-076.

Pesek, J.J. and Matyska, M.T. (1996) Separation of tetracyclines by high-performance capillary electrophoresis and capillary electrochromatography. *Journal of Chromatography A*, **736**, 313-320.

Poli, D., Bergamaschi, E., Manini, P., Andreoli, R., and Mutti, A., (1999) Solid-phase microextraction gas chromatographic-mass spectrometric method for the determination of inhalation anesthetics in urine. *Journal of Chromatography B*, **732**, 115-125.

Pouliquen, H., Le Bris, H. and Pinault, L. (1992) Experimental study of the therapeutic application of oxytetracycline, its attenuation in sediment and sea water, and implication for farm culture of benthic organisms. *Marine Ecology Progress Series*, **89**, 93-98.

Pouliquen, H., Le Bris, H. and Pinault, L., (1993) Experimental study on the decontamination kinetics of seawater polluted by oxytetracycline contained in effluents released from a fish farm located in a salt marsh. *Aquaculture*, **112**, 113-123.

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

Rabølle, M. and Spliid, N.H. (2000) Sorption and mobility of metronidazole, olaquindox, oxytetracycline and tylosin in soil. *Chemosphere* **40**,: 715-722.

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

Ridsdill-Smith, T.J. (1988) Survival and reproduction of Musca vetustissima Walker (Diptera muscidae) and a scarabaeine dung beetle in dung cattle treated with avermectin B1. *Journal of Australian Entomological Society*, **27**, 175-178.

Ridsdill-Smith, T.J. (1993) Effects of avermectin residues in cattle dung on dung beetle (Coleoptera: Scarabaeidae) reproduction and survival. *Veterinary Parasitology*, **48**, 127-137.

Sams, R. (1993) Chemical assay of abermectins by high performance liquid chromatography with fluorescence detection. *Veterinary Parasitology*, **48**, 59-66.

Samuelsen, O.B. (1989) Degradation of oxytetracycline in seawater at two different temperatures and light intensities and the persistence of oxytetracycline in the sediment from a fish farm. *Aquaculture*, **83**, 7-16

Samuelsen, O.B., Solheim, E. and Lunestad, B.T. (1991) Fate and microbiological effects of furazolidone in a marine aquaculture sediment. *The Science of the Total Environment*, **108**, 275-283.

Samuelsen, O.B., Lunestad, B.T., Husevåg, B., Hølleland, T. and Ervik, A. (1992) Residues of oxolinic acid in wild fauna following medication in fish farms. *Diseases of Aquatic Organisms*, **12**, 111-119.

Samuelsen, O.B., Torsvik, V. and Ervik, A. (1992a) Long-range changes in oxytetracycline concentration and bacterial resistance towards oxytetracycline in a fish farm sediment after medication. *The Science of the Total Environment*, **114**, 25-36.

Samuelsen, O.B., Lunestad, B.T., Ervik, A. and Fjelde, S. (1994) Stability of antibacterial agents in an artificial marine aquaculture sediment studied under laboratory conditions. *Aquaculture*, **126**, 283-290.

Schenck, F.J. and Callery, P.S. (1998) Chromatographic methods of analysis of antibiotics in milk. *Journal of Chromatography A*, **812**, 99-109.

Schering Plough Animal Health (1998) SLICE technical monograph. Schering Plough Animal Health, Union, New Jersey: 0-32.

Schmidt, C.D. (1983) Activity of an avermectin against selected insects in aging manure. *Environmental Entomology*, **12**, 455-457.

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

SEPA (1999) Enamectin benzoate an environmental risk assessment. Report of the SEPA Fish Farm Advisory Group, SEPA 66/99.

SEPA (2000) Long-term biological monitoring trends in the Tay System 1988-1999. Scottish Environment Protection Agency, Eastern Region.

Shappell, N.W., Larsen, G.L. and Bakke, J.E. (1999) Identification of the major urinary and fecal metabolites of 3,5-dinitrobenzamide in chickens and rats. *Chemosphere*, **38**(8), 1757-1762.

Shore, L.S., Shemesh, M. and Cohen, R. (1988) The role of oestradial and oestrone in chicken manure silage in hyperoestrogenism in cattle. *Australian Veterinary Journal*, **65**, 67.

Smith, P. (1996) Is sediment deposition the dominant fate of oxytetracycline used in marine salmonid farms: a review of available evidence. *Aquaculture*, **146**, 157-169.

Sommer, C. and Overgaard Nielsen, B. (1992) Larvae of the dung beetle *Onthophagus gazella* F. (Col., Scarabaeidae) exposed to lethal and sublethal ivermectin concentrations. *Journal of Applied Entomology*, **114**, 502-509.

Sommer, C., Steffansen, B., Overgaard Nielsen, B., Grønvold, J., Kagn-Jensen, K.M., Brøchner Jespersen, J., Springborg, J. and Nansen, P. (1992) Ivermectin excreted in cattle dung after sub-cutaneous injection or pour-on treatment:concentrations and impact on dung fauna. *Bulletin of Entomological Research*, **82**, 257-264.

Sommer, C., Gronvold, J., Holter, P. and Nansen, P. (1993) Effect of ivermectin on two afrotropical beetles Onthophagus gazella and Diastellopalpus quinquedens (Coleoptera: Scarabaeidae). *Veterinary Parasitology*, **48**, 171-179.

Sommer, C. and Steffansen, B. (1993) Changes with time after treatment in the concentrations of ivermectin in fresh cow dung and in cow pats aged in the field. *Veterinary Parasitology*, **48**, 67-73.

Spaepen, K.R.I., Leemput, L.J.J., Wislocki, P.G. and Verschueren, C. (1997) A uniform procedure to estimate the predicted environmental concentration of the residues of veterinary medicines in soil. *Environmental Toxicology and Chemistry*, **16**(9), 1977-1982.

Special Waste Regulations 1996, Statutory Instrument 1996 No.972, ISBN 0110528654.

Stead, D.A. (2000) Current methodologies for the analysis of aminoglycosides. *Journal of Chromatography B*, **747**, 69-93.

Steel, J.W. (1993) Pharmacokinetics and metabolism of avermectins in livestock. *Veterinary Parasitology*, **48**, 45-57.

Stout, S.J., Wu, J., daCunha, A.R., King, K.G. and Lee, A. (1991) Maduramycin α: Characterisation of ^{14}C-derived residues in turkey excreta. *Journal of Agricultural and Food Chemistry*, **39**, 386-391.

Strong, L. (1992) Avermectins: a review of their impact on insects of cattle dung. *Bulletin of Entomological Research*, **82**, 265-274.

Strong, L. (1993) Overview: the impact of avermectins on pastureland ecology. *Veterinary Parasitology*, **48**, 3-17.

Strong, L. and Brown, T.A. (1987) Avermectins in insect control and biology: a review. *Bulletin of Entomological Research*, **77**, 357-389.

Strong, L. and James, S. (1993) Some effects of ivermectin on the yellow dung fly, Scatophaga stercoraria. *Veterinary Parasitology*, **48**, 181-191.

Strong, L. and Wall, R. (1994) Effects of ivermectin and moxidectin on the insects of cattle dung. *Bulletin of Entomological Research*, **84**, 403-409.

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

Sweeney, D.J., Kennington, A. and Donoho, A.L. (1996) Tissue residues and metabolism of narasin in chicken. *Journal of Agricultural and Food Chemistry*, **44**, 2829-2834.

Takeba, K., Fujinuma, K., Sakamoto, M., Miyazaki, T., Oka, H., Itoh, Y. and Nakazawa, H., (2000) Simultaneous determination of triclabendazole and its sulphoxide and sulphone metabolites in bovine milk by high-performance liquid chromatography. *Journal of Chromatography A*, **882**, 99-107.

Taylor, S.M. (1999) Sheep scab – environmental considerations of treatment with doramectin. *Veterinary Parasitology*, **83**, 309-317.

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

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

Thain, J.E., Davies, I.M., Rae, G.H. and Allen, Y.T. (1997) Acute toxicity of ivermectin to the lugworm *Arenicola marina*. *Aquaculture*, **159**, 47-52.

Thorpe, J.E., Talbot, C., Miles, M.S., Rawlings, C. and Keay, D.S. (1990) Food consumption in 24 hours by Atlantic salmon (*Salmo salar* L) in a sea-cage. *Aquaculture*, **90**, 41-47.

Thurman, E.M. and Lindsey, M.E. (2000) Transport of antibiotics in soil and their potential for ground-water contamination. Poster presented at The SETAC World Congress, Brighton, May 2000.

Tomlin, C.D.S. (1997) The pesticide manual: Eleventh edition. BCPC, Bracknell, UK.

Turner,M.J. and Schaeffer, J.M. (1989) Mode of action of ivermectin. In Campbell, W.C. (Ed.) Ivermectin and Abamectin. Springer, New York.

US EPA (1997) Profile of the pharmaceutical manufacturing industry. EPA/310-R-97-005, US EPA Office of Compliance, Washington, DC.

US EPA (2001) ECOTOX Database System. Prepared for US EPA, Office of Research and Development, National Health and Environmental Effects Research Laboratory, Mid-Continent Ecology Division (MED), Duluth, Minnesota by OAO Corporation, Duluth, Minnesota. Contract 68-W5-0065, April 2001.

van Dijk, J. and Keukens, H.J. (2000) The stability of some veterinary drugs and coccidiostats during composting and storage of laying hen and broiler faeces. In van Ginkel, L.A. and Ruiter, A. (Eds.) Residues of Veterinary Drugs in Food. Proceedings of the Euroresidue IV conference, Veldhoven, The Netherlands, 8-10 May, 2000.

van Tonder, E.C., de Villiers, M.M., Handford, J.S., Malan, C.E.P. and du Preez, J.L., (1996) Simple, robust and accurate high-performance liquid chromatography method for the analysis of several anthelmintics in veterinary formulations. *Journal of Chromatography A*, **729**, 267-272

Velagaleti, R.R., Davis, M.L. and O'Brien, G.K. (1993) The bioavailability of 14C-sarafloxicin hydrochloride in three soils and a marine sediment as determined by biodegradation and sorption/desorption parameters. Poster presented at the American Chemical Society E-Fate meeting, 28th March, 1993.

Velagaleti, R. and Gill, M. (in press) Degradation and depletion of pharmaceuticals in the environment. In Daughton, C.G. and Ternes, T.A. (Eds) Proceedings of the American Chemical Society. Issues in the analysis of environmental endocrine disruptors. San Francisco, CA, 27 March, 2000.

VICH (unpublished) Analysis of data and information to support a PEC soil trigger value for Phase I.

VICH (2000) Environmental impact assessment (EIAs) for veterinary medicinal products (VMPs) – Phase 1. VICH GL6 (Ecotoxicity Phase 1), June 2000, For Implementation at Phase 7.

Vink, K., Dewi, L., Bedaux, J., Tompot, A., Hermans, M. and VanStraalen, N.M. (1995) The importance of the exposure route when testing the toxicity of pesticides to saprotrophic isopods. *Environmental Toxicology and Chemistry*, **14**, 1225-1232.

Virtue, W.A. (1992) A survey of sheep dipping installations and practices in the Tweed River Purification Board area. Scotland and Northern Ireland Forum for Environmental Research Sheep-dip Seminar, 11 November 1992. Perth, Scotland, 1992.

Virtue, W.A. and Church, A.M. (1993) A survey of sheep-dipping practices in the River Tweed Catchment. *Journal of the Chartered Institute of Water and Environmental Management*, **7**, 395-403.

Virtue, W.A. and Clayton, J.W. (1997) Sheep dip chemicals and water pollution. *The Science of the Total Environment*, **194/195**, 207-217.

VMD (2000) Changing the legal classification in the United Kingdon of a veterinary medicinal product. VMD Guidance Note, AMELIA 17, September 2000.

VMD (2001) Veterinary medicinal products (dips, injectables, pour ons ans sprays) authorised in the UK for use as ectoparasiticides in sheep. Veterinary Medicines Directorate, January 2001.

VMD (2001a) Sales of antimicrobial products used as veterinary medicines and growth promoters in the UK in 1999. Report obtained from VMD website.

VMD (2001b) Code of practice on the responsible use of animal medicines. Veterinary Medicines Directorate. Obtained from web site: http://www.vmd.gov.uk/old_vmd_web_pages/code of practice.pdf

Walker, D.K. and Fenner, K.S., (2000) A sensitive method for the measurement of the novel pet endectomide, selamectin (UK-124,114), in dog and cat plasma by chemical derivatisation and high-performance liquid chromatography with fluorescence detection. *Journal of Pharmaceutical and Biomedical Analysis*, **24**, 105-111.

Wall, R. and Strong, L. (1987) Environmental consequences of treating cattle with the antiparasitic drug ivermectin. *Nature* **327**, 418-421.

Warman, P.R. (1980) The effect of amprolium and aureomycin on the nitrification of poultry manure-amended soil. *Journal Soil Science Society of America*, **44**(6), 1333-1334.

Warman, P.R. and Thomas, R.L. (1981) Chlortetracycline in soil amended with poultry manure. *Canadian Journal of Soil Science*, **61**(1), 161-163.

Webb, S.F. (2001) A data-based perspective on the environmental risk assessment of human pharmaceuticals I – collation of available ecotoxicity data. In: Kümmerer, K. (Ed.), Pharmaceuticals in the Environment - Sources, Fate, Effects and Risks. Springer-Verlag, Germany.

Weereasinghe, C.A. and Towner, D. (1997) Aerobic biodegradation of virginamycin in soil. *Environmental Toxicology and Chemistry*, **16**(9), 1873-1876.

Wigman, L.S., Darrington, R.T. and Young, J.W. (1998) An accurate procedure for the analysis of azithromycin in ferret feces using solid phase extraction and HPLC, *Journal of Liquid Chromatographic and Related Technology*, **21**(6), 819-828.

Wollenberger, L., Halling-Sørensen, B. and Kusk, K.O. (2000) Acute and chronic toxicity of veterinary antibiotics to Daphnia magna. *Chemosphere*, **40**(7), 723-730.

WRc-NSF (2000) The development of a model for estimating the environmental concentrations (PECs) of veterinary medicines in soil following manure spreading (Project Code VM0295). Final Project Report to MAFF.

Wright, D.H., Herman, V.K., Konstantinides, F.N. and Rotschafer, J.C., (1998) Determination of quinolone antibiotics in growth media by reversed-phase high-performance liquid chromatography. *Journal of Chromatography A*, **709**, 97-104.

Yeager, R.L. and Halley, B.A. (1990) Sorption/desorption of [14C] efrotomycin with soils. *Journal of Agricultural and Food Chemistry*, **38**, 886-890.

Yorke, J.C. and Froc, P., (2000) Quantitation of nine quinolones in chicken tissues by high-performance liquid chromatography with fluorescence detection. *Journal of Chromatography A*, **882**, 63-77.

GLOSSARY OF TERMS

Abiotic degradation

Degradation of a compound via purely physical or chemical mechanisms. Examples include *hydrolysis* and *photolysis*.

Acute toxicity

Ability of a substance to cause adverse effects on an organism within a short period following dosing or exposure.

Adsorption

A process in which a solute becomes physically associated with a solid sorbent by a process equivalent to the sorbate's condensation onto the surface(s) of the sorbent.

Aminoglycosides

A group of broad spectrum antibiotics active against many aerobic gram-negative and some gram-positive bacteria. They are mostly produced by fungi and contain an amino sugar, and amino-or guanido-substituted inositol ring which are attached by a glycosidic linkage to a hexose nucleus resulting in a polycationic and highly polar compound. They inhibit bacterial protein synthesis by binding to a site on the 30S ribosomal subunit thereby altering codon anticodon recognition. Common examples are streptomycin, gentamicin, and neomycin.

Analgesic

An agent that alleviates pain without causing loss of consciousness.

Anthelmintic

A compound that kills or expels parasitic intestinal worms (helminths) and flukes.

Antibiotic

Compound isolated from one living organism or produced synthetically that kills or inhibits the growth of other organisms. Antibiotics may have antibacterial, antifungal, antiviral, antiparasitic, or even anticancer activity. The term is loosely used as a synonym for more specific categories such as anticancer, antimicrobial, or antibacterial drug.

Anticoccidial

A chemical agent effective against the control of infections of the intestinal tract caused by single cell parasites. Used in all areas of livestock farming, especially poultry rearing, to prevent and control infections.

Antifungal agents

Agents destructive to fungi, suppressing their growth or reproduction, and effective against fungal infections. They differ from industrial fungicides, in that they are restricted to action against fungi present in human or animal tissues.

Antimicrobial

A drug for killing microorganisms, or suppressing their multiplication or growth.

Antiparasitic

A substance or chemical which kills parasites. May be sub-divided into the following therapeutic categories: antinematodal, anticestodal or antitrematodal, antiprotazoal or insecticide.

Amphenicols

A group of compounds active against both gram-positive and gram-negative bacteria. Derived from some strains of *Streptomyces venezuelae*, or synthetically prepared they are active against both gram-positive and gram-negative bacteria and exert their action by targeting the bacterial ribosome thus inhibiting the bacterial protein biosynthesis. Includes the compounds chloramphenicol, thiamphenicol and florfenicol. Chloramphenicol was used in veterinary medicine but it is now forbidden in EC in animal husbandry.

Aquaculture

The propagation and rearing of aquatic species in controlled or selected environments.

Bambermycins

Bambermycins are an antibiotic complex containing principally moenomycin A and C and which is obtained from *Streptomyces bambergiensis*. Bambermycin is used as a feed additive in veterinary medicine to promote growth.

Barbiturate

A widely used group of sedative drugs made from barbituric acid.

beta-LACTAMs

The beta-lactam family of antibiotics includes many of the most heavily used antibacterials in clinical medicine. All members of the family consist of a beta-lactam ring and a carboxyl group. They are active against both gram-positive and gram-negative bacteria and inhibit bacterial cell wall synthesis. The majority of clinically useful beta-lactam belong either to the

penicillin or cephalosporin group. Other beta-lactams include the monobactams and beta-lactamase inhibitors (e.g., clavulanic acid).

Bioaccumulation

Progressive increase in the amount of a substance in an organism or part of an organism which occurs because the rate of intake exceeds the organisms ability to remove the compound from the body.

Bioavailabilty

Extent to which a compound residue can be taken up into an organism from its food and environment, and the rate at which this occurs.

BioConcentration Factor (BCF)

The ratio of the test substance concentration in (part of) an organism (e.g., fish, plant) to the concentration in a medium (e.g., water, soil) at steady state.

Biodegradation

The transformation of a material resulting from the complex enzymatic action of microorganisms (e.g., bacteria, fungi). Usually leads to the disappearance of the parent structure and to the formation of smaller chemical species, some of which are used for cell anabolism. Although typically used with reference to microbial activity, it may also refer to general metabolic breakdown of a substance by any living organism.

Chemotherapeutant

Any defined chemical (drug) used to treat disease caused by an invading organism, e.g., bacteria, virus, protozoan, cancer cells or metazoan.

Cephalosporin derivatives

A large class of semisynthetic antibiotics similar both chemically and in their mode of action to penicillin's and derived from Cephalosporin C, a natural antibiotic. The active nucleus consists of a six-membered dihydrothiazine ring fused to a beta-lactam ring. Cephalosporins have some desirable qualities that are generally deficient in penicillins. They inhibit the synthesis of the bacterial cell wall and most are resistant to degradation by certain bacterial enzymes. The most recently synthesised cephalosporins have good activity against gram-positive and gram-negative bacteria.

Chronic toxicity

Capacity for a compound to produce injury following chronic exposure or to produce effects that persist whether or not they occur immediately upon exposure or are delayed.

Degradation

Process by which a compound is broken down to simpler structures through biological or abiotic mechanisms.

Desorption

Depletion of one or more sorbed components in an interfacial layer.

Diaminopyrimidines

Includes the compound trimethoprim, an antibacterial agent that, like sulfonamides, inhibits the bacterial folic acid synthesis, but at a different stage in the metabolic pathway. It has a similar spectrum of activity to the sulfonamides and is given alone or in conjunction with a sulfonamide. Trimethoprim is active against a wide range of microorganisms including *E. Coli* and some Klebsiella, Proteus and Staphylococcus species.

Digestive enhancers

Also called performance enhancers or antibiotic growth promoters, digestive enhancers are compounds that are added to animal fed to improve feed conversion capability and hence growth rates of an animal. Includes antimicrobial compounds and some hormones.

Disappearance time 90 (DT_{90})

Time required for concentrations of a material to decrease to 10% of initial values (e.g., from 0.6 mg kg^{-1} to 0.06 mg kg^{-1}) (units:days).

Ectoparasiticide

Antiparasitic agent used for the treatment of external parasites.

Endectocide

Antiparasitic agent used to control both external and internal parasites.

Endoparasiticide

Antiparasitic agent used for the treatment of internal parasites.

Environmental introduction concentration ($EIC_{aquatic}$)

The calculated initial concentration of a veterinary medicinal product released to surface water from an aquaculture facility. For calculating the $EIC_{aquatic}$ a total residue concept is adopted.

Glycopeptides/polypeptides

The glycopeptides have a very complex structure and are poorly resorbed by the gastrointestinal tract. Glycopeptides disturb the peptidiglycan synthesis and have then the same effect as the β-lactams but their site of action is different and is upstream the site of action of the β-lactams. The parent compound of the Glycopeptide family is the vancomycin. Avoparcin is a glycopeptide antibiotic produced by *Amycolatopsis coloradensis* (*Streptomyces candidus*). It is exclusively used as a feed additive in veterinary medicine to promote growth. Vancomycin is used in veterinary medicine but it has been also used as a feed additive in animal husbandry.

Half-life (disappearance time 50) (DT_{50})

Time required to reduce by one-half the concentration of a material in a medium (e.g., soil or water) or organism (e.g., fish tissue) by transport, degradation, transformation, or depuration (units:days).

Hydrolysis

Reaction in which a chemical bond is cleaved and a new bond formed with the oxygen atom of a molecule of water.

Limit of detection (LOD)

Lowest concentration of a compound residue in a defined matrix where positive identification can be achieved using a specific method.

Lincosamides

Lincosamides are a small group of antibiotics active against many gram-positive bacteria and also against some protozoal organisms. They are generally inactive against gram-negative bacteria but are synergistic with aminoglycosides against these bacteria. Lincosamides are inhibitors of bacterial protein biosynthesis, they block the bacterial ribosomes similarly to macrolides.

Lowest observed effect concentration (LOEC)

The lowest concentration of a material used in a toxicity test that has a statistically significant adverse effect on the exposed population of test organisms compared with the controls.

Macrolides

A group of antibiotics produced by various strains of Streptomyces that have a complex macrocyclic structure. Used clinically as broad spectrum antibiotics, particularly against gram-positive bacteria. The macrolides target the bacterial ribosome and inhibit the bacterial protein biosyntheisis.

Macrolide endectins

A group of compounds that possess broad spectrum of antiparasitic activity against nematodes and arthropods. Used to control filarids, gastrointestinal parasites, lungworms and infective skin parasites amongst others. They comprise of the avermectin class of compounds and produce flaccid paralysis in parasites.

Median effective concentration (EC_{50})

Statistically derived concentration of a compound in an environmental medium expected to produce a certain effect in 50% of the test organisms in a given population under defined conditions.

Median lethal concentration (LC_{50})

Statistically derived concentration of a compound in an environmental medium expected to kill 50% of test organisms in a given population under defined conditions. Often expressed as a time-dependant value (e.g., 24-h or 96-h LC50; the concentration estimated to be lethal to 50% of the test organisms after 24 or 96 h of exposure). The LC50 may be derived by observation, interpolation, or by calculation.

Median lethal dose (LD_{50})

Statistically derived dose of a compound expected to kill 50% of test organisms in a given population under a defined set of conditions. Normally expressed as mg of test material per kg of body weight of the organism.

Mesocosm

Man-made outdoor study system containing associated organism and abiotic components that is large enough to be representative of a natural ecosystem, yet small enough to be experimentally manipulated.

Minimum inhibitory concentration (MIC)

The lowest concentration of a test chemical that will inhibit the growth of test micro-organisms *in vitro*.

Microcosm

Man-made, generally indoor study system containing associated organism and abiotic components that is large enough to be representative of a natural ecosystem, yet small enough to be experimentally manipulated.

No observed effect concentration (NOEC)

The highest concentration of a material in a toxicity test that has no statistically significant adverse effect on the exposed population of test organisms compared to the controls.

Nonsteroidal anti-inflammatory drug (NSAID)

A large group of anti-inflammatory agents that work by inhibiting the production of prostaglandins.

Octanol-water partition coefficient (K_{ow})

The ratio of a chemical's solubility in *n*-octanol and water at steady state; also expressed as *P*. The logarithm of *P* or K_{ow} (i.e., log *P* or log K_{ow}) is used as an identification of a chemical's propensity for bioconcentration by organisms.

Organophosphates

Organophosphate compounds cover a huge range of chemicals with a very wide spectrum of physical and chemical properties. They act by forming irreversible phosphoryl-acetyl-cholinesterase intermediates, thereby inactivating the enzyme that terminates neurotransmission at cholinergic junctions. Some are highly acutely toxic, but they usually are not persistent in the environment.

Photolysis

Chemical reaction caused by indirect or direct sunlight in which a bond is cleaved.

Phytotoxicity

Toxicity of environmental pollutants determined on the growth and survival of plants.

Pleuromutilin derivatives

Diterpene antimicrobials active against gram-positive micro-organisms and mycoplasma by inhibiting protein sythesis at the ribosomal level. Includes the compounds tiamulin and valnemulin used in veterinary medicine for the treatment and prophylaxis of dysentery, pneumonia and mycoplasmal infections in pigs and poultry.

Predicted environmental concentration (PEC)

Predicted concentration of a material within an environmental compartment based on estimates of quantities released, discharge patterns and inherent disposition of the pesticide (fate and distribution) as well as the nature of the specific receiving ecosystem.

Quinolones

A family of synthetic antibiotics structurally related to naladixic acid and principally active against gram-negative bacteria. The mode of action is not fully understood, but it has been demonstrated that they inhibit the action of bacterial DNA gyrase enzymes. The fluoroquinolones are very active against aerobic gram-negative organisms and less active against gram-positive bacteria. Their activity against anaerobics is poor.

Run-off

The portion of a material (precipitation or other) on an area that is discharged from the area through stream channels. That which is lost without entering the soil is called surface run-off and that which enters the soil before reaching a stream channel is called subsurface run-off or seepage flow.

Soil organic partition coefficient (K_{oc})

Ratio of a compound concentration sorbed in the organic matter component of soil or sediment to that in the aqueous phase at equilibrium.

Soil partition coefficient (K_d)

Experimental ratio of a chemical's concentration in the soil to that in the aqueous (dissolved) phase at equilibrium. It is valid only for the specific concentration and solid/solution ratio of the test. The K_d is a distribution coefficient reflecting the relative affinity of a compound for adsorption by soil solids and its potential for leaching movement through soil.

Sub-lethal

Below the concentration that directly causes death. Exposure to sublethal concentrations of a material may produce less obvious effects on behaviour, biochemical and/or physiological function, and histology of organisms.

Sulphonamides

Sulfonamides are antimicrobial agents used extensively in animal husbandry for the treatment of infections and at sub-therapeutic doses for the promotion of growth in animals for food production. They are a group of drugs derived from sulphanilamide (a red dye) and act by blocking folic acid synthesis from p aminobenzoic acid (PABA), because they are competitive analogues. Sulphonamides are active against gram-positive cocci (hemolytic streptococci,

pneummocci and some staphylococci), some gram-negative bacteria (Pastuerella spp., E. coli and Salmonella spp.) and a number of protazoa.

Synthetic pyrethroids

Synthetic pyrethroids are compounds derived from pyrethrum, a natural insecticide that is formed by some plants. The characteristic molecular group of pyrethroids is the cyclopropane-carboxyl-group combined by an esterbond to an aromatic group. Pyrethroids act by affecting a range of neurocells of the central and peripheral nervous system. The neurotoxic effects disturb the behaviour and physiology of the target organism resulting in paralysis.

Tetracyclines

Antibacterial compounds that are commonly used for the prevention and/or treatment of diseases in livestock production. As a feed additive in subtherapeutic doses, tetracyclines contribute to the maintenance of optimal health and thus promote growth in food producing animals. Represent broad spectrum antibiotics that blocks binding of aminoacyl tRNA to the ribosomes of both gram-positive and gram-negative organisms (and those of organelles). Classical tetracyclines are derived from *Streptomyces spp*., but newer derivatives are semisynthetic.

Topical

Pertaining to a particular surface area, as a topical anti-infective applied to a certain area of the skin and affecting only the area to which it is applied.

APPENDIX A REPORT OF THE VETERINARY MEDICINES WORKSHOP

Report of the Veterinary Medicines in the Environment Workshop
29th March 2001, Burlington Hotel, Birmingham.

Background: In order to gain a greater understanding of the environmental risks associated with the use of veterinary medicines the Agency have recently funded an R & D project to review available data on exposures routes, environmental fate, behaviour and effects of all generic groups of veterinary medicines. The findings of this review were presented at a workshop for Agency staff and key external stakeholders on the 29th March 2001.

Aim of workshop: The purpose of the workshop was to present, and gain feedback on, the findings of the review, conclusions and recommendations. The outcome of the workshop would be used to shape the final report.

Summary: The day started with a brief presentation introducing the R & D project and the reasons why the Agency had funded a review of veterinary medicines in the environment. Carol Long (VMD) then provided an overview of the regulatory process for veterinary medicines, including an update on current developments in the global harmonisation (VICH) of guidelines for the conduct of environmental risk assessments of veterinary medicines. Andrew Forbes (Merial Animal Health) presented an industry view point on the environmental risk assessment of veterinary medicines, looking in particular at endectocides.

An overview of the Agency's review of veterinary medicines in the environment was presented by Alistair Boxall (Cranfield Centre for EcoChemistry) together with the recommendations and conclusions from the review. The discussion that followed raised questions over the reliability of the data collected and the quality assurance procedures employed. It was recognised that particularly for data on persistence, where many of the studies had been conducted a long time ago, the data may not be as good quality as would be produced today. Data had only been sourced from the open literature and so there were quite a few gaps and full study details were not always provided. For example, terrestrial ecotoxicity data was limited and only available for a few active ingredients. The possibility of using a QSAR approach to fill data gaps was suggested. Recent work using such an approach for human pharmaceuticals has indicated that the currently available QSARs may not be of significant value at the present time.

Data on environmental fate, behaviour and effects are already submitted to the regulatory authority (VMD) and it was felt by some that risks to the environment were already adequately identified and address through the regulatory process. However, a requirement for environmental data as part of the authorisation for veterinary medicines was only introduced quite recently. Once authorised a product is then reviewed every five years. Environmental data is thus only now being collected for those veterinary medicines which were authorised before the requirement for environmental data came into force.

It was highlighted that much of the data that has been produced is commercially confidential and thus not widely available. Because of this, with the exception of companies involved and the VMD, little is known regarding the environmental impact of many veterinary medicines. It was stressed that the purpose of the Agency's review is to inform monitoring programmes and identify and prioritise veterinary medicines of possible concern. If environmental concerns were identified the Agency would be seeking further information and reassurance from VMD and the industry.

Industry representatives were supportive of the Agency's approach and offered their assistance. VMD explained that they have an agreement with the Agency to provide data upon request (after first seeking agreement from the company involved). It was also noted there is an expectation that the current blanket data protection approach will be removed via the Freedom of Information Act over the next few years.

With regards the prioritisation process used in the review, surprise was expressed that products used in aquaculture were not listed in the top 50, when these were known to be of concern. Whilst data is available on these chemicals not all of the issues concerning the use of fish farm chemicals have been addressed. The usage data on which the prioritisation process has been based has not included products supplied via agricultural merchants and so has not included products such as sheep dips and anthelmintics. This will need to be addressed further. The need for a 'reality check' on any list produced was acknowledged.

The possibility of taking a different view point and using ecosystem receptors to identify problems as an alternative prioritisation mechanism was suggested.

In the afternoon, participants were involved in one of three syndicate groups: usage/exposure pathways, aquatic environment and terrestrial environment. Each group was given two questions to answer. A summary of the key points from each syndicate group are listed below.

(i) Usage/Exposure pathways syndicate group.

Q 1. Have we got the right data ?
The usage data obtained from IMS Health is not a comprehensive survey as it only covers medicines prescribed by vets. Other routes of supply such as the AHDA (agricultural merchants etc.) are not included. This explains the discrepancy between VMDs usage data for antibiotics and data derived from the IMS Health data (medicated feedstuffs have not been included in the IMS Health data). VMD have data on the sales of organosphosphorous compounds in sheep dip and this should be incorporated onto the review.

The main groups missing from the usage list are synthetic pyrethroids, avermectins and in-feed coccidiostats. Hormones were raised as another possible group for further consideration. Whilst they are now banned as growth promoters they still have other uses and their significance should be assessed. It was recommended that NOAH should be contacted for further information on this point.

Q2. Has the project identified the most significant pathways ?
The use of veterinary medicines in aquaculture was considered to be a significant route of exposure to the environment, because of the direct addition, in many instances, of medicines into the environment.

The route of administration should be considered when assessing environmental exposure. For example, pour-on products are much more likely to enter the environment directly than an injectable product.

The group identified inappropriate disposal of spent dip, unused products and containers as a potentially significant exposure pathway, but was unsure how the scale and significance of this exposure route could be addressed.

The issue of the significance of treatment of companion animals, for example treating dogs with topical flea treatments was raised. In general this is thought to be a minor exposure route but is this really the case?

There was speculation over the statement that manufacture of veterinary medicines is low risk in terms of environmental exposure. This exposure route does appear to be tightly regulated but the issue could be addressed further through discussion with NOAH. A list of all licensed manufacture sites is available on the Medicines Control Agency web-site and may be useful source of further information.

(ii) Aquatic environment

Q1. Which groups of veterinary medicines are of most concern to the aquatic environment and why ?
Q2. Are these concerns adequately addressed through current regulatory and non-regulatory controls ?

Fish farm medicines (especially sea lice treatments), all compounds with insecticidal activity and compounds which are used to treat whole herds/flocks were identified as the main concerns for the aquatic environment.

Insecticides are generally very toxic to aquatic life and broad spectrum insecticides can impact on biodiversity. In addition to their toxicity, the route of administration of many insecticides can lead to significant environmental exposure (e.g. sea-lice treatments in aquaculture, sheep dipping). Treatment of whole herds/flocks of animals at the same time will lead to greater environmental exposure. Some medicines are used prophylactically and so release to the environment may be continuous. The question of what is a significant in terms of number of animals treated (i.e. what should the definition of a whole herd/flock be) was raised.

The group raised concerns over the current regulatory practice of using exposure trigger values to determine whether or not an environmental risk assessment is required. It was felt that a more appropriate approach would be to consider the exposure and effects of each individual compound and determine the risk accordingly.

There is evidence to suggest levels of faecal coliforms in some coastal waters are increasing, or at least remaining constant, despite the introduction of more sewage treatment. Run-off from agricultural land spread with slurry is thought to be the cause of this. This would indicate that excreted veterinary medicines and their metabolites may also be entering the aquatic environment via this route. Concern was expressed over handling of slurry in general. The group felt that further investigation of this issue as a route of veterinary medicines to the environment should be considered. (Comment from ABAB – we have just detected oxytetracycline in a drainflow sample soon after slurry application – based on it's Koc we would not expect OTC to be mobile, the most likely explanation is that the particle-associated substance is being transported through macropores to the field drains).

The prioritisation approach adopted for the purposes of the review had considered that immobile compounds were of low risk to the aquatic environment, but the group queried how immobile such compounds really were, in terms of transport of suspended particulate matter via surface run-off and soil erosion.

For aquaculture in particular, the group had a number of additional comments. The spatial extent of aquaculture and hence the national significance was unknown. It was felt there was a lack of knowledge over impacts on biodiversity as a consequence of the use of fish farm medicines. The presence of farms for the purpose of coarse fish re-stocking was also unknown. In addition, concern was expressed over the possible indirect effects (primarily on human health) as a result of consumption of shellfish contaminated during treatment of fish locally.

The issue of disposal of used containers was raised. It was felt that there was little regulatory control as farmers are exempt from waste regulations. It was noted that the issue of agricultural waste was currently under consultation. VMD requested good advice from the Agency for inclusion onto product labels.

Concern over possible 'off label' uses of veterinary medicines was raised. VMD explained they have a Residues Surveillance program with the specific purpose of monitoring for the use of products not authorised for use in fish farms.

The issue of potential for groundwater contamination was discussed and it was felt that this should also be considered along with the potential for humans to be exposed to veterinary medicines in groundwater.

(iii) Terrestrial environment

Q1. Which groups of veterinary medicines are of most concern to the aquatic environment and why ?
Q2. Are these concerns adequately addressed through current regulatory and non-regulatory controls ?
Substances perceived to be of concern by this group were as follows:

Organophosphate and synthetic pyrethroid compounds. Exposure routes, e.g. disposal of used sheep dip, route of administration (topical treatments) and possibility of high concentrations in manure are significant. Concern was also expressed over indirect effects on birds and other organisms through the consumption of contaminated insects, and/or loss of prey items.

Antibiotics. These compounds are widely available (e.g. feed additives, growth promoters). They can be very persistent (DT_{50}'s > 300 d) and bind strongly to soil. It was noted that metabolites typically behave differently in the environment to the parent compound because of different physico-chemical properties. Metabolites were considered to be as important as the parent compound when considering environmental risk. The group questioned whether the presence of antibiotics in soil may interact with the degradation rates of any pesticides used subsequently on those soils.

Endocrine disrupting chemicals. The group felt sources of potential endocrine disrupting chemicals warranted further consideration

Anthelmintics. The need to consider both direct and indirect affects was raised. It was noted that this group should not be restricted to macrocyclic lactones but consider other chemical groups such as benzimidazoles.

Additional general comments the group had included noting that bioaccumulation potential was missing from the criteria used in the review to prioritise concerns. Concern was also expressed over the way the prioritisation approach was quite 'broad brush', using data for a few members of the group which were not necessarily representative of the whole group. The need for a 'safety net' in the Agency's prioritisation process was recognised. The possibility of synergistic effects was also raised, although it was felt that this was not generally an issue of major concern.

The importance of nature conservation and the extent to which the regulatory approach should consider special, sensitive species was also raised. The group felt that indirect effects were as important as direct effects and felt that the VICH guidelines currently under discussion should take account of this. This issue is currently under discussion in other areas such as pesticides and GMO's.

General conclusions

- Participants were supportive of the Agency's need to conduct the review.
- Industry and VMD offered to supply additional information/data upon request.
- It was recognised that it can be difficult to prioritise chemicals as there will always be exceptions to every rule. For this reason a 'reality check' will be necessary once a list is compiled.
- Factors to consider further in the prioritisation process included bioaccumulation potential, immobility (wrt transport of SPM), validity of the 'broad brush' approach adopted and the alternative approach of using ecosystem receptors to prioritise concerns.
- The principal exposure pathways for veterinary medicines in the environment had been identified in the review. Route of administration is an important consideration in

assessing environmental exposure.

- There is no-one single comprehensive usage survey for all veterinary medicines, but several different sources each providing useful data and representing different aspects of veterinary medicine usage.
- Both 'off-label' use and inappropriate disposal of unused product and contaminated containers were raised as potential areas of concern, but scale and significance of the problem were unknown.
- Veterinary medicines perceived to be of most concern were organophosphate and synthetic pyrethroids (especially their use in aquaculture and sheep dipping), antibiotic and anthelmintic compounds (especially when used to treat whole herds/flocks) and compounds used prophylactically, which may result in continuous low level release into the environment.
- Veterinary medicines as a source of endocrine disrupting chemicals into the environment should be investigated further.
- Indirect effects were considered as important as direct effects.
- Metabolites were considered to be as important as the parent compound when considering environmental risk.

The final draft report of the review will be circulated for further comment to all participants of the workshop and those invited but unable to attend. The final report will be produced in June 2001.

APPENDIX B CALCULATIONS FOR USAGE

Synthetic pyrethroids

The concentration of diazinon in currently approved products is 16% and one part of the preparation is mixed with 400 parts water (VMD, 2001).

The concentration of the synthetic pyrethroids in dips ranges from 6 – 10% and one part of preparation is mixed with 400-1400 parts of water (VMD, 2001).

Assuming the same number of sheep are treated by each dip type and taking the dilution of 1 in 400 and the top concentration, a rough estimate of usage can be obtained using the following calculation:

10%/16% x 7.4 million sheep/40 million sheep x 50.2 tonnes = 5.8 tonnes

Macrocyclic lactones

The concentration of the active substance in a macrocyclic lactone injection is 1% (VMD, 2001). The dose applied to an animal is dependent on body weight. Using an average lamb weight of 36 kg and an average sheep weight of 82 kg and the number of sheep treated by injection, the total amount of macrocyclic lactones can be calculated, i.e.:

1. for a lamb the amount administered is 10 mg, assuming 9 million lambs are treated then the total active used will be 90 kg

2. for a sheep the total amount administered is 20 mg, assuming 9 million sheep are treated then the total amount of active used will be 180 kg

3. the amount used in the UK is therefore likely to lie between 90 and 180 kg.

APPENDIX C RELATIVE RANKING OF USAGE OF VETERINARY MEDICINES IN THE UK

Therapeutic class	Chemical group	Animals treated	Usage (Tonnes)	Source	Major usage substances	Source	Completeness of data (usage)
Antimicrobials	tetracyclines	cattle, pigs, poultry, sheep, fish	192	VMD	oxytetracycline chlortetracycline tetracycline	IMS	*
Antimicrobials	potentiated sulphonamides	cattle, pigs, poultry, sheep, fish	82	VMD	sulphadiazine sulphadimidine trimethoprim baquiloprim	IMS	*
Endoparasiticides - coccidiostats	-	cattle, game birds, pigs, poultry, sheep	66	VMD	amprolium clopidol dimetridazole lasalocid sodium maduramicin narasin nicarbazin robenidine hydrochloride	IMS	***
Antimicrobials	β-lactams	cattle, pigs, poultry, sheep, fish	52	VMD	amoxicillin procaine penicillin procaine benzylpenicillin clavulanic acid	IMS	*

[1] estimates based on usage of organophosphate sheep dips; * complete dataset; ** prediction based on complete dataset; *** dataset may be incomplete so estimates of usage may be lower than actual values and major compounds may have been omitted.

Therapeutic class	Chemical group	Animals treated	Usage (Tonnes)	Source	Major usage substances	Source	Completeness of data (usage)
Ectoparasiticides - sheep dips	organophosphates	sheep	50.2	VMD	diazinon	VMD	*
Antimicrobials	macrolides	cattle, pigs, poultry, sheep	29	VMD	tylosin	IMS	*
Growth promoters	-	cattle, pigs, poultry	28	VMD	monensin salinomycin sodium flavophospolipol	IMS	***
Antimicrobials	aminoglycosides	cattle, pigs, poultry, sheep	20	VMD	dihydrostreptomycin neomycin apramycin avilamycin flavomycin	IMS	*
Neurological preparations - general anaesthetics	-	companion animals, horses	13.8	IMS	isoflurane halothane	IMS	*
Endoparasiticides - wormers	pyrimidines	cattle, sheep, horses, companion animals	6.2	IMS	morantel pyrantel emboate	IMS	***

[1] estimates based on usage of organophosphate sheep dips; * complete dataset; ** prediction based on complete dataset; *** dataset may be incomplete so estimates of usage may be lower than actual values and major compounds may have been omitted.

Therapeutic class	Chemical group	Animals treated	Usage (Tonnes)	Source	Major usage substances	Source	Completeness of data (usage)
Ectoparasiticides - sheep dips	pyrethroids	sheep	1.7-5.8	VMD[1]	cypermethrin flumethrin	VMD[1]	**
Endoparasiticides - wormers	azoles	cattle, sheep, goats, pigs, horses, companion animals	4.1	IMS	triclabendazole fenbendazole levamisole	IMS	***
Endoparasiticides - wormers	macrolide endectins	cattle, sheep, goats, pigs, horses, companion animals	4.1	IMS	ivermectin	IMS	***
Antimicrobials - other antibiotics	-	pigs, fish, companion animals	3.4	IMS	cephalexin florfenicol tilmicosin oxolinic acid	IMS	***
Neurological preparations - euthanasia products	-	cattle, companion animals, small farm animals	2.7	IMS	pentobarbitone sodium	IMS	*

[1] estimates based on usage of organophosphate sheep dips; * complete dataset; ** prediction based on complete dataset; *** dataset may be incomplete so estimates of usage may be lower than actual values and major compounds may have been omitted.

Therapeutic class	Chemical group	Animals treated	Usage (Tonnes)	Source	Major usage substances	Source	Completeness of data (usage)
Neurological preparations - local anaesthetics	-	cattle, sheep, pigs, goats, horses, companion animals	2.4	IMS	procaine hydrochloride lido/lignocaine hydrochloride	IMS	***
Antimicrobials	pleuromutilins	cattle, pigs poultry	1.4	IMS	tiamaulin	IMS	***
Antimicrobials	lincosamides	cattle, pigs, poultry, sheep	1.4	IMS	lincomycin clyndamycin	IMS	**
Antimicrobials - antifungals	azoles	horses, companion animals	1.1	IMS	miconazole	IMS	*
Endoparasiticides - wormers	others	cattle, sheep, goats, horses	1.05	IMS	nitroxynil	IMS	***
Antimicrobials	fluoroquinolones	cattle, pigs, poultry, sheep, fish	1	VMD	enrofloxacin sarafloxacin	IMS	*
Antimicrobials - antifungals	others	horses	0.89	IMS	griseofulvin	IMS	*

[1] estimates based on usage of organophosphate sheep dips; * complete dataset; ** prediction based on complete dataset; *** dataset may be incomplete so estimates of usage may be lower than actual values and major compounds may have been omitted.

Therapeutic class	Chemical group	Animals treated	Usage (Tonnes)	Source	Major usage substances	Source	Completeness of data (usage)
Antimicrobials - antifungals	bigaunide/ gluconate	cattle, sheep, pigs, goats, horses, companion animals	0.83	IMS	chlorhexidine	IMS	***
Neurological preparations - tranquilisers	-	cattle, pigs, horses, companion animals	0.73	IMS	phenobarbitone	IMS	*
Anti-inflammatory preparations - NSAIDS	-	cattle, pigs, horses, companion animals	0.70	IMS	phenylbutazone caprofen	IMS	*
Neurological preparations - analgesics	-	cattle, pigs, horses, companion animals	0.67	IMS	metamyzole	IMS	*
Hormones	-	cattle, pigs, sheep, goat, companion animals	0.47	IMS	altrenogest progesterone medroxyprogesterone	IMS	*
Enteric preparations (inc. bloat remedies)	-	cattle, pigs, companion animals	0.4	IMS	dimethicone proloxalene	IMS	***

[1] estimates based on usage of organophosphate sheep dips; * complete dataset; ** prediction based on complete dataset; *** dataset may be incomplete so estimates of usage may be lower than actual values and major compounds may have been omitted.

Therapeutic class	Chemical group	Animals treated	Usage (Tonnes)	Source	Major usage substances	Source	Completeness of data (usage)
Endoparasiticides - antiprotozoals	-	cattle, sheep, poultry, pigeons	0.18	IMS	toltrazuril decoquinate diclazuril	IMS	***
Endectocides	macrocyclic lactone injections	sheep	0.09-0.18	VMD[1]	ivermectin doramectin moxidectin	VMD[1]	**
Ectoparasiticides - others	-	pigs, horses, companion animals	?	-	phosmet piperonyl butoxide	IMS	-
Ectoparasiticides - sheep dips	amidines	sheep	?	-	amitraz	VMD	-
Ectoparasiticides - spray and pour-ons for sheep	-	sheep	?	-	deltamethrin cypromazine cypermethrin	VMD	-
Ectoparasiticides - aquaculture treatments	-	fish	?	-	emamectin benzoate	-	-

[1] estimates based on usage of organophosphate sheep dips; * complete dataset; ** prediction based on complete dataset; *** dataset may be incomplete so estimates of usage may be lower than actual values and major compounds may have been omitted.

Therapeutic class	Chemical group	Animals treated	Usage (Tonnes)	Source	Major usage substances	Source	Completeness of data (usage)
Antiseptics	-	cattle, sheep, pigs, horses	?	-	insufficient information	-	-
Anti-inflammatory preparations	steroids	cattle, sheep pigs companion animals	?	-	insufficient information	-	-
Diuretics	-	cattle, horses, companion animals	?	-	insufficient information	-	-
Cardiovascular and respiratory treatments	-	cattle, sheep, pigs, companion animals	?	-	insufficient information	-	-
Locomotor treatments	-	cattle, companion animals	?	-	insufficient information	-	-
Immunological products	-	cattle, sheep, pigs, goats, poultry, fish companion animals	?	-	insufficient information	-	-

[1] estimates based on usage of organophosphate sheep dips; * complete dataset; ** prediction based on complete dataset; *** dataset may be incomplete so estimates of usage may be lower than actual values and major compounds may have been omitted.

APPENDIX D ANALYTICAL EXTRACTION METHODS

Compound	Media	Extraction Method	Reference
amprolium	chicken faeces	67% methanol – extractant filtered through fibreglass and purified using Sep Pak aluminium cartridge	van Dijk and Keukens, 2000
amprolium	chicken plasma	0.2-ml plasma plus 0.1-ml internal standard solution and 0.5-ml of 0.33 M perchloric acid solution vortex mixed in test tube for 30 sec, centrifuged for 10 min at 2150-g, supernatant separated and allowed to stand for 3 hours	Hamamoto *et al.,* 1997
azithromycin	ferret faeces	faeces dried under vacuum, extracted using 15-ml methylene chloride and shaking for 30-mins, 5-ml of extract loaded onto Baker 500-mg SPE silica gel cartridge, washed with 20-ml of methylene chloride and eluted with 8-ml of 0.1% TFA in water/methanol (70:30) and then diluted to 10-ml using acetonitrile/methanol/0.05M phosphate buffer at pH 7.5 (44:29:27)	Wigman *et al*., 1998
cefaclor	human serum and urine	serum: 5-ml of sample spiked with compound, 5-ml of 10% trichloroacetic acid added for deprotination, mixture blended in a vortex mixer, centrifuged at 3000-rpm for 15-mins, 1-ml of supernatant made up to 10-ml volume with water urine: 5-ml of sample spiked with compound, 5-ml methanol added, blended in a vortex mixer, centrifuged at 1500-rpm for 3-mins, 1-ml of supernatant made up to 10-ml volume with water	Hefnawy *et al*., 1999
cefadroxil	human serum and urine	serum: 5-ml of sample spiked with compound, 5-ml of 10% trichloroacetic acid added for deprotination, mixture blended in a vortex mixer, centrifuged at 3000-rpm for 15-mins, 1-ml of supernatant made up to 10-ml volume with water urine: 5-ml of sample spiked with compound, 5-ml methanol added, blended in a vortex mixer, centrifuged at 1500-rpm for 3-mins, 1-ml of supernatant made up to 10-ml volume with water	Hefnawy *et al*., 1999
cephalexin	human serum and urine	serum: 5-ml of sample spiked with compound, 5-ml of 10% trichloroacetic acid added for deprotination, mixture blended in a vortex mixer, centrifuged at 3000-rpm for 15-mins, 1-ml of supernatant made up to 10-ml volume with water urine: 5-ml of sample spiked with compound, 5-ml methanol added, blended in a vortex mixer, centrifuged at 1500-rpm for 3-mins, 1-ml of supernatant made up to 10-ml volume with water	Hefnawy *et al*., 1999

Compound	Media	Extraction Method	Reference
cephradine	human serum and urine	serum: 5-ml of sample spiked with compound, 5-ml of 10% trichloroacetic acid added for deprotination, mixture blended in a vortex mixer, centrifuged at 3000-rpm for 15-mins, 1-ml of supernatant made up to 10-ml volume with water urine: 5-ml of sample spiked with compound, 5-ml methanol added, blended in a vortex mixer, centrifuged at 1500-rpm for 3-mins, 1-ml of supernatant made up to 10-ml volume with water	Hefnawy *et al*., 1999
chlortetracycline	slurry treated soil water	100-g dried soil stirred with 100-ml of methanol containing 5% acetic acid at pH 2.8 for two hours then centrifuged at 5000g for 10 minutes and filtered, residue re-extracted with 50-ml of acidic methanol and extracts combined, evaporated under vacuum at 40°C and redissolved in 3-ml methanol 100-ml of water loaded onto Baker SDB 1 SPE cartridge, washed with ammonium acetate, eluted with methanol/acetic acid, evaporated to dryness and redissolved in 200-µl of methanol	Hamscher *et al*., 2000 Hamscher *et al*., 2000c
chlortetracycline	surface and ground water hog lagoon waste water	50-ml of sample pumped through on-line C18 SPE cartridge and then eluted directly onto column with mobile phase of 80% A: 0.1% trifluoroacetic acid in methanol/acetonitrile/water (2:7:91) 20% B: methanol	Meyer *et al*., 2000
ciprofloxacin	pig and rabbit plasma	samples centrifuged at 2000-g for 5-mins, 0.5-ml (pig) or 0.1-ml (rabbit) of supernatant applied to Sep-Pak C18 SPE cartridge followed by 0.25-ml of water, cartridge washed using 0.5-ml of water then 0.5-ml acetonitrile, dried and eluted with 0.1-ml (pig) or 0.15-ml (rabbit) of methanol containing 2% hydrochloric acid then 1.4-ml (pig) or 1.35-ml (rabbit) of water	Manceau *et al*., 1999
clopidol	chicken tissue	10-g of minced tissue mixed with 20-g sodium sulphate and 50-ml acetonitrile, homogenised for 2min at 10000-rpm and centrifuged for 5 min at 3000-rpm. Extract poured onto aluminium column, tissue re-extracted with further 50-ml acetonitrile and extracts combined, passed through aluminium column then anion exchange column in tandem, rinsed with 20-ml methanol and anion exchange column eluted with 20-ml 0.5% acetic acid/methanol, rotary evaporated to dryness at 60ºC and redissolved in 1-ml methanol	Pang *et al.,* 2000
clopidol	poultry feed	10-g of pulverised feed weighed into 250-ml glass jar, moistened with 5-ml water, 45-ml of water/dimethylformamide 5/95 added and shaken for 1 hour. 10-ml supernatant centrifuged for 5 min at 3000-rpm and 5-ml of this supernatant pipetted onto SPE Al-B aluminium column, first 1-ml of eluate discarded and next 2-ml collected for analysis	Dusi *et al.,* 2000

Compound	Media	Extraction Method	Reference
cypermethrin	soil and groundwater	10-g ground soil spiked with compound, passed through 55-mesh sieve and placed in extraction thimble. Extracted with n-hexane for 8 hours in soxhlet extractor at a flow ratio of 10 cycles/hour, extract rotary evaporated to dryness, redissolved in 10-ml acetonitrile and passed through Sep-Pak C18 cartridge, cartridge washed in 2-ml acetonitrile and eluates combined and evaporated to 1-ml under nitrogen. 500-ml water sample double extracted by shaking with two separate 50-ml aliquots of n-hexane for 2 min each, recombining extracts, passing through sodium sulphate and rotary evaporating to dryness and eluting with 1-ml of acetonitrile	Martínez Galera *et al.,* 1996
cypermethrin	water, sand and biological materials	water extracted twice with hexane at 10:1 ratio of water:hexane followed by 20:1 ratio, extracts combined and dried with sodium sulphate, evaporated to 10-ml and then further evaporated to 1-ml under nitrogen sand or biological materials homogenised, ground in 200-ml hexane and mixed for 30 min. Extract decanted and residue further washed with 50-ml hexane, combined extract concentrated to few ml and compound isolated by filtration on deactivated florisil with 7-ml hexane and eluate concentrated to 1-ml	Lutnicka *et al.,* 1999
deltamethin	water, sand and biological materials	water extracted twice with hexane at 10:1 ratio of water:hexane followed by 20:1 ratio, extracts combined and dried with sodium sulphate, evaporated to 10-ml and then further evaporated to 1-ml under nitrogen sand or biological materials homogenised, ground in 200-ml hexane and mixed for 30 min. Extract decanted and residue further washed with 50-ml hexane, combined extract concentrated to few ml and compound isolated by filtration on deactivated florisil with 7-ml hexane and eluate concentrated to 1-ml	Lutnicka *et al.,* 1999
diazinon	water and soil	water: 1000-ml water placed in 2000-ml Teflon separating funnel and extracted into 1000-ml cyclohexane by shaking for 30 seconds, organic layer removed and filtered into 200-ml TurboVap tube, process repeated using 50-ml cyclohexane which is combined with initial extract. Extract blown down in TurboVap to 0.5-ml under nitrogen at 40ºC, internal standard added and transferred to GC vial soil: sample air dried and ground into fine powder, 50-g placed in 250-ml Teflon bottle, 100-ml cyclohexane added, extracted ultrasonically for 15 minutes, filtered into 200-ml TurboVap tube, extract blown down in TurboVap to 0.5-ml under nitrogen at 40ºC, internal standard added and transferred to GC vial	Health and Safety Laboratories, 2001, pers.comm.
diazinon	river water	sample filtered to 0.45-µm, 100-ml of sample automatically pre-concentrated onto disposable pre-columns packed with 10-µm LiChrospher Si100 RP-18 SPE stationary phase, column transferred automatically to elution position in-line with analytical column and eluted with LC mobile phase (acetonitrile:0.05M ammonium formate)	Lacorte and Barceló, 1995

Compound	Media	Extraction Method	Reference
dimetridazole	poultry meat	4-g minced sample, with internal standard, 1.6-ml 0.5 M, pH 8.8 phosphate buffer added, vortex mixed for 20 sec, 8-ml ethyl acetate added, vortex mixed for 20 sec and shaken for 10 min, centrifuged for 10 min at 8000-g. 6.8-ml organic phase transferred to flask, evaporated to dryness under vacuum at 35ºC, residue mixed with 400-µl 0.2% formic acid and 400-µl of hexane/tetrachloromethane 1:1, mixture centrifuged for 2 min at 17300-g, aqueous phase transferred for analysis	Hurtaud-Pessel *et al.,* 2000
doramectin	cattle plasma	1-ml sample transferred into tube, 0.5-ml of 30% acetonitrile containing internal standard added, sample mixed, transferred onto 96-well SPE block, drawn through block, washed with 1-ml water drawn through block, transferred to 96-well deep polypropylene plate, 1-ml methanol added as eluant, drawn through block and then evaporated to dryness in deep well plate. 100-µl of 50% triethylamine in acetonitrile then 150-µl of 33% trifluoroacetic anhydride added to each well to give fluorescent derivative, volume reduced to 100-µl, 250-µl of 2.0 M ammonia in methanol added to each well, volume reduced to 100-µl, 100-µl acetonitrile added to each well and plate placed in autosampler for analysis	Harrison and Walker, 1998
enrofloxacin	pig and rabbit plasma	samples centrifuged at 2000-g for 5-mins, 0.5-ml (pig) or 0.1-ml (rabbit) of supernatant applied to Sep-Pak C18 SPE cartridge followed by 0.25-ml of water, cartridge washed using 0.5-ml of water then 0.5-ml acetonitrile, dried and eluted with 0.1-ml (pig) or 0.15-ml (rabbit) of methanol containing 2% hydrochloric acid then 1.4-ml (pig) or 1.35-ml (rabbit) of water	Manceau *et al*., 1999
fenbendazole	veterinary formulations	tablet, powder or liquid formulation dissolved in methanol containing 10% formic acid	van Tonder *et al.*, 1996
halothane	human urine	10-ml urine transferred into 20-ml glass vials containing 1-g sodium chloride and 200-µl sulphuric acid with airtight plugs. Solid phase micro-extraction (SPME) fibres suspended above the solution for 15-20 min and then inserted in to GC injection port for thermal desorption	Poli*, et al.,* 1999
isoflurane	human urine	10-ml urine transferred into 20-ml glass vials containing 1-g sodium chloride and 200-µl sulphuric acid with airtight plugs. Solid phase micro-extraction (SPME) fibres suspended above the solution for 15-20 min and then inserted in to GC injection port for thermal desorption.	Poli*, et al.,* 1999

Compound	Media	Extraction Method	Reference
ivermectin	surface runoff water subsurface runoff water soil cattle faeces	water: samples allowed to settle for at least one hour, and applied to XAD-2 column, eluted with methanol, evaporated to dryness and redissolved in methanol soil: 50-g sample ground and sieved and extracted using methanol which is then washed with isooctane and diluted with pH 7 phosphate buffer, then extracted using methylene chloride which is evaporated to small volume and cleaned using silanised celite column, eluant then evaporated to dryness, derivatised with acetic anhydride/dimethyl formamide/1-methylimidazole, and then cleaned using Sep-Pak treatment faeces: sample homogenised with acetone-water and extracted using isooctane which is then evaporated and then solvent-solvent distributions are performed into acetonitrile out of hexane and into hexane out of acetonitrile-water, solvent then evaporated, derivatised with acetic anhydride/dimethyl formamide/1-methylimidazole, chloroform added, washed through silica gel Sep-Pak, solvent evaporated and redissolved in methanol	Nessel *et al*., 1989
levamisole	porcine tissue	5-g of homogenised tissue, with internal standard, 20-ml hexane/isoamylalcohol 95/5 added, vortex mixed for 15 sec, 10-ml 1 M NaOH added, vortex mixed for 15 sec, placed in ultrasonic bath for 5 min, rotary mixed for 10 min, centrifuged for 10 min at 5000-rpm, upper organic layer transferred to tube containing 15-ml 0.05 M sulphuric acid, rotary mixed for 10 min, aqueous phase then passed through Isolute SCX SPE cartridge, washed with 3-ml water, 1-ml 0.05 M sulphuric acid, 3-ml methanol and eluted with 3-ml ammonia/methanol 25/75, eluate evaporated to dryness under nitrogen at 60ºC, reconstituted in 250-µl of mobile phase (0.1 M ammonium acetate/7.7% tetrahydrofuran/0.3% triethylamine)	Cherlet *et al.,* 2000
lignocaine	human plasma	1-ml plasma, spiked with internal standard, 2-ml water an d 2-ml acetonitrile added, vortex mixed, centrifuged for 20 min at 2200-g, supernatant separated, 0.5-ml 0.2 M sodium hydroxide added and then extracted with 6-ml n-hexane and vortex mixed for 2 min, centrifuged for 15 min at 2200-g, 5-ml organic phase transferred to tube and evaporated to dryness then reconstituted in 120-µl mobile phase (8 mM sodium dihydrogen orthophosphate/0.1 M sodium chloride/4% 2-propanol/0.6% diethylamine at pH7.05)	Abraham *et al.,* 1997
meticlorpindol	chicken faeces	ammonia/methanol 50/950 – extract filtered and purified with aluminium column, aliquot evaporated and redissolved in methanol/phosphate buffer 230/770	van Dijk and Keukens, 2000
nicarbazin	chicken faeces	dimethyl formamide at 70ºC – extract filtered through paper filter and diluted with sodium acetate buffer/acetonitrile 50/50	van Dijk and Keukens, 2000

Compound	Media	Extraction Method	Reference
nicarbazin	poultry feed	10-g of pulverised feed weighed into 250-ml glass jar, moistened with 5-ml water, 45-ml of water/dimethylformamide 5/95 added and shaken for 1 hour. 10-ml supernatant centrifuged for 5 min at 3000-rpm and 5-ml of this supernatant pipetted onto SPE Al-B aluminium column, first 1-ml of eluate discarded and next 2-ml collected for analysis	Dusi *et al.,* 2000
ormetoprim	marine sediment	1-g of homogenised sediment extracted using 4-ml of acetone, vortex mixed for 30-s, sonicated for 2.25-min, centrifuged at 1500-rpm for 5-mins at 5²C and the supernatent decanted, repeated twice using 3-ml acetone each time. Combined supernatent centrifuged at 3200-rpm for 20-min, filtered and evaporated to 1-ml	Capone *et al*., 1996
oxytetracycline	seawater	2-ml of sample filtered to 0.45-µm and 1.5-ml of filtrate centrifuged at 11000-g for 5-min at 4°C	Pouliquen *et al*., 1993
oxytetracycline	sediments	5-g sample blended three times with 20, 20 and 10-ml of 0.1M EDTA-McIlvaine buffer at pH 4, centrifuged, filtered, supernatant loaded onto Bondelut C18 SPE cartridge, washed with 20-ml water and eluted with 10-ml of 0.01M methanolic oxalic acid	Jacobsen and Berglind, 1988
oxytetracycline	slurry treated soil water	100-g dried soil stirred with 100-ml of methanol containing 5% acetic acid at pH 2.8 for two hours then centrifuged at 5000g for 10 minutes and filtered, residue re-extracted with 50-ml of acidic methanol and extracts combined, evaporated under vacuum at 40°C and redissolved in 3-ml methanol 100-ml of water loaded onto Baker SDB 1 SPE cartridge, washed with ammonium acetate, eluted with methanol/acetic acid, evaporated to dryness and redissolved in 200-µl of methanol	Hamscher *et al*., 2000 Hamscher *et al*., 2000c
oxytetracycline	surface and ground water hog lagoon waste water	50-ml of sample pumped through on-line C18 SPE cartridge and then eluted directly onto column with mobile phase of 80% A: 0.1% trifluoroacetic acid in methanol/acetonitrile/water (2:7:91) 20% B: methanol	Meyer *et al*., 2000
oxytetracycline	marine sediment crab/oyster tissue	1-g of homogenised sediment extracted using 4-ml of 0.1M EDTA/McIlvaine buffer at pH 4.0, vortex mixed for 30-s, sonicated for 2.25-min, centrifuged at 1500-rpm for 5-mins at 5²C and the supernatent decanted, repeated twice using 3-ml buffer each time. Combined supernatent centrifuged at 3200-rpm for 20-min, filtered, loaded onto Waters Sep-Pak Plus C18 cartridge, washed with 20-ml distilled water and eluted with 8-ml of methanolic oxalic acid and evaporated under vacuum 1-g homogenised tissue extracted in same manner as above except 01M citric acid/0.2M Na2HPO4 (62:38 at pH 4) used as buffer	Capone *et al*., 1996

Compound	Media	Extraction Method	Reference
penicillin	soil treated with feces	5-g of soil/feces mixture added to 200-ml 50% methanol, pH adjusted to 8.0 with phosphate buffer, gently refluxed for 10 min, extract cooled, filtered, evaporated to 30-ml and diluted 1:10 with pH 7.0 phosphate buffer	Gavalchin and Katz, 1994
penicillin-G	equine urine and plasma	Sample, with internal standard, adjusted to pH 7.0 by adding 3-ml 0.1 M phosphate buffer. 150-µl of urine or 2-ml plasma loaded onto Chemsep C18 SPE cartridge, rinsed with 5-ml water, dried under 10 bar air for 2 min and eluted with 5-ml methanol. Elute evaporated to dryness and then reconstituted in 300-µl distilled water, pencillin derivatised by adding 150-µl to urine or 200-µl to plasma elute of 2 M 1,2,4-triazole in 0.001 M mercuric chloride and heating at 65ºC for 15 min and then vortex mixing and finally filtering to 0.1-µm (plasma only)	Luo *et al.,* 1998
procaine	equine urine and plasma	5-ml urine, with internal standard, adjusted to pH 9.75-10.25 with 1-1.5-ml 1N ammonium hydroxide, 5-ml dichloromethane added, mixed for 10 min, centrifuged for 10 min at 2500-g and the organic layer evaporated to dryness in a water bath at 65ºC. Reconstituted in 200-µl methanol 2-ml plasma, with internal standard added, adjusted to pH 10 with 3-ml 0.1 M, pH 10 phosphate buffer, 5-ml dichloromethane added, mixed for 10 min, centrifuged for 10 min at 2500-g and the organic layer evaporated to dryness in a water bath at 65ºC. Reconstituted in 200-µl methanol	Luo *et al.,* 1998
selamectin	dog and cat plasma	samples vortexed mixed, centrifuged at 2500-g for 5-mins, 1.0-ml (dog) or 0.2-ml (cat) supernatant added to glass tube with internal standard, 1-ml of acetonitrile added, vortex mixed, passed through Isolute cartridges, washed with 1-ml of water, dried, eluted with 2 0.5-ml fractions of methanol into tapered glass tubes then evaporated to dryness. 100-µl of 50% triethylamine in acetonitrile then 150-µl of 33% trifluoroacetic acid in acetonitrile were added to the tubes then the volume was concentrated to 75-µl, 250-µl of 2-M ammonia solution in methanol was added then the volume concentrated to 75-µl again and then 200-µl of acetonitrile was added	Walker and Fenner, 2000
streptomycin	soil treated with feces	5-g of soil/feces mixture added to 200-ml 50% methanol, pH adjusted to 8.0 with phosphate buffer, gently refluxed for 10 min, extract cooled, filtered, evaporated to 30-ml and diluted 1:10 with pH 7.0 phosphate buffer	Gavalchin and Katz, 1994
streptomycin	food	5-g tissue homogenised, 20-ml 0.01 M perchloric acid at pH 2.0 added, homogenised for 5 min, centrifuged for 15 min at 2800 rpm, liquid phase filtered then loaded onto cation exchange SPE cartridge, washed with 5-ml water then eluted with 25-ml 0.2 M phophate buffer at pH 8.0. 2-ml of 0.5 M sodium 1-heptane sulphonate added and solution adjusted to pH 2.0 with phosphoric acid. Extract then loaded onto C18 SPE cartridge, washed with 10-ml water, 4-ml terbutylmethylether/hexane 4:1 and eluted with 5-ml 10 mM methanolic sodium 1-heptane sulphonate, 2-ml 10 mM sodium 1-heptane sulphonate at pH 3.3 added and extract evaporated at 100 mbar at 65ºC and reconstituted with 5-ml of 10 mM sodium 1-heptane sulphonate at pH 3.3	Edder *et al.,* 1999

Compound	Media	Extraction Method	Reference
sulfacetamide	surface waters effluent	200-1000-ml of sample adjusted to pH 2.5 loaded onto 200-mg LiChrolut EN SPE cartridge and eluted with 3-ml methanol/water 1:1 and 10-ml methanol	Hartig *et al*., 1999
sulfacetamide	swine wastewater	50-ml of sample adjusted to pH 6.6 with acetic acid and extracted using 90-ml ethyl acetate in three steps, then evaporated at 90°C and redissolved in 5-ml 0.01M HCl and made up to 50-ml with water	Jen *et al*., 1998
sulfachloropyridazine	chicken faeces	boiling sodium hydroxide - extract centrifuged, acidified, recentrifuged and neutralised	van Dijk and Keukens, 2000
sulfadiazine	surface waters effluent	200-1000-ml of sample adjusted to pH 2.5 loaded onto 200-mg LiChrolut EN SPE cartridge and eluted with 3-ml methanol/water 1:1 and 10-ml methanol	Hartig *et al*., 1999
sulfadiazine	swine wastewater	50-ml of sample adjusted to pH 6.6 with acetic acid and extracted using 90-ml ethyl acetate in three steps, then evaporated at 90°C and redissolved in 5-ml 0.01M HCl and made up to 50-ml with water	Jen *et al*., 1998
sulfadimethoxine	surface waters effluent	200-1000-ml of sample adjusted to pH 2.5 loaded onto 200-mg LiChrolut EN SPE cartridge and eluted with 3-ml methanol/water 1:1 and 10-ml methanol	Hartig *et al*., 1999
sulfadimethoxine	marine sediment	1-g of homogenised sediment extracted using 4-ml of acetone, vortex mixed for 30-s, sonicated for 2.25-min, centrifuged at 1500-rpm for 5-mins at 5²C and the supernatent decanted, repeated twice using 3-ml acetone each time. Combined supernatent centrifuged at 3200-rpm for 20-min, filtered and evaporated to 1-ml	Capone *et al*., 1996
sulfamerazine	surface waters effluent	200-1000-ml of sample adjusted to pH 2.5 loaded onto 200-mg LiChrolut EN SPE cartridge and eluted with 3-ml methanol/water 1:1 and 10-ml methanol	Hartig *et al*., 1999
sulfamerazine	swine wastewater	50-ml of sample adjusted to pH 6.6 with acetic acid and extracted using 90-ml ethyl acetate in three steps, then evaporated at 90°C and redissolved in 5-ml 0.01M HCl and made up to 50-ml with water	Jen *et al*., 1998
sulfamethazine	surface waters effluent	200-1000-ml of sample adjusted to pH 2.5 loaded onto 200-mg LiChrolut EN SPE cartridge and eluted with 3-ml methanol/water 1:1 and 10-ml methanol	Hartig *et al*., 1999
sulfamethazine	swine wastewater	50-ml of sample adjusted to pH 6.6 with acetic acid and extracted using 90-ml ethyl acetate in three steps, then evaporated at 90°C and redissolved in 5-ml 0.01M HCl and made up to 50-ml with water	Jen *et al*., 1998

Compound	Media	Extraction Method	Reference
sulfamethazine	swine urine and plasma swine tissue	EIA; urine and serum diluted 10-100 times in phosphate buffered saline (PBS); 10-g tissue minced, 40-ml PBS at pH 7.2 added and homogenised for 2-mins, filtered, 2-ml aliquot taken and filtered to 0.45-µm HPLC: 5-g tissue minced, 20-ml methylene chloride added, mixed for 30-s and centrifuged for 10-mins at 2000-g, supernatant filtered and dried over glasswool and sodium sulphate, extract then loaded onto Sep-Pak silica cartridge, washed with 5-ml methylene chloride, dried and eluted using 6-ml of 0.05M phosphate buffer at pH 10; urine samples adjusted to pH 6.5-7.0 using 0.25M acetic acid, plasma and pH adjusted urine then treated as per tissue samples	Haasnoot *et al*., 1996
sulfamethizole	surface waters effluent	200-1000-ml of sample adjusted to pH 2.5 loaded onto 200-mg LiChrolut EN SPE cartridge and eluted with 3-ml methanol/water 1:1 and 10-ml methanol	Hartig *et al*., 1999
sulfamethoxazole	surface waters effluent	200-1000-ml of sample adjusted to pH 2.5 loaded onto 200-mg LiChrolut EN SPE cartridge and eluted with 3-ml methanol/water 1:1 and 10-ml methanol	Hartig *et al*., 1999
sulfamethoxazole	swine wastewater	50-ml of sample adjusted to pH 6.6 with acetic acid and extracted using 90-ml ethyl acetate in three steps, then evaporated at 90°C and redissolved in 5-ml 0.01M HCl and made up to 50-ml with water	Jen *et al*., 1998
sulfamethoxypyridazine	surface waters effluent	200-1000-ml of sample adjusted to pH 2.5 loaded onto 200-mg LiChrolut EN SPE cartridge and eluted with 3-ml methanol/water 1:1 and 10-ml methanol	Hartig *et al*., 1999
sulfamonomethoxine	swine wastewater	50-ml of sample adjusted to pH 6.6 with acetic acid and extracted using 90-ml ethyl acetate in three steps, then evaporated at 90°C and redissolved in 5-ml 0.01M HCl and made up to 50-ml with water	Jen *et al*., 1998
sulfanilamide	surface waters effluent	200-1000-ml of sample adjusted to pH 2.5 loaded onto 200-mg LiChrolut EN SPE cartridge and eluted with 3-ml methanol/water 1:1 and 10-ml methanol	Hartig *et al*., 1999
sulfaquinoxaline	surface waters effluent	200-1000-ml of sample adjusted to pH 2.5 loaded onto 200-mg LiChrolut EN SPE cartridge and eluted with 3-ml methanol/water 1:1 and 10-ml methanol	Hartig *et al*., 1999
sulfathiazole	surface waters effluent	200-1000-ml of sample adjusted to pH 2.5 loaded onto 200-mg LiChrolut EN SPE cartridge and eluted with 3-ml methanol/water 1:1 and 10-ml methanol	Hartig *et al*., 1999

Compound	Media	Extraction Method	Reference
sulfathiazole	swine wastewater	50-ml of sample adjusted to pH 6.6 with acetic acid and extracted using 90-ml ethyl acetate in three steps, then evaporated at 90°C and redissolved in 5-ml 0.01M HCl and made up to 50-ml with water	Jen *et al*., 1998
sulfisomidine	surface waters effluent	200-1000-ml of sample adjusted to pH 2.5 loaded onto 200-mg LiChrolut EN SPE cartridge and eluted with 3-ml methanol/water 1:1 and 10-ml methanol	Hartig *et al*., 1999
sulphisoxazole	surface waters effluent	200-1000-ml of sample adjusted to pH 2.5 loaded onto 200-mg LiChrolut EN SPE cartridge and eluted with 3-ml methanol/water 1:1 and 10-ml methanol	Hartig *et al*., 1999
tetracycline	slurry treated soil water	100-g dried soil stirred with 100-ml of methanol containing 5% acetic acid at pH 2.8 for two hours then centrifuged at 5000g for 10 minutes and filtered, residue re-extracted with 50-ml of acidic methanol and extracts combined, evaporated under vacuum at 40°C and redissolved in 3-ml methanol 100-ml of water loaded onto Baker SDB 1 SPE cartridge, washed with ammonium acetate, eluted with methanol/acetic acid, evaporated to dryness and redissolved in 200-µl of methanol	Hamscher *et al*., 2000 Hamscher *et al*., 2000c
tetracycline	surface and ground water hog lagoon waste water	50-ml of sample pumped through on-line C18 SPE cartridge and then eluted directly onto column with mobile phase of 80% A: 0.1% trifluoroacetic acid in methanol/acetonitrile/water (2:7:91) 20% B: methanol	Meyer *et al*., 2000
triclabendazole	bovine milk	5.0-g milk weighed into 50-ml tubes, 5-g sodium sulphate and 20-ml acetonitrile added, homogenised, centrifuged for 10 min at 3000-rpm, supernatant transferred to 200-ml separatory funnel, repeated with 10-ml acetonitrile and further supernatant added to funnel. extracts rinsed with 20-ml of n-hexane saturated with acetonitrile, lower layer removed and evaporated under vacuum, 1-ml 0.1 M potassium phosphate monobasic added, sonicated for 1 min, 5-ml 0.1 M sodium hydrogencarbonate added and sonicated for 1 min, extract applied to Bond Elut C18 SPE cartridge, rinsed with 2-ml water, dried, and eluted with 2-ml acetonitrile	Takeba *et al.,* 2000
tylosin	slurry treated soil water	100-g dried soil stirred with 100-ml of methanol containing 5% acetic acid at pH 2.8 for two hours then centrifuged at 5000g for 10 minutes and filtered, residue re-extracted with 50-ml of acidic methanol and extracts combined, evaporated under vacuum at 40°C and redissolved in 3-ml methanol 100-ml of water loaded onto Baker SDB 1 SPE cartridge, washed with ammonium acetate, eluted with methanol/acetic acid, evaporated to dryness and redissolved in 200-µl of methanol	Hamscher *et al*., 2000 Hamscher *et al*., 2000c

APPENDIX E ANALYTICAL METHODS

Compound	Media	Analytical Method	Recovery	LOD/LOQ	Reference
albendazole	veterinary formulations	HPLC UV 254-nm	100.2-104.2%	not given (>8µg ml^{-1})	van Tonder *et al*., 1996
amprolium	chicken faeces	Ion pair LC UV 268-nm	not given	not given	van Dijk and Keukens, 2000
amprolium	chicken plasma	HPLC fluorescence ex 400-nm em 460-nm	97.7±10.7% at 20 ng ml^{-1} 98.6±4.1% at 50 ng ml^{-1} 105.1±5.3% at 100 ng ml^{-1}	2 ng ml^{-1} (LOD) 5 ng ml^{-1} (LOQ)	Hamamoto *et al.,* 1997
azithromycin	ferret faeces	HPLC UV 205-nm	97±0.6%	Not given	Wigman *et al*., 1998
cefaclor	human serum and urine tablets	Fluorescence ex 372-nm em 472-nm	89.1±2.11% serum 92.8±2.11% urine	5 ng ml^{-1} (LOD) 50 ng ml^{-1} (LOQ)	Hefnawy *et al*., 1999
cefadroxil	human serum and urine tablets	Fluorescence ex 370-nm em 472-nm	88.6±1.27% serum 93.4±1.25% urine	5 ng ml^{-1} (LOD) 50 ng ml^{-1} (LOQ)	Hefnawy *et al*., 1999
cephalexin	human serum and urine tablets	Fluorescence ex 372-nm em 478-nm	89.0±1.89% serum 93.8±1.4% urine	5 ng ml^{-1} (LOD) 50 ng ml^{-1} (LOQ)	Hefnawy *et al*., 1999
cephradine	human serum and urine tablets	Fluorescence ex 372-nm em 478-nm	89.8±0.86% serum 92.2±1.91% urine	5 ng ml^{-1} (LOD) 25 ng ml^{-1} (LOQ)	Hefnawy *et al*., 1999
chlortetracycline	buffers	HPCE UV 254-nm CEC UV 254-nm	not given	5-10 µg ml^{-1} (LOD)	Pesek and Matyska, 1996
chlortetracycline	surface and ground water hog lagoon waste water	radioimmunoassay LC MS	not given	1 µg l^{-1} (LOD immunoassay) 0.5 µg l^{-1} (LOD MS)	Meyer *et al*., 2000
chlortetracycline	soil and water amended with manure	LC MS MS	not given	1 µg kg^{-1}	Hamscher *et al*., 2000b

Compound	Media	Analytical Method	Recovery	LOD/LOQ	Reference
chlortetracycline	slurry treated soil water	LC MS MS HPLC microbiology	83% soil 107% water	0.7 µg kg^{-1} (LOD soil MS) 0.1-0.3 µg l^{-1} (LOD water MS) 0.8 µg l^{-1} (LOD water microbiology) 12 µg kg^{-1} (LOD soil microbiology)	Hamscher *et al*., 2000 Hamscher *et al*., 2000c
ciprofloxacin	growth media	HPLC UV 280-nm	97.31%	0.1 µg ml^{-1} (LOQ)	Wright *et al*., 1998
ciprofloxacin	pig and rabbit plasma	HPLC UV 277-nm	92±6% pig plasma	0.019 µg ml^{-1} (LOD pig plasma) 0.050 µg ml^{-1} (LOQ pig plasma)	Manceau *et al*., 1999
ciprofloxacin	chicken tissue	HPLC F ex 280-nm em 450-nm	67±10.5%	2 µg kg^{-1} (LOD)	Yorke and Froc, 2000
clopidol	chicken tissue	HPLC-MS	91.6±10.1% at 0.010 mg kg^{-1} 97.3±5.7% at 10.0 mg kg^{-1}	0.005 mg kg^{-1} (LOD) 0.010 mg kg^{-1} (LOQ)	Pang *et al.,* 2000
clopidol	poultry feed	HPLC DAD 265-nm	98±5%	2.5 mg kg^{-1} (LOD)	Dusi *et al.,* 2000
cypermethrin	soil and groundwater	HPLC UV 210-nm	89.7-112.8% groundwater 81.8-100.3% soil	not given	Martínez Galera *et al.,* 1996
cypermethrin	water, sand and biological materials	GC ECD	85-118% water	not given	Lutnicka *et al.,* 1999
danofloxacin	chicken tissue	HPLC F ex 294-nm em 514-nm	59±5.25%	7.5 µg kg^{-1} (LOD)	Yorke and Froc, 2000
deltamethrin	water, sand and biological materials	GC ECD	85-118% water	not given	Lutnicka *et al.,* 1999
diazinon	water and soil	GC-mass selective detection	125±6% water	2.5 ng l^{-1} (LOD water) 7.5 ng l^{-1} (LOQ water) 50 ng kg^{-1} (LOD soil) 150 ng kg^{-1} (LOQ soil)	Health and Safety Laboratories, 2001
diazinon	river water	on-line SPE-LC-MS	not given	0.004 µg l^{-1} (LOD)	Lacorte and Barceló, 1995

Compound	Media	Analytical Method	Recovery	LOD/LOQ	Reference
difloxacin	chicken tissue	HPLC F ex 280-nm em 450-nm	75±6.75%	0.5 µg kg^{-1} (LOD)	Yorke and Froc, 2000
dimetridazole	poultry meat	LC-MS	97±17%	sub 5 µg kg^{-1} (LOD)	Hurtaud-Pessel *et al.,* 2000
doramectin	cattle plasma	HPLC fluorescence ex 360-nm em 470-nm	73%	0.5 ng ml^{-1} (LOQ)	Harrison and Walker, 1998
doxycycline	buffers	HPCE UV 254-nm CEC UV 254-nm	not given	5-10 µg ml^{-1} (LOD)	Pesek and Matyska, 1996
enrofloxacin	pig and rabbit plasma tissue cage fluid (TCF)	HPLC UV 277-nm	90±5% pig plasma 108±9% rabbit plasma 102±7% rabbit TCF	0.021 µg ml^{-1} (LOD pig plasma) 0.050 µg ml^{-1} (LOQ pig plasma) 0.010 µg ml^{-1} (LOD rabbit plasma) 0.020 µg ml^{-1} (LOQ rabbit plasma) 0.050 µg ml^{-1} (LOD rabbit TCF) 0.120 µg ml^{-1} (LOQ rabbit TCF)	Manceau *et al*., 1999
enrofloxacin	chicken tissue	HPLC F ex 280-nm em 450-nm	77±8.5%	0.5 µg kg^{-1} (LOD)	Yorke and Froc, 2000
eprinomectin	bovine plasma	HPLC F ex 365-nm em 475-nm	>84.9%	0.05 ng ml^{-1} (LOQ)	Antonian *et al*., 1998
ethinyloestradiol	effluent, rivers, reservoirs, potable water	immunoassay	1 ng l^{-1}	not given	Aherne and Briggs, 1989
fenbendazole	veterinary formulations	HPLC UV 254-nm	99.6±0.89%	not given	van Tonder *et al.*, 1996
flumequine	chicken tissue	HPLC F ex 312-nm em 366-nm	70±5.5	3 µg kg^{-1} (LOD)	Yorke and Froc, 2000
flumequine	seawater	HPLC UV 280-nm	not given	not given	Lunestad *et al*., 1995
furazolidone	seawater	HPLC UV 365-nm	not given	not given	Lunestad *et al*., 1995
halothane	human urine	GC-MS	not given	20-30 ng l^{-1} (LOD)	Poli*, et al.,* 1999
isoflurane	human urine	GC-MS	not given	15-20-ng l^{-1} (LOD)	Poli*, et al.,* 1999

Compound	Media	Analytical Method	Recovery	LOD/LOQ	Reference
ivermectin	surface runoff water subsurface runoff water soil cattle faeces	HPLC F wavelengths not given	not given	10 ppt (LOD in water) 1 ppb (LOD in soil) 10 ppb (LOD in faeces)	Nessel *et al*., 1989
lasalocid	poultry feed	HPLC UV 305-nm	85-100%	20-40 mg kg^{-1} (LOD)	Dusi and Gamba, 1999
levamisole	porcine tissue	LC-MS-MS	not given	3.10 ng g^{-1} muscle and fat (LOD) 4.20 ng g^{-1} kidney (LOD) 2.60 ng g^{-1} skin/fat (LOD) 3.19 ng g^{-1} liver (LOD) 5 ng g^{-1} all (LOQ)	Cherlet *et al.,* 2000
lignocaine	human plasma	HPLC UV 214-nm	>95% from 20-1000 ng ml^{-1}	10 ng ml^{-1} (LOD)	Abraham *et al.,* 1997
marbofloxacin	chicken tissue	HPLC F ex 294-nm em 514-nm	64±7.5%	35 µg kg^{-1} (LOD)	Yorke and Froc, 2000
meclocycline	buffers	HPCE UV 254-nm CEC UV 254-nm	not given	5-10 µg ml^{-1} (LOD)	Pesek and Matyska, 1996
methacycline	buffers	HPCE UV 254-nm CEC UV 254-nm	not given	5-10 µg ml^{-1} (LOD)	Pesek and Matyska, 1996
meticlorpindol	chicken faeces	HPLC UV 265-nm	not given	not given	van Dijk and Keukens, 2000
minocycline	buffers	HPCE UV 254-nm CEC UV 254-nm	not given	5-10 µg ml^{-1} (LOD)	Pesek and Matyska, 1996
monensin	poultry feed	HPLC UV 392-nm	85-100%	20-40 mg kg^{-1} (LOD)	Dusi and Gamba, 1999
nalidixic acid	chicken tissue	HPLC F ex 312-nm em 366-nm	71±7%	7.5 µg kg^{-1} (LOD)	Yorke and Froc, 2000
narasin	poultry feed	HPLC UV 392-nm	85-100%	20-40 mg kg^{-1} (LOD)	Dusi and Gamba, 1999
nicarbazin	chicken faeces	HPLC UV 344-nm	not given	not given	van Dijk and Keukens, 2000

Compound	Media	Analytical Method	Recovery	LOD/LOQ	Reference
nicarbazin	poultry feed	HPLC DAD 345-nm	95±4%	1 mg kg^{-1} (LOD)	Dusi *et al.,* 2000
norethisterone	effluent, rivers, reservoirs, potable water	immunoassay	2 ng l^{-1}	not given	Aherne and Briggs, 1989
ofloxacin	growth media	HPLC UV 280-nm	96.81%	0.1 µg ml^{-1} (LOQ)	Wright *et al*., 1998
ormethoprim	seawater	HPLC UV 230-nm	not given	not given	Lunestad *et al*., 1995
ormetoprim	marine sediment	HPLC DAD 270-nm	not calculated	0.25 µg ml^{-1} (LOD extract)	Capone *et al*., 1996
oxolinic acid	chicken tissue	HPLC F ex 312-nm em 366-nm	73±6.5%	12 µg kg^{-1} (LOD)	Yorke and Froc, 2000
oxolinic acid	seawater	HPLC UV 280-nm	not given	not given	Lunestad *et al*., 1995
oxytetracycline	buffers	HPCE UV 254-nm CEC UV 254-nm	not given	5-10 µg ml^{-1} (LOD)	Pesek and Matyska, 1996
oxytetracycline	surface and ground water hog lagoon waste water	radioimmunoassay LC MS	not given	1 µg l^{-1} (LOD immunoassay) 0.5 µg l^{-1} (LOD MS)	Meyer *et al*., 2000
oxytetracycline	marine sediment	HPLC	not given	1.2 µg g^{-1} (LOQ)	Kerry *et al*., 1996
oxytetracycline	marine sediment crab/oyster tissue	HPLC UV 365-nm	5-70% sediment 65-80% tissue	0.2 µg g^{-1} (LOD sediment) 0.1 µg g^{-1} (LOD tissue)	Capone *et al*., 1996
oxytetracycline	seawater	HPLC UV 365-nm	not given	not given	Lunestad *et al*., 1995
oxytetracycline	seawater	HPLC UV 355-nm	91.9±3.14%	0.01 µg ml^{-1} (LOD) 0.05 µg ml^{-1} (LOQ)	Pouliquen *et al*., 1993
oxytetracycline	sediment	HPLC UV 350-nm	not given	not given	Jacobsen and Berglind, 1988
oxytetracycline	slurry treated soil water	LC MS MS HPLC microbiology	63% soil 86% water	0.7 µg kg^{-1} (LOD soil MS) 0.1-0.3 µg l^{-1} (LOD water MS)	Hamscher *et al*., 2000 Hamscher *et al*., 2000c

Compound	Media	Analytical Method	Recovery	LOD/LOQ	Reference
oxytetracycline	sediment seawater	HPLC UV 365-nm	98.4% sediment 99.5% seawater	0.1 ppm (LOD sediment) 0.1 ppm (LOD seawater)	Samuelsen 1989
penicillin	soil treated with feces	TLC	not given	not given	Gavalchin and Katz, 1994
penicillin-G	equine urine and plasma	HPLC UV 288-nm	72.9-80.0% plasma 71.7-92.2% urine	0.05 µg ml^{-1} plasma 0.10 µg ml^{-1} urine	Luo *et al.,* 1998
procaine	equine urine and plasma	HPLC UV 288-nm	76.0-94.1% plasma 70.9-88.8% urine	0.01 µg ml^{-1} plasma and urine	Luo *et al.,* 1998
salinomycin	poultry feed	HPLC UV 392-nm	85-100%	20-40 mg kg^{-1} (LOD)	Dusi and Gamba, 1999
sarafloxacin	chicken tissue	HPLC F ex 280-nm em 450-nm	71±7.5%	1 µg kg^{-1} (LOD)	Yorke and Froc, 2000
selamectin	dog and cat plasma	HPLC F ex 360-nm em 450-nm	30-63%	0.2 ng ml^{-1}	Walker and Fenner, 2000
sparfloxacin	growth media	HPLC UV 280-nm	99.55%	0.1 µg ml^{-1} (LOQ)	Wright *et al*., 1998
streptomycin	soil treated with feces	microbiological assay	not given	not given	Gavalchin and Katz, 1994
streptomycin	food	HPLC fluorescence ex 260-nm em 435-nm	88±5.6% milk 91±3.6% honey 81±4.8% meat 81±2.9% liver	0.005 mg kg^{-1} honey (LOD) 0.01 mg kg^{-1} honey (LOQ) 0.03 mg kg^{-1} milk and meat(LOD) 0.05 mg kg^{-1} milk and meat (LOQ) 0.1 mg kg^{-1} liver and kidney (LOD) 0.2 mg kg^{-1} liver and kidney (LOQ)	
sulfacetamide	surface waters effluent	HPLC UV 260-nm and HPLC MS MS	87-99% water 32-79% effluent	0.2 mg l^{-1} (LOD UV) 0.6 mg l^{-1} (LOQ UV) 3.5 µg l^{-1} (LOD MS) 9.6 µg l^{-1} (LOQ MS)	Hartig *et al*., 1999
sulfacetamide	swine wastewater	HPLC UV 260-nm	86±4.4%	4 µg l^{-1} (LOD)	Jen *et al*., 1998

Compound	Media	Analytical Method	Recovery	LOD/LOQ	Reference
sulfachloropyridazine	chicken faeces	HPLC UV 450-nm	80-100%	not given	van Dijk and Keukens, 2000
sulfadiazine	surface waters effluent	HPLC UV 260-nm and HPLC MS MS	92-93% water 79-94% effluent	0.3 mg l^{-1} (LOD UV) 0.8 mg l^{-1} (LOQ UV) 0.3 µg l^{-1} (LOD MS) 0.8 µg l^{-1} (LOQ MS)	Hartig *et al*., 1999
sulfadiazine	swine wastewater	HPLC UV 260-nm	99±2.6%	4 µg l^{-1} (LOD)	Jen *et al*., 1998
sulfadiazine	seawater	HPLC UV 270-nm	not given	not given	Lunestad *et al*., 1995
sulfadiazine	sediment	HPLC UV 270-nm	80.0±5.9%	-	Samuelsen 1994
sulfadimethoxine	surface waters effluent	HPLC UV 260-nm and HPLC MS MS	80-88% water 82-93% effluent	0.6 mg l^{-1} (LOD UV) 1.7 mg l^{-1} (LOQ UV) 1.0 µg l^{-1} (LOD MS) 2.8 µg l^{-1} (LOQ MS)	Hartig *et al*., 1999
sulfadimethoxine	marine sediment	HPLC DAD 270-nm	not calculated	0.125 µg ml^{-1} (LOD extract)	Capone *et al*., 1996
sulfadimethoxine	seawater	HPLC UV 270-nm	not given	not given	Lunestad *et al*., 1995
sulfadimethoxine	sediment	HPLC UV 270-nm	79.4±2.3%	-	Samuelsen 1994
sulfamerazine	surface waters effluent	HPLC UV 260-nm and HPLC MS MS	90-97% water 60-101% effluent	0.4 mg l^{-1} (LOD UV) 1.1 mg l^{-1} (LOQ UV) 0.6 µg l^{-1} (LOD MS) 1.7 µg l^{-1} (LOQ MS)	Hartig *et al*., 1999
sulfamerazine	swine wastewater	HPLC UV 260-nm	95±2.6%	10 µg l^{-1} (LOD)	Jen *et al*., 1998
sulfamethazine	surface waters effluent	HPLC UV 260-nm and HPLC MS MS	88-89% water 68-85% effluent	0.5 mg l^{-1} (LOD UV) 1.4 mg l^{-1} (LOQ UV) 1.3 µg l^{-1} (LOD MS) 3.6 µg l^{-1} (LOQ MS)	Hartig *et al*., 1999

Compound	Media	Analytical Method	Recovery	LOD/LOQ	Reference
sulfamethazine	swine wastewater	HPLC UV 260-nm	90±4.0%	15 µg l^{-1} (LOD)	Jen *et al*., 1998
sulfamethazine	swine urine and plasma swine tissue	EIA HPLC UV 261-nm	80±12% HPLC urine and plasma 78±10% HPLC tissue 87±7% EIA tissue	50 µg l^{-1} (LOD urine and plasma HPLC) 10 µg kg^{-1} (LOD tissue HPLC) <2 µg l^{-1} (blank urine and plasma EIA <3 µg kg^{-1} (blank tissue EIA)	Haasnoot *et al*., 1996
sulfamethizole	surface waters effluent	HPLC UV 260-nm and HPLC MS MS	77-80% water 48-75% effluent	0.4 mg l^{-1} (LOD UV) 1.1 mg l^{-1} (LOQ UV) 0.2 µg l^{-1} (LOD MS) 0.6 µg l^{-1} (LOQ MS)	Hartig *et al*., 1999
sulfamethoxazole	surface waters effluent	HPLC UV 260-nm and HPLC MS MS	98-99% water 77-96% effluent	0.2 mg l^{-1} (LOD UV) 0.6 mg l^{-1} (LOQ UV) 0.9 µg l^{-1} (LOD MS) 2.5 µg l^{-1} (LOQ MS)	Hartig *et al*., 1999
sulfamethoxazole	swine wastewater	HPLC UV 260-nm	92±3.0%	12 µg l^{-1} (LOD)	Jen *et al*., 1998
sulfamethoxypyridazine	surface waters effluent	HPLC UV 260-nm and HPLC MS MS	82% water 64-84% effluent	0.2 mg l^{-1} (LOD UV) 0.6 mg l^{-1} (LOQ UV) 1.0 µg l^{-1} (LOD MS) 2.8 µg l^{-1} (LOQ MS)	Hartig *et al*., 1999
sulfamonomethoxine	swine wastewater	HPLC UV 260-nm	94±3.2%	15 µg l^{-1} (LOD)	Jen *et al*., 1998
sulfanilamide	surface waters effluent	HPLC UV 260-nm and HPLC MS MS	29-32% water 18-40% effluent	0.4 mg l^{-1} (LOD UV) 1.1 mg l^{-1} (LOQ UV) 3.7 µg l^{-1} (LOD MS) 10.2 µg l^{-1} (LOQ MS)	Hartig *et al*., 1999

Compound	Media	Analytical Method	Recovery	LOD/LOQ	Reference
sulfaquinoxaline	surface waters effluent	HPLC UV 260-nm and HPLC MS MS	78-85% water 71-82% effluent	0.6 mg l^{-1} (LOD UV) 1.7 mg l^{-1} (LOQ UV) 0.8 µg l^{-1} (LOD MS) 2.2 µg l^{-1} (LOQ MS)	Hartig *et al*., 1999
sulfathiazole	surface waters effluent	HPLC UV 260-nm and HPLC MS MS	81-93% water 70-83% effluent	0.4 mg l^{-1} (LOD UV) 1.1 mg l^{-1} (LOQ UV) 1.3 µg l^{-1} (LOD MS) 3.6 µg l^{-1} (LOQ MS)	Hartig *et al*., 1999
sulfathiazole	swine wastewater	HPLC UV 260-nm	97±1.6%	10 µg l^{-1} (LOD)	Jen *et al*., 1998
sulfisomidine	surface waters effluent	HPLC UV 260-nm and HPLC MS MS	87-100% water 71-89% effluent	0.3 mg l^{-1} (LOD UV) 0.8 mg l^{-1} (LOQ UV) 3.2 µg l^{-1} (LOD MS) 8.8 µg l^{-1} (LOQ MS)	Hartig *et al*., 1999
9 sulfonamides	standards	GC AED	not given	not given	Chiavarino 1998
sulphisoxazole	surface waters effluent	HPLC UV 260-nm and HPLC MS MS	94% water 71-93% effluent	0.4 mg l^{-1} (LOD UV) 1.1 mg l^{-1} (LOQ UV) 1.3 µg l^{-1} (LOD MS) 3.6 µg l^{-1} (LOQ MS)	Hartig *et al*., 1999
tetracycline	buffers	HPCE UV 254-nm CEC UV 254-nm	not given	5-10 µg ml^{-1} (LOD)	Pesek and Matyska, 1996
tetracycline	surface and ground water hog lagoon waste water	radioimmunoassay LC MS	not given	1 µg l^{-1} (LOD immunoassay) 0.5 µg l^{-1} (LOD MS)	Meyer *et al*., 2000
tetracycline	soil and water amended with manure,	LC MS MS	not given	1 µg kg^{-1}	Hamscher *et al*., 2000b
triclabendazole	bovine milk	HPLC UV 295-nm	89.1±1.6%	0.006 µg g^{-1} (LOD) 0.030 g g^{-1} (LOQ)	Takeba *et al.,* 2000

Compound	Media	Analytical Method	Recovery	LOD/LOQ	Reference
trimethoprim	seawater	HPLC UV 230-nm	not given	not given	Lunestad *et al*., 1995
tetracycline	slurry treated soil water	LC MS MS HPLC microbiology	62% soil 88% water	0.7 µg kg^{-1} (LOD soil MS) 0.1-0.3 µg l^{-1} (LOD water MS)	Hamscher *et al*., 2000 Hamscher *et al*., 2000c
tylosin	slurry treated soil water	LC MS MS HPLC microbiology	64% soil 108% water	0.2 µg kg^{-1} (LOD soil MS) 0.1-0.3 µg l^{-1} (LOD water MS) 0.8 µg l^{-1} (LOD water microbiology) 12 µg kg^{-1} (LOD soil microbiology)	Hamscher *et al*., 2000 Hamscher *et al*., 2000c
17 sulfonamides Trimethoprim Pyrimethamine 10 ß-lactams	waters	CE UV 205-nm	not given	not given	Hows 1997

APPENDIX F ENVIRONMENTAL MONITORING DATA

Compound	Therapeutic use	Concentration detected (ng l^{-1} unless otherwise stated)	LOD (ng l^{-1} unless otherwise stated)	Country	Reference
Surface water					
Freshwater/marine water					
chlorfenvinphos	Ectoparasiticide	nd-30800	5.0-400	England & Wales	EA (1997)
		<20-3068	20	Scotland	Littlejohn and Melvin(1991)
		1-355	2-20000	England & Wales	EA (2001)
chloramphenicol	Antibiotic	0.06 µg l^{-1}	0.02 µg l^{-1} (LOQ)	Germany	Hirsch *et al* (1999)
chlortetracycline	Antibiotic	0.5 µg l^{-1}	0.5 µg l^{-1}	USA	Meyer *et al* (2000)
coumaphos	Ectoparasiticide	30	10-50	England & Wales	EA (1997)
cypermethrin	Ectoparasiticide	nd-200	0.1-500	England & Wales	EA (1997)
		1-85100	1-2000	England & Wales	EA (2001)
diazinion	Ectoparasiticide	nd-2500	1.0-1000	England & Wales	EA (1997)
		<10-108	10	Scotland	Littlejohn and Melvin (1991)
		3-0.58 x 10^6	3	Scotland	Virtue and Clayton (1997)
		1-5000	1-12500	England & Wales	EA (2001)
emamectin benzoate	Ectoparasiticide	nd	0.2 µg l^{-1}	Scotland	SEPA (1999)
fenchlorphos	Ectoparasiticide	<10-777	10	Scotland	Littlejohn and Melvin (1991)
flumethrin	Ectoparasiticide	1-2190	1-45000	England & Wales	EA (2001)
propetamphos	Ectoparasiticide	nd-1200	4.5-200	England & Wales	EA (1997)
		<10-2173	10	Scotland	Littlejohn and Melvin (1991)
		3-19.2 x 10^6	3	Scotland	Virtue and Clayton (1997)
		1-11738000	1-10000	England & Wales	EA (2001)
Groundwater					
chlorfenvinphos	Ectoparasiticide	nd-70	5.0-200	England & Wales	EA (1997)
		15-20	1-20000	England & Wales	EA (2001)
chlortetracycline	Antibiotic	0.17-0.22 µg l^{-1}	0.1-0.3 µg l^{-1}	Germany	Hamscher *et al* (2000)
diazinon	Ectoparasiticide	nd-216	5.0-200	England & Wales	EA (1997)
		26-190	5-10000	England & Wales	EA (2001)

Compound	Therapeutic use	Concentration detected (ng l^{-1} unless otherwise stated)	LOD (ng l^{-1} unless otherwise stated)	Country	Reference
oxytetracycline	Antibiotic	0.15-0.19 µg l^{-1}	0.1-0.3 µg l^{-1}	Germany	Hamscher *et al* (2000)
propetamphos	Ectoparasiticide	nd-489	4.7-100	England & Wales	EA (1997)
		29-110	1-10000	England & Wales	EA (2001)
sulfamethazine	Antibiotic	0.08-0.16 µg l^{-1}	0.02 µg l^{-1} (LOQ)	Germany	Hirsch *et al* (1999)
tetracycline	Antibiotic	0.11-0.27 µg l^{-1}	0.1-0.3 µg l^{-1}	Germany	Hamscher *et al* (2000)
tylosin	Antimicrobial	0.13-0.42±0.47 µg l^{-1}	0.1-0.3 µg l^{-1}	Germany	Hamscher *et al* (2000)
Surface/sub-surface run-off					
ivermectin	Endectocide	<1.1-4.4	-	USA	Nessel *et al* (1989)
Sediment					
oxytetracycline	Antibiotic	0.1-4.9 mg kg^{-1} dry matter	-	Norway	Jacobsen and Berglind (1988)
		0.05-16 µg g^{-1}	0.05 µg g-1	Finland	Björklund *et al* (1990)
		0.8-6.3 µg g^{-1}	0.05 µg g^{-1}	Finland	Björklund *et al* (1991)
		189-285 µg g^{-1}	0.1 µg g^{-1}	Norway	Samuelsen *et al* (1992a)
		<1.2 µg g^{-1} – 10.9±6.5 µg g^{-1}	1.2 µg g^{-1}	Ireland	Coyne *et al* (1994)
		0.2-4 µg g^{-1}	0.2 µg g^{-1}	USA	Capone *et al* (1996)
		1.3-4.5 µg g^{-1}	1.2 µg g^{-1}	Ireland	Kerry *et al* (1996)
desmethylamino metabolite	derivative of emamectin benzoate	>0.5 µg kg^{-1} (wet wt.)	0.25 µg kg^{-1} (wet wt.)	Scotland	SEPA (1999)
emamectin benzoate	Ectoparasiticide	0.25-2.73 µg kg^{-1}	0.25 µg kg^{-1} (wet wt.)	Scotland	SEPA (1999)
ivermectin	Ectoparasiticide	trace-6.8 ng g^{-1}	0.5 ng g^{-1}	Ireland	Canavan *et al* (2000)
oxolinic acid	Antimicrobial	<0.05-0.2 µg g^{-1}	0.05 µg g^{-1}	Finland	Björklund *et al* (1991)
settled particulate matter					
desmethylamino metabolite	derivative of emamectin benzoate	1.9-30 µg kg^{-1}	0.25 µg kg^{-1} (wet wt.)	Scotland	SEPA (1999)
emamectin benzoate	Ectoparasiticide	75.1-366 µg kg^{-1}	0.25 µg kg^{-1} (wet wt.)	Scotland	SEPA (1999)
Flocculent material from seabed					
emamectin benzoate	Ectoparasiticide	nd	0.25 µg kg^{-1} (wet wt.)	Scotland	SEPA (1999)

Compound	Therapeutic use	Concentration detected (ng l^{-1} unless otherwise stated)	LOD (ng l^{-1} unless otherwise stated)	Country	Reference
Soil					
chlortetracycline	Antibiotic	0.7±0.2-9.5±2.8 µg kg^{-1}	0.7 µg kg^{-1}	Germany	Hamscher *et al* (2000)
		<1-26.4 µg kg^{-1}	1 µg kg^{-1}	Germany	Hamscher *et al* (2000a)
		1.2-41.8 µg kg^{-1}	1 µg kg^{-1}	Germany	Hamscher *et al* (2000b)
ivermectin	Endectocide	0.1-2 µg kg^{-1}	1 µg kg^{-1}	USA	Nessel *et al* (1989)
monensin	Coccidiostat	0.8-1.08 mg kg^{-1}	-	Canada	Donoho (1984)
oxytetracycline	Antibiotic	0.9±0.1-8.6±4.5 µg kg^{-1}	0.7 µg kg^{-1}	Germany	Hamscher *et al* (2000)
tetracycline	Antibiotic	1.2±0.1-12.3±5.6 µg kg^{-1}	0.7 µg kg^{-1}	Germany	Hamscher *et al* (2000)
		<1-32.2 µg kg^{-1}	1 µg kg^{-1}	Germany	Hamscher *et al* (2000a)
		1.1-39.6±33.6 µg kg^{-1}	1 µg kg^{-1}	Germany	Hamscher *et al* (2000b)
tylosin	Antimicrobial	nd/trace	0.2 µg kg^{-1}	Germany	Hamscher *et al* (2000)
Faeces and urine					
Cattle faeces/manure					
[^{14}C]ceftiofur	Antibiotic	11.3-216.1 mg kg^{-1} (equivalent)	-	USA	Gilbertson *et al* (1990)
chlortetracycline	Antibiotic	7.6±2.7 µg kg^{-1}	-	Germany	Hamscher *et al* (2000b)
ivermectin	Endectocide	12-75 µg kg^{-1}	10 µg kg^{-1}	USA	Nessel *et al* (1989)
		0.3±0.0-9.0±0.7 mg kg^{-1}	0.03 mg kg^{-1}	Denmark	Sommer and Steffansen (1993)
		0.2-3.8 mg kg^{-1} (dry wt)	-	Tanzania	Sommer and Overgaard Nielsen (1992)
		0.07-0.36 mg kg^{-1} (wet wt.)	-	Australia	Cook *et al* (1996)
		0.353 mg kg^{-1}	-	USA	Merck, Sharpe & Dohme (1983) cited in Strong (1992)
		13-80 µg kg^{-1}	-	USA	Halley *et al* (1986)
		0.24-0.27	-	USA	Halley *et al* (1989)
monensin	Coccidiostat	0.7-4.7	-	Canada	Donoho (1984)
sulphadimethoxine	Antimicrobial	300-900 mg kg^{-1}	-	Italy	Brambilla, unpublished data (1993) cited in Migliore *et al* (1995)
tetracycline	Antibiotic	2.5±1.2 µg kg^{-1}	-	Germany	Hamscher *et al* (2000b)
Pig faeces/manure					
chlortetracycline	Antibiotic	3.4-1001.6 µg kg^{-1}	-	Germany	Hamscher *et al* (2000b)

Compound	Therapeutic use	Concentration detected (ng l^{-1} unless otherwise stated)	LOD (ng l^{-1} unless otherwise stated)	Country	Reference
ivermectin	Endectocide	0.22-0.24 mg kg^{-1}	-	USA	Halley *et al* (1989)
tetracycline	Antibiotic	44.4-132.4 µg kg^{-1}	-	Germany	Hamscher *et al* (2000b)
Sheep faeces/manure					
ivermectin	Endectocide	0.63-0.714 mg kg^{-1}	-	USA	Halley *et al* (1989)
Poultry faeces/manure					
chlortetracycline	Antibiotic	22.5 µg g^{-1}	-	Canada	Warman and Thomas (1981)
[^{14}C]narasin	Antibiotic	1±0.3-725±60.3 µg kg^{-1} (equivalent)	-	USA	Catherman *et al* (1991)
Horse faeces/manure					
ivermectin	Endectocide	0.05-8.47 µg g^{-1}	0.05 µg g^{-1}	USA?	Jernigan *et al* (1990) cited in Sams (1993)
Fauna					
Wild fish					
emamectin benzoate	Ectoparasiticide	0.25-1.23 µg kg^{-1}	0.25 µg kg^{-1} (wet wt.)	Scotland	SEPA (1999)
oxytetracycline	Antibiotic	0.05-1.3 µg g^{-1}	0.05 µg g^{-1}	Finland	Björklund *et al* (1990)
oxolinic acid	Antimicrobial	0.01-13.59 µg g^{-1}	0.003-0.01 µg g^{-1}	Norway	Samuelsen *et al* (1992)
		<0.08-15.74 µg g^{-1}	-	Norway	Ervik *et al* (1994)
flumequine	Antimicrobial	0.06-1.12 µg g^{-1} (mean conc.)	-	Normay	Ervik *et al* (1994)
Shellfish					
desmethylamino metabolite	derivative of emamectin benzoate	trace	0.25 µg kg^{-1} (wet wt.)	Scotland	SEPA (1999)
emamectin benzoate	Ectoparasiticide	trace	0.25 µg kg^{-1} (wet wt.)	Scotland	SEPA (1999)
oxolinic acid	Antimicrobial	0.03-3.77 µg g^{-1}	0.003-0.01 µg g^{-1}	Norway	Samuelsen *et al* (1992)
Crustacea					
emamectin benzoate	Ectoparasiticide	0.25-5 µg kg^{-1}	0.25 µg kg^{-1} (wet wt.)	Scotland	SEPA (1999)
oxolinic acid	Antimicrobial	0.05-1.48 µg g^{-1}	0.003-0.01 µg g^{-1}	Norway	Samuelsen *et al* (1992)
oxytetracycline	Antibiotic	0.1-3.8 µg g^{-1}	0.1 µg g^{-1}	USA	Capone *et al* (1996)

APPENDIX G ABSORPTION AND EXCRETION OF COMMONLY USED VETERINARY MEDICINES

Compound	Animals studied	Absorbed	Excreted	Major metabolites	Reference
Actaplanin	cattle, rats	-	100% of the applied radioactivity excreted. In rats the majority was the parent compound. In steers actaplanin comprised around 33% of the excreted radioactivity	hydrolysis products	
Amprolium	rats		82 % of oral dose excreted in faeces, 45-64% of this as the parent amprolium		CVMP (1999)
Avilamycin	pigs, rats	-	98% of the applied dose excreted in the urine and faeces, 8% of this was parent avilamycin	flambic acid	Magnussen *et al*. (1991)
Bacitracin	chickens, pigs	poorly absorbed (oral)	98% of oral dose excreted in urine and faeces. Faeces mainly contains bacitracin and metabolites	desamidobasitracin catabolic peptides	CVMP (1998)
Ceftiofur	calves, pigs, sheep	poorly absorbed (oral)	70-95% of administered dose excreted within 24 h, only a small amount of which was the parent compound	desfuroylceftiofur desfuroylceftiofur cysteine disuphide	CVMP (1999a); Beconi-Barker *et al*. (1996)
Chlortetracycline	poultry	-	manure from birds treated with feed containing 11 μg g-1 CTC contained 22.5 μg g-1 CTC	-	Warman and Thomas (1981)

Compound	Animals studied	Absorbed	Excreted	Major metabolites	Reference
Diclazuril	Rats, rabbits, chickens, turkeys, goats	-	>98% of administered dose excreted within 10 d, of which the parent compound diclazuril accounted for 85-95%	4-amino-2,6-dichloro-α–(4-chlorophenyl) benzeneacetonitrile (8%)	CVMP (1996)
Difloxacin	cattle, pigs	88 – 95%	Effectively eliminated as the parent compound	Only minor metabolism; major metabolites being N-desmethyldifloxacin and the N-oxide of difloxacin	CVMP (1998a)
dimetridazole	-	-	Extensive metabolism of parent compound and rapid elimination of the metabolites produced	-	CVMP (1992)
3,5-dinitrobenzamide	chickens	significant absorption	58% of the dose excreted in the urine and 21% excreted in the faeces.	Major urinary metabolites were 3-amino-5-nitrobenzamide (30% of radioactivity in urine); 3-acetamido-5-nitrobenzamide (29%); 3-acetamido-5-aminobenzamide (9%) 3,5-diacetamidobenzamide (3%). The major metabolite in the faeces was 3-acetamido-5-nitrobenzamide (67% of faecal radioactivity)	Shappell *et al.*, 1999
Doramectin	cattle, rat, dog	rapidly absorbed	87% of administered dose excreted after 14 d, 6-24% of the applied dose was excreted unchanged	3-O-desmethyldoramectin (8-19%)	CVMP (1997a)

Compound	Animals studied	Absorbed	Excreted	Major metabolites	Reference
Enrofloxacin	rats	75%	Most of the administered radioactivity eliminated in the urine and faeces; 17% as the parent compound	ciprofloxacin (31%); enrofloxacin amide (23%)	CVMP (1998b)
Eprinomectin	rats, calves	ns	17-99% of applied dose excreted in faeces, 82-87% as the parent compound	24a-hydroxymethyl metabolite	CVMP (1996a)
Erythromycin	humans	<50%		des-N-methy;-erythromycin	CVMP (2000)
Florfenicol	cattle, pigs, chickens	75% (intramuscular)	80-98% of applied dose excreted after 1-19 d, the major fraction being in the urine. The parent compound represented the major fraction of the radioactivity (42-60%)	florfenicol amine florfenicol oxamic acid florfenicol alcohol	CVMP (1999b); CVMP (1999c)
Flubendazole	rat, dog and target species, hens	Low oral bioavailability	> 50% of the applied dose excreted unchanged	reduction of the ketone functional group and hydrolysis of the carbamate moeity	CVMP (1997b); CVMP (1999d)
Flumequine	ruminant calves	ns	90 % of the applied dose excreted 80% of which was unchanged flumequine	7-hydroxy-flumequine	CVMP (1996b)
Halofuginone	rats, mice, calves	81% (oral)	78-92% of the applied dose excreted within 12-14 h. 90% as unchanged halofuginone.	ns	CVMP (1998c)
Ivermectin	cattle, sheep, rats	ns	63-98% of the applied dose excreted 39-78% of which was unchanged ivermectin	24-hydroxymethyl-H_2B1a; 3-O-desmethyl-H_2B1a; 3-O-desmethyl-H_2B1b	CVMP (1998d); Steel (1993)

Compound	Animals studied	Absorbed	Excreted	Major metabolites	Reference
Lincomycin	humans, dogs, rats	25-50% (oral)	44 - 91% of applied dose excreted 40% of which was unchanged lincomycin	lincomycin sulfoxide; N-desmethyl derivative; N-desmethyl-lincomycin-sulfoxide	CVMP (1998e)
Maduramicin	turkeys	-	50.8 – 85.7% of the applied dose excreted after 3 d withdrawal. The parent compound comprised 23% of the excreted material	didemethylated maduramicin	Stout *et al*. (1991)
Narasin	chickens	-	Narasin accounted for 3% of the radioacivity in excreta. Fifteen metabolites were identified accounting for around 50% of the radioactivity in excreta.	trihydronarasin (13%)	Sweeney *et al* (1996)
Neomycin	humans, cattle	1-11% (oral)	after oral administration, 90% of applied dose excreted in the faeces 70-80% as the parent compound	negligible transformation	CVMP (2000a)
Oxolinic acid	rodents, humans, fish, poultry	variable depending on species, formulation, meal influence and disease status	rapid – with between 41 and 100% of the applied dose being excreted in 48 h	extensively metabolised to oxilinic acid glucoronide, non-glucoronide metabolites and glucoronides derived from metabolites	CVMP (1998f)
Oxytetracycline, tetracycline and chlortetracycline	ns	rapidly but moderately absorbed from the gastrointestinal tract	Eliminated mainly in the urine as unchanged drug	minimal metabolism	CVMP (1995)
Pirlimycin	humans, rats	ns	65% of administered dose excreted after 5 d.	pirlimycin sulphoxide	CVMP (2000b)

Compound	Animals studied	Absorbed	Excreted	Major metabolites	Reference
Propetamphos	ns	rapidly and almost completely absorbed	Eliminated mostly via exhaled air as carbon dioxide	carbon dioxide	CVMP (1999e)
Streptomycin	animals and humans	poorly absorbed (oral)	Majority of oral dose excreted in the faeces. After parenteral dosing, drug excreted unchanged in the urine	ns	CVMP (2000c)
Tilmicosin	cattle, pigs	quickly absorbed from the injection site (cattle)	80% of orally administered radioactivity excreted via faeces, 20-65% of this as the parent compound	N-desmethyl tilmicosin	CVMP (1999f)
Toltrazuril	piglets, chickens, rats	-	49-90% of administered radioactivity excreted within 21 d, the parent compound toltrazuril accounting for 0-93%	toltrazuril-sulfoxide (15%) toltrazuril-sulfone (16-27% WAK 5665-2 (49%)	CVMP (1998g); CVMP (1999g) CVMP (2000d)
Trimethoprim	humans, pigs, poultry	>95% (oral)	46% of applied dose excreted in urine and faeces after 8 h, 22% of which was unchanged trimethoprim	1-N-oxide and 3-N-oxide metabolites; 4-hydroxy and 3-hydroxy derivatives	CVMP (1997c)
Tylosin	rat, cattle, dogs, pigs	low oral bioavailability (22.5%)	94-100% of the administered radioactivity excreted in the faeces, consisting predominantly of tylosin A, tylosin D and a metabolite	dihydrodesmycosin	CVMP (1997d)

APPENDIX H RESULTS OF SORPTION STUDIES ON A RANGE OF VETERINARY MEDICINES

Data provided in this Appendix and Appendix I have been assessed on their reliability and classified* into the following five review codes:

1. Experimental value retrieved from a source in which the method of determination has been clearly described, or in which a method is referred to and recovery information is provided.

2. Experimental value retrieved from a source in which the method of determination has been clearly described, or in which a method is referred to. The method is deemed *invalid* however and not suited for the determination of the property in question; the presented figure is considered to be *unreliable.*

3. Experimental value retrieved from a source in which method of determination has *not* been clearly described, or in which *no* method is referred to. Reliability of presented figure cannot be judged.

4. Review paper whereby the data has been transferred from an independently compiled data set.

5. Abstract or foreign paper in which the data are available only in a limited format, such as conference proceeding abstracts.

*An adaptation of the classification of reliability of physico-chemical data, taken from Belfroid *et al*. (1996).

Compound	Test Matrix	Kd	Koc	Reference	Review code
Avermectin B_{1a}	clay loam soil	147 (131-161)	5300	Gruber *et al* (1990)	1
	sand	17.4 (9.74-29.1)	30000	Gruber *et al* (1990)	1
	silt loam soil	80.2 (30.2-144)	6600	Gruber *et al* (1990)	1
Chlorfenvinphos	-	-	295	Briggs (1981)	4
Ciprofloxacin	centric flurisol	427	61000	Nowara *et al* (1997)	1
Efrotomycin	silt loam soil	18	1460	Yeager and Halley (1990)	1
	loam soil	8.3	580	Yeager and Halley (1990)	1
	sandy loam soil	51	8000	Yeager and Halley (1990)	1
	clay loam soil	290	11000	Yeager and Halley (1990)	1
Enrofloxacin	Rhodic ferrasol	3037	186342	Nowara *et al* (1997)	1
	Glegic cambisol	5612	768740	Nowara *et al* (1997)	1
	Haplic podsol	1230	99975	Nowara *et al* (1997)	1
	Rendzic leptosol	260	16506	Nowara *et al* (1997)	1
	Centric flurisol	496	70914	Nowara *et al* (1997)	1
	montmorollonite	6310	-	Nowara *et al* (1997)	1
	kaolinite	3548	-	Nowara *et al* (1997)	1
	illite	4670	-	Nowara *et al* (1997)	1
	vermiculite	5986	-	Nowara *et al* (1997)	1
Coumaphos	-	-	5778-21120	Tomlin (1997)	4
Deltamethrin	-	-	460000-16300000	Tomlin (1997)	4
Diazinon	-	-	229	Briggs (1981)	4
	-	-	1549	Melancom *et al*. (1986)	1
FCQA*	centric flurisol	285	40714	Nowara *et al* (1997)	1
Ivermectin	clay loam	333	12600	Halley *et al* (1989)	3
	silty clay loam	227	15700	Halley *et al* (1989)	3

Compound	Test Matrix	Kd	Koc	Reference	Review code
Metronidazole	sandy loam soil	0.67	42	Rabølle and Spliid (2000)	1
	sandy soil	0.54	39	Rabølle and Spliid (2000)	1
	sandy loam soil	0.62	56	Rabølle and Spliid (2000)	1
	loamy sand soil	0.57	38	Rabølle and Spliid (2000)	1
Ofloxacin	centric flurisol	309	44143	Nowara *et al* (1997)	1
Olaquindox	sandy loam soil	1.67	104	Rabølle and Spliid (2000)	1
	sandy soil	1.21	86	Rabølle and Spliid (2000)	1
	sandy loam soil	1.27	116	Rabølle and Spliid (2000)	1
	loamy sand soil	0.69	46	Rabølle and Spliid (2000)	1
Oxytetracycline	sandy loam soil	680	42506	Rabølle and Spliid (2000)	1
	sandy soil	670	47881	Rabølle and Spliid (2000)	1
	sandy loam soil	1026	93317	Rabølle and Spliid (2000)	1
	loamy sand soil	417	27792	Rabølle and Spliid (2000)	1
Sulfamethazine	clay loam soil	0.6	60	Thurman and Lindsey (2000)	3
Tetracycline	clay loam soil	>400	40000	Thurman and Lindsey (2000)	3
Tylosin	sandy loam soil	128	7988	Rabølle and Spliid (2000)	1
	sandy soil	10.8	771	Rabølle and Spliid (2000)	1
	sandy loam soil	62.3	5664	Rabølle and Spliid (2000)	1
	loamy sand soil	8.3	553	Rabølle and Spliid (2000)	1

*- fluorochloroquinolone carboxylic acid

APPENDIX I ENVIRONMENTAL FATE AND BEHAVIOUR

Compound	Test matrix/system	$t_{1/2}$ (d)	Reference	Review code
Ampicillin	sewage treatment	48 % biodegradable	Richardson and Bowron (1985)	2
Amprolium	laying hen faeces	30% degraded after 3 months	Van Dijk and Keukens (2000)	2
	broiler faeces	34% degraded after 8 d	Van Dijk and Keukens (2000)	2
Bacitracin	mixture of soil and chicken manure (20°C)	22.5	Gavalchin and Katz (1994)	2
	mixture of soil and chicken manure (30°C)	12	Gavalchin and Katz (1994)	2
Bambermycins	mixture of soil and chicken manure (20°C)	<25	Gavalchin and Katz (1995)	2
	mixture of soil and chicken manure (30°C)	<30	Gavalchin and Katz (1995)	2
Ceftiofam	OECD 301 D	10% degraded after 40 d	Al-Ahmad *et al.* (1999)	1
Ceftiofur	clay loam soil	22.2	Gilbertson *et al.* (1990)	1
	sandy soil	49.0	Gilbertson *et al.* (1990)	1
	silty clay loam soil	41.4	Gilbertson *et al.* (1990)	1
	aqueous hydrolysis (pH 5)	100	Gilbertson *et al.* (1990)	1
	aqueous hydrolysis (pH 7)	8.0	Gilbertson *et al.* (1990)	1
	aqueous hydrolysis (pH 9)	4.2	Gilbertson *et al.* (1990)	1
Chloramphenicol	freshwater and marine sediment (aerobic)	< 12	Lai *et al.* (1995)	1
	freshwater and marine sediment (anaerobic)	< 4	Lai *et al.* (1995)	1
	marine sediment (aerobic)	2.4-18.4	Chien *et al.* (1999)	1
	marine sediment (anaerobic)	0.4-2.4	Chien *et al.* (1999)	1
	freshwater sediment (aerobic)	transformation rate 1.9 – 6.6 mg l^{-1} d^{-1}	Bohm (1996)	5
	freshwater sediment (anaerobic)	transformation rate 20.6 – 24.8 mg l^{-1} d^{-1}	Bohm (1996)	5
	marine sediment (aerobic)	transformation rate 1.9 – 6.0 mg l^{-1} d^{-1}	Bohm (1996)	5
	marine sediment (anaerobic)	transformation rate 17.7 – 20.9 mg l^{-1} d^{-1}	Bohm (1996)	5
Chlorfenvinphos	field dt50	4-30 weeks	Reported in Lewis (1998)	4
	biodegradation in water	<25	Reported in Lewis (1998)	4
	sandy loam	<5 weeks	Reported in Lewis *et al.* (1993)	4

Compound	Test matrix/system	$t_{1/2}$ (d)	Reference	Review code
Chlorfenvinphos	high O.M soil	< 9 weeks	Reported in Lewis *et al.* (1993)	4
cont-d	sand	< 4 months	Reported in Lewis *et al.* (1993)	4
	peat	< 4 months	Reported in Lewis *et al.* (1993)	4
Chlorhexidine	sewage treatment	non-degradable	Richardson and Bowron (1985)	2
Chlortetracycline	mixture of soil and chicken manure (30°C)	44% removed after 30 d	Gavalchin and Katz (1994)	2
	mixture of soil and chicken manure (20°C)	no degradation after 30 d	Gavalchin and Katz (1994)	2
Ciprofloxacin	OECD 301 D	no degradation after 40 d	Al-Ahmad *et al.* (1999)	1
Coumaphos	photolysis on soil surface	23.8 d	Tomlin (1997)	4
	distilled water, pH4	33	Reported in Lewis *et al.* (1993)	4
	pond water, pH5.5	<7	Reported in Lewis *et al.* (1993)	4
	distilled water, pH7.0	347	Reported in Lewis *et al.* (1993)	4
	distilled water, pH8.5	29	Reported in Lewis *et al.* (1993)	4
	sandy loam soil	300	Reported in Lewis *et al.* (1993)	4
	silty loam soil	200	Reported in Lewis *et al.* (1993)	4
Cypermethrin	hydrolysis in soil	within 16 weeks	Tomlin (1997)	4
	degradation in water	5	Tomlin (1997)	4
Danofloxacin	three different soil types	87-143	Chen *et al*. (1997)	2
Deltamethrin	microbial degradation in soil	within 1-2 weeks	Tomlin (1997)	4
	DT50 laboratory aerobic	21-25	Tomlin (1997)	4
	DT50 laboratory anaerobic	31-36	Tomlin (1997)	4
	field DT50	<23	Tomlin (1997)	4
Diazinon	Water (conditions not reported), pH 3.1, 20°C	0.5	Reported in Lewis *et al.* (1993)	4
	Water (conditions not reported), pH 7.4, 20°C	185	Reported in Lewis *et al.* (1993)	4
	Water (conditions not reported), pH 10.4, 20°C	6	Reported in Lewis *et al.* (1993)	4
	Water ethanol (99:1 v/v), pH4.5, 25±3°C	3.2	Reported in Lewis *et al.* (1993)	4
	Water ethanol (99:1 v/v), pH 7.0, 25±3°C	70	Reported in Lewis *et al.* (1993)	4
	Water ethanol (99:1 v/v), pH 8.0, 25±3°C	54	Reported in Lewis *et al.* (1993)	4

Compound	Test matrix/system	$t_{1/2}$ (d)	Reference	Review code
Diazinon cont-d	Aqueous solution, pH 5.0, 20°C	3.8	Reported in Lewis *et al.* (1993)	4
	Aqueous solution, pH 7.0, 20°C	78	Reported in Lewis *et al.* (1993)	4
	Aqueous solution, pH 9.0, 20°C	40	Reported in Lewis *et al.* (1993)	4
	Aqueous solutions 0-28 ‰ salinity, 10°C	>100	Reported in Lewis *et al.* (1993)	4
	Aqueous solutions 0-28 ‰ salinity, 20°C	55 to >85	Reported in Lewis *et al.* (1993)	4
	Water pH 6.4-6.8	<30	Reported in Lewis *et al.* (1993)	4
	Sterile soil, pH 4.7	43.8	Reported in Lewis *et al.* (1993)	4
	Sterile sandy loam	88	Reported in Lewis *et al.* (1993)	4
	Sterile organic soil	46	Reported in Lewis *et al.* (1993)	4
	Flooded soil (previously treated), pH 6.0	1.7	Reported in Lewis *et al.* (1993)	4
	Flooded soil (not previously treated)	9.9	Reported in Lewis *et al.* (1993)	4
	Soil – type not given, 25 °C	11	Reported in Lewis *et al.* (1993)	4
	Loam soil, 10°C	21-35	Reported in Lewis *et al.* (1993)	4
	Humic, sandy soil, 10°C	112	Reported in Lewis *et al.* (1993)	4
	Photodegradation in soil	12-132 hours	Reported in Lewis *et al.* (1993)	4
Dichlorvos	biologically active soils and water systems	<1	Tomlin (1997)	4
Emamectin benzoate	marine sediments	164-175	CORDAH (1999)	1
	aerobic soil	193.4	CORDAH (1999)	1
	anaerobic soil	427	CORDAH (1999)	1
	aerobic soil for 30 d then anaerobic	174	CORDAH (1999)	1
	hydrolysis pH 5.2-8.0	stable over 6 weeks	SEPA (1999)	4
	hydrolysis pH9	19.5 weeks	SEPA (1999)	4
	photolysis in solution	1.4-22.4	SEPA (1999)	4
	photolysis/biodegradation in soil	5	SEPA (1999)	4
Erythromycin	sewage treatment	non-biodegradable	Richardson and Bowron (1985)	2
Ethinyl estradiol	activated sludge STW	99.9% removal	Ternes *et al.* (1999)	1
	biological filter STW	92% removal	Ternes *et al.* (1999)	1
	activated sludge STW	64% removal	Ternes *et al.* (1999)	1

Compound	Test matrix/system	$t_{1/2}$ (d)	Reference	Review code
Florfenicol	marine sediment (0-1 cm depth)	1.7	Hektoen *et al.* (1995)	2
	marine sediment (5-7 cm depth)	7.3	Hektoen *et al.* (1995)	2
Flumequine	marine sediment (0-1 cm depth)	60	Hektoen *et al.* (1995)	2
	marine sediment (5-7 cm depth)	>300	Hektoen *et al.* (1995)	2
	marine sediment	155	Hansen *et al.* (1993)	2
	marine sediment	no degradation after 180 d	Samuelsen *et al.* (1994)	2
	photodegradation in water	96 % degraded after 9 d	Lunestad *et al.* (1995)	
Flumethrin	Polluted water, 20°C	>9 months	Reported in Lewis (1998)	4
	Clean water, 30°C	>3 months	Reported in Lewis (1998)	4
Furazolidone	marine sediment	0.75	Samuelsen *et al.* (1991)	1
	photodegradation in water	92 % degraded after 9 d	Lunestad *et al.* (1995)	2
Ivermectin	photodegradation in water	<0.5	Halley *et al.* (1993)	4
	soil/faeces mixtures (summer)	7-14	Halley *et al.* (1989)	4
	soil/faeces mixtures (winter)	91-217	Halley *et al.* (1993)	4
	sandy loam soil	14-28	Bull *et al.* (1984)	1
	clay soil	28-56	Bull *et al.* (1984)	1
	sandy soil	56	Bull *et al.* (1984)	1
	dung	limited degradation after 45 d	Sommer *et al.* (1992)	2
Meropenem	OECD 301 D	7% degraded after 40 d	Al-Ahmad *et al.* (1999)	1
Meticlorpindol	laying hen faeces	68% degraded after 3 months	Van Dijk and Keukens (2000)	2
	broiler faeces	12% degraded after 8 d	Van Dijk and Keukens (2000)	2
Metronidazole	clay soil	13.1 – 26.9	Ingerslev and Halling-Sørensen (2001)	1
	sandy soil	9.7 – 14.7	Ingerslev and Halling-Sørensen (2001)	1
	sewage treatment	non-degradable	Richardson and Bowron (1985)	2
	closed bottle test	non-degradable	Kummerer *et al.* (2000)	1

Compound	Test matrix/system	$t_{1/2}$ (d)	Reference	Review code
Nicarbazin	broiler faeces	41% degraded after 8 d	Van Dijk and Keukens (2000)	2
Olaquindox	clay soil	5.8 – 7.5	Ingerslev and Halling-Sørensen (in press)	1
	sandy soil	5.9 – 8.8	Ingerslev and Halling-Sørensen (in press)	1
Ormethoprim	marine sediment	<30	Samuelsen *et al.* (1994)	2
	photodegradation in water	no degradation over 42 d	Lunestad *et al.* (1995)	2
Oxytetracycline	marine sediment (0-1 cm depth)	151	Hektoen *et al.* (1995)	2
	marine sediment (5-7 cm depth)	>300	Hektoen *et al.* (1995)	2
	marine sediment	9-419	Bjorklund *et al.* (1990)	2
	marine sediment	16	Coyne *et al.* (1994)	2
	marine sediment	125	Hansen *et al.* (1993)	2
	marine sediment	70	Jacobsen and Berglind (1988)	1
	marine sediment	30-64	Samuelsen (1989)	2
	marine sediment	87-144	Samuelsen *et al.* (1992a)	2
	marine sediment	41-83	Pouliquen *et al.* (1992)	2
	marine sediment	no degradation after 180 d	Samuelsen *et al.* (1994)	2
	freshwater and marine sediment (aerobic)	< 47 d	Lai *et al.* (1995)	1
	freshwater and marine sediment (anaerobic)	no degradation after 70 d	Lai *et al.* (1995)	1
	photodegradation in water	96% degraded after 9 d	Lunestad *et al.* (1995)	2
	freshwater sediment (aerobic)	transformation rate 1.5 – 3.0 mg l^{-1} d^{-1}	Bohm (1996)	5
	marine sediment (aerobic)	transformation rate 1.3 – 2.7 mg l^{-1} d^{-1}	Bohm (1996)	5
Oxolinic acid	marine sediment (0-1 cm depth)	151	Hektoen *et al.* (1995)	2
	marine sediment (5-7 cm depth)	>300	Hektoen *et al.* (1995)	2
	marine sediment	165	Hansen *et al.* (1993)	2
	marine sediment	48	Samuelsen (1992a)	2
	marine sediment	no degradation after 180 d	Samuelsen *et al.* (1994)	2
	photodegradation in water	88 % degraded after 9 d	Lunestad *et al.* (1995)	2

Compound	Test matrix/system	$t_{1/2}$ (d)	Reference	Review code
Penicillin	mixture of soil and chicken manure	< 3 h	Gavalchin and Katz (1994)	2
	OECD 301 D	36 % degraded after 40 d	Al-Ahmad *et al.* (1999)	1
Propetamphos	hydrolysis pH3	11	Reported in Lewis (1998)	4
	hydrolysis pH6	1 year	Reported in Lewis (1998)	4
	hydrolysis pH9	41	Reported in Lewis (1998)	4
	photolysis in aqueous solution	5	Reported in Lewis (1998)	4
Sarafloxicin	marine sediment (0-1 cm depth)	151	Hektoen *et al.* (1995)	2
	marine sediment (5-7 cm depth)	>300	Hektoen *et al.* (1995)	2
	marine sediment	0.06% degraded after 83 d	Marengo *et al.* (1997)	1
	loam soil	87-92 % degraded after 80 d	Marengo *et al.* (1997)	1
	silt loam soil	82-89 % degraded after 80 d	Marengo *et al.* (1997)	1
	sandy loam soil	69-82 % degraded after 80 d	Velagaleti *et al.* (1993)	1
	loam soil	0.66 % degraded after 65 d	Velagaleti *et al.* (1993)	1
	silty clay loam soil	0.43 % degraded after 65 d	Velagaleti *et al.* (1993)	1
	sandy clay loam soil	0.40 % degraded after 65 d	Velagaleti *et al.* (1993)	1
	photodegradation in water	< 1 h	Davis *et al.* (1993)	1
Sulfachloropyrazine	laying hen faeces	71% degraded after 3 months	Van Dijk and Keukens (2000)	2
	broiler faeces	65% degraded after 8 d	Van Dijk and Keukens (2000)	2
Sulfadiazine	marine sediment (0-1 cm depth)	50	Hektoen *et al.* (1995)	2
	marine sediment (5-7 cm depth)	100	Hektoen *et al.* (1995)	2
	marine sediment	no degradation after 180 d	Samuelsen *et al.* (1994)	2
	photodegradation in water	26% degraded after 21 d	Lunestad *et al.* (1995)	2
Sulfamethoxazole	OECD 301 D	no degradation after 40 d	Al-Ahmad (1999)	1
Sulfadimethoxine	marine sediment	20 % degraded after 180 d	Samuelsen *et al.* (1994)	2
	photodegradation in water	18 % degraded after 21 d	Lunestad *et al.* (1995)	2
Tetracycline	photodegradation in water	3 h	Oka *et al.* (1989)	1

Compound	Test matrix/system	$t_{1/2}$ (d)	Reference	Review code
Trimethoprim	marine sediment (0-1 cm depth)	75	Hektoen *et al.* (1995)	2
	marine sediment (5-7 cm depth)	100	Hektoen *et al.* (1995)	2
	marine sediment	<60 d	Samuelsen *et al.* (1994)	2
	photodegradation in water	no degradation over 42 d	Lunestad *et al.* (1995)	2
Tylosin	mixture of soil and chicken faeces	< 5 d	Galvachin and Katz (1994)	2
	clay soil	3.3 – 8.1	Ingerslev and Halling-Sørensen (2001)	1
	sandy soil	4.1 – 4.2	Ingerslev and Halling-Sørensen (2001)	1
	pig slurry	< 2	Loke *et al.* (2000)	1
Virginamycin	sandy silt soil	40% mineralized after 64 d	Weerasinghe and Tower (1997)	1
	silty sand soil	30% mineralized after 64 d	Weerasinghe and Tower (1997)	1
	silty sand soil	25% mineralized after 64 d	Weerasinghe and Tower (1997)	1
	silty clay loam soil	21% mineralized after 64 d	Weerasinghe and Tower (1997)	1
	clay loam soil	18% mineralized after 64 d	Weerasinghe and Tower (1997)	1
	silty clay loam soil	12% mineralized after 12 d	Weerasinghe and Tower (1997)	1

APPENDIX J AQUATIC TOXICITY

Data provided in this Appendix and Appendix K have been assessed on their reliability and classified* into the following five review codes:

1. Meets all the following criteria:
   - Methodology section published or well documented procedures
   - Satisfactory control
   - Measured toxicant concentration
   - For organic and non-metallic inorganic chemicals, the test water temperature, pH and dissolved oxygen are reported
   - For metals, the test water temperature, pH, dissolved oxygen and either alkalinity or hardness are reported (the latter two not for saltwater test)
2. Meets some criteria:
   - Control mortality not reported
   - No solvent control when a solvent is used in the test
   - Unmeasured toxicant concentration
   - Test water chemistry variables not reported or incomplete
3. Does not meet criteria:
   - Methods section shows weaknesses in experimental procedures, or insufficient methodology description
   - Control mortality unsatisfactory
   - A static test with unmeasured concentrations was conducted in the presence of precipitate or some undissolved chemical or in an unacceptable container
   - The test was conducted with chlorinated tap water, distilled water or rain water
   - All residue effects, as they do not meet BCF criteria
4. Abstract or foreign paper
   - Indicates that data are available only in a limited format, such as conference proceeding abstracts. The English abstract and/or table of data are used to review not translated papers
5. Data transferred from an independently compiled data set. Data have been quality assured in the original data set and meet the minimum data parameter requirements.

Taken from Belfroid *et al.* (1996)

Compound	Test organism	Toxic effect	Concentration (mg l^{-1})	Reference	Review code
Abamectin	*Crassostrea virginica*	96 hr LC50	430	Reported in Davies *et al.* (1997)	5
	Daphnia magna	48 hr LC50	0.34	Reported in Davies *et al.* (1997)	5
	Panaeus duorarum	96 hr LC50	1.6	Reported in Davies *et al.* (1997)	5
	Mysidopsis bahia	96 hr LC50	0.022	Reported in Davies *et al.* (1997)	5
	Callenectes sapidus	96 hr LC50	153	Reported in Davies *et al.* (1997)	5
Aminosidine	*D. magna*	24 hr LC50	1055	Reported in Holten Lützhøft *et al*. (1999)	5
	D. magna	48 hr EC50	503	Reported in Holten Lützhøft *et al*. (1999)	5
	D. magna	phototactic behaviour increased	10	Reported in Holten Lützhøft *et al*. (1999)	5
	Artemia (nauplii)	48 hr EC50	2220	Migliore *et al.* (1997)	2
	Artemia (nauplii)	72 hr EC50	846.5	Migliore *et al.* (1997)	2
Amoxillin	*Microcystis aeruginosa*	EC50	0.0037	Holten Lützhøft *et al*. (1999)	2
	Selenastrum capricornutum	NOEC	250	Holten Lützhøft *et al*. (1999)	2
	Rhodomonas salina	EC50	3108	Holten Lützhøft *et al*. (1999)	2
Amitraz	*Acanthocyclops vernalis*	96 hr EC50	58.5	US EPA (2001)	5
	Ankistiodesmus falcatus	10 d EC50 (histology)	1.9	US EPA (2001)	5
	Anabaena flosaquae	5 d EC50	3.4	US EPA (2001)	5
	Asellus brevicaudis	48 hr LC50	>100	US EPA (2001)	5
	Chlorella vulgaris	96 hr NOEC	100	US EPA (2001)	5
	C.. virginica	14 d LC50	255.44	US EPA (2001)	5
	Cypidopsis vidua	48 hr LC50	32	US EPA (2001)	5
	Cyprinodon variegatus	96 LC50	>1000	US EPA (2001)	5
	D. magna	48 hr EC50	18-30	US EPA (2001)	5
	Gammarus fasciatus	48 hr LC50	100	US EPA (2001)	5
	Lepomis macrochirus	96 hr LC50	10-1000	US EPA (2001)	5
	Notropis atherinoides	96 hr LC50	420	US EPA (2001)	5
	Oncorhynchus mykiss	96 hr LC50	243	US EPA (2001)	5
	Pimephales promelas	96 hr LC50	100	US EPA (2001)	5
	Poecilia reticulata	96 hr LC50	410	US EPA (2001)	5
	S. capricornutum	5 d EC50	2.3	US EPA (2001)	5
	S. capricornutum	96 hr NOEC	1	US EPA (2001)	5
	Unspecified algae	72 hr EC50	12	Lewis and Bardon (1998)	5
	D. magna	48 hr EC50	0.035	Lewis and Bardon (1998)	5
	Unspecified fish	96 hr LC50	0.74	Lewis and Bardon (1998)	5

Compound	Test organism	Toxic effect	Concentration (mg l^{-1})	Reference	Review code
Ampicillin	*Vibrio fischeri*	24 hr EC50	163	Backhaus and Grimme (1999)	3
Azamethiphos	*Homarus americanus*	48 hr LC50	0.00103-0.00357	US EPA (2001)	5
	Lepeophtheirus salmonis	40 min (behaviour)	0.1	US EPA (2001)	5
	Lepeophtheirus salmonis	40 min (increased mortality)	0.1	US EPA (2001)	5
Bacitracin	*Artemia salina* (nauplii)	24 hr EC50	34.1	Migliore *et al*. (1997)	2
	A. salina (nauplii)	48 hr EC50	21.8	Migliore *et al*. (1997)	2
	A. salina	LC100	6.3	Migliore *et al*. (1997)	2
	A salina. (cysts)	Hatching	25	Migliore *et al*. (1997)	2
	D. magna	24 hr LC50	126.4	Reported in Webb (2001)	5
	D. magna	48 hr LC50	30.5	Reported in Holten Lützhøft *et al*. (1999)	5
	D. magna	phototactic behaviour decreased	10	Reported in Holten Lützhøft *et al*. (1999)	5
Benzyl alcohol	*D. magna*	24 hr EC50 (behaviour)	55-400	US EPA (2001)	5
	Haematococcus pluvialis	4 hr EC50 (histology)	2600	US EPA (2001)	5
	Leuciscus idus melanotus	48 hr LC50	646	US EPA (2001)	5
	Aedes aegypti	24 hr EC50	105-129	US EPA (2001)	5
	Aedes scutellaris	24 hr EC50	110-126	US EPA (2001)	5
	L. machrochirus	96 hr LC50	10	US EPA (2001)	5
	Mendia beryllina	96 hr LC50	15	US EPA (2001)	5
	P. promelas	96 hr LC50	460	US EPA (2001)	5
	Tetrahymena pyriformis	48 hr EC50	853	US EPA (2001)	5
	Petromyzon marinus	24 EC50	5	US EPA (2001)	5
Benzyl penicillin	*M. aeruginosa*	7 d EC50	0.006	Halling-Sørensen (2000)	2
	S. capricornutum	72 hr NOEC	100	Halling-Sørensen (2000)	2
Chloramphenicol	*A. salina*	24 hr LC50	2042	Reported in Webb (2001)	5
	Brachionus calyciflorus	24 hr LC50	2074	Reported in Webb (2001)	5
	D. magna	24 hr EC50	543	Reported in Webb (2001)	5
	D. magna	24 hr EC50	1086	Reported in Webb (2001)	5
	Streptocephalus proboscideus	24 hr LC50	305	Reported in Webb (2001)	5
	Vibrio fischeri	24 hr EC50	0.0643	Backhaus and Grimme (1999)	3
	Scenedesmus vacuolatus	inhibition of reproduction	4.07	Meyer *et al.* (2001)	3

Compound	Test organism	Toxic effect	Concentration (mg l^{-1})	Reference	Review code
Chlorfenvinphos	*S. quadricauda*	24 h EC100 (photosynthesis)	100	Reported in Lewis *et al.* (1993)	5
	Lemna minor	9-10 d interruption of chlorophyll	0.6	Reported in Lewis *et al.* (1993)	5
	D. magna	24 hr LC50	0.00028	Reported in Lewis *et al.* (1993)	5
	D. magna	48 hr LC50	0.0001	Reported in Lewis *et al.* (1993)	5
	G. fasciatus	24 hr LC50	0.027	Reported in Lewis *et al.* (1993)	5
	G. fasciatus	96 hr LC50	0.0096	Reported in Lewis *et al.* (1993)	5
	Pteronarcys californica	24 hr LC50	0.0058	Reported in Lewis *et al.* (1993)	5
	Pteronarcyc californica	96 hr LC50	0.0007	Reported in Lewis *et al.* (1993)	5
	Culex pipiens	72 hr LC100	0.002	Reported in Lewis *et al.* (1993)	5
	Carp	24 hr LC50	0.055	Reported in Lewis *et al.* (1993)	5
	Carp	48 hr LC50	0.045-0.27	Reported in Lewis *et al.* (1993)	5
	Lebistes reticulatus	24 hr LC50	2.1	Reported in Lewis *et al.* (1993)	5
	L. reticulatus	48 hr LC50	1.78	Reported in Lewis *et al.* (1993)	5
	L. reticulatus	96 hr LC50	1.5	Reported in Lewis *et al.* (1993)	5
	L. reticulatus (juvenile)	24 hr LC50	1.4-2.7	Reported in Lewis *et al.* (1993)	5
	L. reticulatus (juvenile)	24 hr external symptoms of poisoning	0.5	Reported in Lewis *et al.* (1993)	5
	L. macrochirus	24 hr LC50	0.0028-0.05	Reported in Lewis *et al*. (1993)	5
	L. macrochirus	96 hr LC50	0.023	Reported in Lewis *et al.* (1993)	5
	P. reticulata	24 hr LC50	2.03	Reported in Lewis *et al.* (1993)	5
	P. reticulata	48 hr LC50	0.53	Reported in Lewis *et al*. (1993)	5
	P. reticulata	72 – 96 hr LC50	1.56	Reported in Lewis *et al.* (1993)	5
	Rasbora heteromorpha	24 hr LC50	0.36	Reported in Lewis *et al.* (1993)	5
	R. heteromorpha	48 hr LC50	0.27	Reported in Lewis *et al*. (1993)	5
	R. heteromorpha	96 hr LC50	0.32	Reported in Lewis *et al*. (1993)	5
	O. mykiss	24 hr LCC50	1.65	Reported in Lewis *et al*. (1993)	5
	O. mykiss	96 hr LC50	0.51	Reported in Lewis *et al*. (1993)	5
	Carrassius auratus	48 hr LC50	0.34	Reported in Lewis *et al.* (1993)	5
	Scenedesmus subspicatus	72 hr EC50 (inhibition of growth)	1.94	Reported in Lewis (1998)	5
	S. subspicatus	96 hr EC50 (inhibition of growth)	1.36	Reported in Lewis (1998)	5
	S. subspicatus	96 hr NOEC (inhibition of growth)	0.246	Reported in Lewis (1998)	5
	S. subspicatus	96 hr LOEC (inhibition of growth)	0.788	Reported in Lewis (1998)	5
	S. capricornutum	96 hr EC50 (inhibition of growth)	1.6	Reported in Lewis (1998)	5
	D. Magna	24 hr EC50 (immobilisation)	0.0012	Reported in Lewis (1998)	5
	D. Magna	48 hr EC50 (immobilisation)	0.00025	Reported in Lewis (1998)	5
	D. Magna	24 hr EC50	0.0018	Reported in Lewis (1998)	5

Compound	Test organism	Toxic effect	Concentration (mg l^{-1})	Reference	Review code
	D. Magna	48 hr EC50	0.00046	Reported in Lewis (1998)	5
	Ceriodaphnia dubia	48 hr LC50	0.0004	Reported in Lewis (1998)	5
Chlortetracycline	*M aeruginosa*	7 d EC50	0.05	Halling-Sørensen (2000)	2
	S. capricornutum	72 hr EC50	3.1	Halling-Sørensen (2000)	2
Cinoxacin	*V. fischeri*	24 hr EC50	0.117	Backhaus *et al*. (2000)	1
	S. vacuolatus	EC50	>26	Backhaus *et al.* (2001)	3
	Anguilla japonica	LC50	73	US EPA (2001)	5
Ciprofloxacin	*M. aeruginosa*	EC50	0.005	Holten Lützhøft and Halling-Sørensen (unpublished)	5
	Pseudomonas putida	EC50 (growth inhibition)	0.08	Kummerer *et al.*(2000)	3
Coumaphos	*Gammarus lacustris* (scud)	24 hr LC50	0.00032	Reported in Lewis *et al.* (1993)	5
	G. lacustris (scud)	48 hr LC50	0.00014	Reported in Lewis *et al.* (1993)	5
	G. lacustris (scud)	96 hr LC50	0.000074	Reported in Lewis *et al*. (1993)	5
	G. lacustris (shrimp)	48 hr LC50	0.002	Reported in Lewis *et al*. (1993)	5
	Simocephalus serrulatus (1st instar)	48 hr LC50	0.0001	Reported in Lewis *et al*. (1993)	5
	S. serrulatus	48 hr LC50	0.001	Reported in Lewis *et al*. (1993)	5
	Hexagenia spp. (naiad)	24 hr LC50	0.43	Reported in Lewis *et al*. (1993)	5
	Hydropsyche spp. (larvae)	24 hr LC50	0.005	Reported in Lewis *et al*. (1993)	5
	O. mykiss (juvenile)	24 hr LC50	2.6-3.0	Reported in Lewis *et al*. (1993)	5
	O. mykiss (juvenile)	48 hr LC50	0.55-1.8	Reported in Lewis *et al*. (1993)	5
	O. mykiss	72 hr LC50	1.5	Reported in Lewis *et al*. (1993)	5
	O. mykiss	96 hr LC50	0.89-1.5	Reported in Lewis *et al*. (1993)	5
	Salmo trutta	24 hr LC50	0.92	Reported in Lewis *et al*. (1993)	5
	S. trutta	48 hr LC50	0.73	Reported in Lewis *et al*. (1993)	5
	Salvelinus fontinalis	24 hr LC50	1.06	Reported in Lewis *et al*. (1993)	5
	S. fontinalis	48 hr LC50	0.8	Reported in Lewis *et al*. (1993)	5
	Salvelinus namaycush (juvenile)	24 hr LC50	6.8	Reported in Lewis *et al*. (1993)	5
	S. namaycusk (juvenile)	48 hr LC50	4	Reported in Lewis *et al*. (1993)	5
	S. namaycush	24 hr LC50	0.99	Reported in Lewis *et al*. (1993)	5
	S. namaycush	96 hr LC50	0.59	Reported in Lewis *et al*. (1993)	5
	Onchorhyncus clarkii	24 hr LC50	1.09	Reported in Lewis *et al*. (1993)	5

Compound	Test organism	Toxic effect	Concentration (mg l^{-1})	Reference	Review code
	O. clarkii	96 hr LC50	0.86	Reported in Lewis *et al*. (1993)	5
	Onchorhyncus kisutch	24 hr LC50	22	Reported in Lewis *et al*. (1993)	5
	O. kisutch	48 hr LC50	20	Reported in Lewis *et al*. (1993)	5
	O. kisutch	72 hr LC50	18	Reported in Lewis *et al*. (1993)	5
	O. kisutch	96 hr LC50	15	Reported in Lewis *et al*. (1993)	5
	Ictalurus punctatus (juvenile)	24 hr LC50	6.8	Reported in Lewis *et al*. (1993)	5
	I. punctatus	24 hr LC50	5.2	Reported in Lewis *et al*. (1993)	5
	I. punctatus	96 hr LC50	0.84	Reported in Lewis *et al*. (1993)	5
	L. macrochirus (juvenile)	24 hr LC50	10.5	Reported in Lewis *et al*. (1993)	5
	L. macrochirus (juvenile)	48 hr LC50	8	Reported in Lewis *et al*. (1993)	5
	L. macrochirus	24 hr LC50	1.1-1.4	Reported in Lewis *et al*. (1993)	5
	L. macrochirus	96 hr LC50	0.18-0.34	Reported in Lewis *et al*. (1993)	5
	P. promelas	96 hr LC50	>18	Reported in Lewis *et al*. (1993)	5
	P. promelas	48 hr LC50	>1	Reported in Lewis *et al*. (1993	5
	Micropterus salmoides	24 hr LC50	1.5	Reported in Lewis *et al*. (1993)	5
	M. salmoides	36 hr LC50	0.5	Reported in Lewis *et al*. (1993)	5
	M. salmoides	96 hr LC50	1.1	Reported in Lewis *et al*. (1993)	5
	L. reticulatus	96 hr LC50	>0.56	Reported in Lewis *et al*. (1993)	5
	R. heteromorpha	24 hr LC50	0.082	Reported in Lewis *et al*. (1993)	5
	R. heteromorpha	48 hr LC50	0.046	Reported in Lewis *et al*. (1993)	5
	Carassius auratus	96 hr LC50	>18	Reported in Lewis *et al*. (1993)	5
	Stizostedion vitreum	24 hr LC50	1.35	Reported in Lewis *et al*. (1993)	5
	S. vitreum	96 hr LC50	0.78	Reported in Lewis *et al*. (1993)	5
	A. salina (larvae (24 hr))	24 hr LC50	21.23	Reported in Lewis (1998)	5
	A. salina (larvae (48 hr))	24 hr LC50	5.51	Reported in Lewis (1998)	5
	A. salina (larvae (72 hr))	24 hr LC50	5.22	Reported in Lewis (1998)	5
Cypermethrin	*D. magna*	48 hr LC50	0.00015	Tomlin (1997)	5
Cypromazine	*D. magna*	48 hr EC50	97.8	US EPA (2001)	5
	Deleatidium spp.	48 hr LC50	>300	US EPA (2001)	5
	Gambusia affinis	72 hr LC50	0.037	US EPA (2001)	5
	I. punctatus	96 hr LC50	91.6	US EPA (2001)	5
	L. macrochirus	96 hr LC50	89.7	US EPA (2001)	5
	O. mykiss	96 hr LC50	87.9	US EPA (2001)	5

Compound	Test organism	Toxic effect	Concentration (mg l^{-1})	Reference	Review code
	Dugesia dorotocephala	72 hr LC50	>10	US EPA (2001)	5
	Dugesia tigrina	72 hr LC50	>10	US EPA (2001)	5
	D. tigrina	72 hr EC50 (reproduction)	>10	US EPA (2001)	5
Deltamethrin	*D. magna*	48 hr LC50	0.0035	Tomlin (1997)	5
	Aedes aegypli	96 hr LC50	0.00015	US EPA (2001)	5
	Alburnus alburnus	7 d LC50	8.8	US EPA (2001)	5
	Americamysis bahia	96 hr LC50	0.0017-0.0037	US EPA (2001)	5
	Anadonta anatina	7 d LC50	8600	US EPA (2001)	5
	Anadonta cygnea	7 d LC50	6300	US EPA (2001)	5
	Baetis parvus	1 hr LC50	0.0004	US EPA (2001)	5
	Bufo arenarium	96 hr LC50	0.0045	US EPA (2001)	5
	Chironomus decorus	24 hr LC50	0.00027-0.0011	US EPA (2001)	5
	Chironomus salinarius	24 hr LC50	0.00071	US EPA (2001)	5
	Chironomus utahensis	24 hr LC50	0.00029	US EPA (2001)	5
	C. virginica	96 hr EC50	17-9-110	US EPA (2001)	5
	C. virginica	96 hr EC50	0.018-0.11	US EPA (2001)	5
	Cricotopus	24 hr LC50	0.00011-0.00015	US EPA (2001)	5
	Ctenopharyngodon idella	96 hr LC50	0.091	US EPA (2001)	5
	C. pipiens	24 hr LC50	0.00002	US EPA (2001)	5
	Cyprinodon macularius	48 hr LC50	0.0006	US EPA (2001)	5
	Cyprinodon variegatus	96 hr LC50	0.00036-0.00058	US EPA (2001)	5
	Cyprinus carpio	96 hr LC50	0.078	US EPA (2001)	5
	Homarus americanus	96 hr LC50	0.0000014	US EPA (2001)	5
	L. macrochirus	96 hr LC50	0.00036-0.0015	US EPA (2001)	5
	Lymnaea acuminata	96 hr LC50	0.44-0.45	US EPA (2001)	5
	O. mykiss	96 hr LC50	0.00025-0.0023	US EPA (2001)	5
	S. salar	96 hr LC50	0.00197	US EPA (2001)	5
	Procladius	24 hr LC50	0.000067	US EPA (2001)	5
	Similium virgatum	1 hr LC50	0.0009	US EPA (2001)	5
	Tanypus nubifer	24 hr LC50	0.00011	US EPA (2001)	5
	Tilapia mossambica	48 hr LC50	0.0008	US EPA (2001)	5
	Tilipia nilotica	96 hr LC50	0.000145	US EPA (2001)	5

Compound	Test organism	Toxic effect	Concentration (mg l^{-1})	Reference	Review code
Diazinon	*Gillia altilis*	96 hr LC50	11	Reported in Lewis *et al*. (1993)	5
	Daphnia sp.	48 hr LC50	0.0009-0.0018	Reported in Lewis et al (1993)	5
	D. magna	48 hr LOEC	0.0015	Burkepile *et al.* (2000)	2
	D. pulex	48 hr EC50	0.0008	Reported in Lewis *et al*. (1993)	5
	G. fasciatus	24 hr LC50	0.008	Reported in Lewis *et al*. (1993)	5
	G. fasciatus	96 hr LC50	0.0002	Reported in Lewis *et al*. (1993)	5
	G. lacustris	24 hr LC50	0.8	Reported in Lewis *et al*. (1993)	5
	G. lacustris	48 hr LC50	0.5	Reported in Lewis *et al*. (1993)	5
	G. lacustris	96 hr LC50	0.2	Reported in Lewis *et al*. (1993)	5
	S. serrulatus	48 hr EC50	0.0014-0.0018	Reported in Lewis *et al*. (1993)	5
	P. californica	24 hr LC50	0.155	Reported in Lewis *et al*. (1993)	5
	P. californica	48 hr LC50	0.06	Reported in Lewis *et al*. (1993)	5
	P. californica	96 hr LC50	0.025	Reported in Lewis *et al*. (1993)	5
	O. mykiss (juvenile)	24 hr LC50	0.38	Reported in Lewis *et al*. (1993)	5
	O. mykiss (juvenile)	48 hr LC50	0.17	Reported in Lewis *et al*. (1993)	5
	O. mykiss (juvenile)	96 hr LC50	0.09	Reported in Lewis *et al*. (1993)	5
	O. mykiss	96 hr LC50	0.02-3.2	Reported in Lewis *et al*. (1993)	5
	S. namaycush	24 hr LC50	2.19	Reported in Lewis *et al*. (1993)	5
	S. namaycush	96 hr LC50	0.6	Reported in Lewis *et al*. (1993)	5
	O. clarkii	24 hr LC50	2.58-3.59	Reported in Lewis *et al*. (1993)	5
	O. clarkii	96 hr LC50	1.7-2.76	Reported in Lewis *et al*. (1993)	5
	S. fontinalis	96 hr LC50	0.77	Reported in Lewis *et al*. (1993)	5
	L. macrochirus (juvenile)	24 hr LC50	0.052-0.36	Reported in Lewis *et al*. (1993)	5
	L. macrochirus (juvenile)	48 hr LC50	0.03	Reported in Lewis *et al*. (1993)	5
	L. macrochirus (juvenile)	96 hr LC50	0.02-0.17	Reported in Lewis *et al*. (1993)	5
	L. macrochirus	48 hr LC50	0.08	Reported in Lewis *et al*. (1993)	5
	L. macrochirus	96 hr LC50	0.09-16	Reported in Lewis *et al*. (1993)	5
	P. promelas (juvenile)	96 hr LC50	7.8	Reported in Lewis *et al*. (1993)	5
	Jordinella floridae	96 hr LC50	1.6	Reported in Lewis *et al*. (1993)	5
	R. heteromorpha	24 hr LC50	1.45	Reported in Lewis *et al*. (1993)	5
	Cyprinus carpio	96 hr LC50	7.6-23.4	Reported in Lewis *et al*. (1993)	5
	Channa punctatus	96 hr LC50	3.1	Reported in Lewis *et al*. (1993)	5
	Saccobranchus fossilis	24 hr LC50	5.14	Reported in Lewis *et al*. (1993)	5
	S. fossilis	96 hr LC50	4.57	Reported in Lewis *et al*. (1993)	5
	Brachydanio rerio	24 hr LC50	2.3	Reported in Lewis *et al*. (1993)	5
	B. rerio	48 hr LC50	2.24	Reported in Lewis *et al*. (1993)	5

Compound	Test organism	Toxic effect	Concentration (mg l^{-1})	Reference	Review code
	B. rerio	72 hr LC50	2.19	Reported in Lewis *et al*. (1993)	5
	B. rerio	96 hr LC50	2.12	Reported in Lewis *et al*. (1993)	5
	Ceriodaphnia dubia	48 hr LOEC	0.0008	Burkepile *et al.* (2000)	2
	Hyallela azteca	48 hr LOEC	0.011	Burkepile *et al.* (2000)	2
	Chironomus tentans	48 hr LOEC	0.0375	Burkepile *et al.* (2000)	2
	P. promelas	48 hr LOEC	12.5	Burkepile *et al.* (2000)	2
	Oryzias latipes	48 hr LC50	4.4	Reported in Larkin and Tjeerdema (2000)	5
	Anguilla anguilla	96 hr LC50	0.8	Reported in Larkin and Tjeerdema (2000)	5
	Cyprinodon variegatus	96 hr LC50	1.4	Reported in Larkin and Tjeerdema (2000)	5
	Ceriodaphnia dubia	48 hr LC50	0.000026-0.00058	Reported in Larkin and Tjeerdema (2000)	5
	D. tigrina	96 hr LC50	0.63+0.2	Reported in Larkin and Tjeerdema (2000)	5
	Brachionus calyciflorus	24 hr LC50	29.22	Reported in Larkin and Tjeerdema (2000)	5
	Chironomus tepperi (4^{th} instar larvae)	LC50	0.0355	Reported in Larkin and Tjeerdema (2000)	5
				Reported in Larkin and Tjeerdema (2000)	5
	M. bahia (juvenile)	96 hr LC50	0.00858	Reported in Larkin and Tjeerdema (2000)	5
	Penaeus duorarum (post-larvae)	96 hr LC50	0.021	Reported in Larkin and Tjeerdema (2000)	5
Dichlorvos	*Daphnia* spp.	48 hr LC50	0.00019	Tomlin (1997)	5
	Daphnia spp.	48 hr LC50	0.00019	Tomlin (1997)	
Doramectin	*D. magna*	48 hr NOEC	0.025	Taylor (1999)	5
	L. macrochirus	96 hr LC50	11	Taylor (1999)	5
	Salmo gairdneri	96 hr LC50	5.1	Taylor (1999)	5
Dimetridazole	*Gyrodactylus salaris*	25% mortality over 1 hr	200	US EPA (2001)	5
	O. mykiss	behavioural effect	200	US EPA (2001)	5
Emamectin benzoate	*Corophium volutator*	10 d LC50 (sediment)	0.193 mg kg^{-1}	CORDAH (1999)	1
	C. volutator	10 d LC50 (water)	0.00632	CORDAH (1999)	1
	Arenicola marina	10 d LC50 (sediment)	0.111 mg kg^{-1}	CORDAH (1999)	1
	Mysidopsis bahia	10 d LC50	0.000043	CORDAH (1999)	1
	C. virginica	96 hr EC50 (shell deposition)	0.53	CORDAH (1999)	1
	C. virginica	96 hr LC50 (calculated)	0.665	CORDAH (1999)	1
	Nephrops norvegicus	96 hr LC50 (water)	0.983	CORDAH (1999)	1
	N. norvegicus	192 hr LC50 (water)	0.572	CORDAH (1999)	1
	N. norvegicus	96 hr NOEC (feed exposure)	68.2 mg kg^{-1}	CORDAH (1999)	1
	Artemia salina	6 h IC100	1.73	CORDAH (1999)	

Compound	Test organism	Toxic effect	Concentration (mg l^{-1})	Reference	Review code
	N. norvegicus	192 hr NOEC (feed exposure)	68.2 mg kg^{-1}	CORDAH (1999)	1
	Crangon crangon	96 hr LC50 (water)	0.242	CORDAH (1999)	1
	C. crangon	192 hr NOEC (water)	<0.16	CORDAH (1999)	1
	C. crangon	96 hr NOEC (feed exposure)	69.3 mg kg^{-1}	CORDAH (1999)	1
	C. crangon	192 hr NOEC (feed exposure)	69.3 mg kg^{-1}	CORDAH (1999)	1
	D. magna	48 hr LC50	0.001	CORDAH (1999)	1
	D.magna	21 d LOEC (reproduction)	0.00016	CORDAH (1999)	1
	D.magna	21 d LC50 (calculated)	0.000128	CORDAH (1999)	1
	Tetranychus urticae	Unspecified	0.3	CORDAH (1999)	1
	O. mykiss	96 hr LC50	0.174	CORDAH (1999)	1
	L. macrochirus	96 hr LC50	0.18	CORDAH (1999)	1
	P. promelas	96 hr LC50	0.194	CORDAH (1999)	1
	P. promelas	ELS LOEC	0.028	CORDAH (1999)	1
	C. variegatus	96 hr LC50	1.34	CORDAH (1999)	1
Enoxacin	*V. fischeri*	24 hr EC50	0.049	Backhaus *et al.* (2000)	1
	S. vacuolatus	EC50	19.7	Backhaus *et al.* (2001)	3
Erythromycin	*D. magna*	24 hr LC50	388	Reported in Webb (2001)	5
	D. magna	48 hr LC50	211	Reported in Webb (2001)	5
	D. magna	48 hr EC50	30.5	Reported in Holten Lützhøft *et al*. (1999)	5
	Artemia (cysts)	120 hr LC100	<10	Migliore *et al.* (1997)	2
	Artemia (cysts)	48 hr NOEC	<10	Migliore *et al.* (1997)	2
Ethinyl estradiol	*D. magna*	24 hr EC50	5.7	Reported in Webb (2001)	5
	D. magna	48 hr EC50	6.4	Reported in Webb (2001)	5
	O. mykiss	96 hr EC50	1.6	Reported in Webb (2001)	5
	P. putida	Microbial growth inhibition	>20	Schweinfurth *et al.* (1996)	5
	Azobacter beijerincki	Microbial growth inhibition	>20	Schweinfurth *et al.* (1996)	5
	Aspergillus niger	Microbial growth inhibition	>20	Schweinfurth *et al.* (1996)	5
	Chaetomium globosum	Microbial growth inhibition	>20	Schweinfurth *et al.* (1996)	5
	Nostoc ellipsporum	Microbial growth inhibition	>20	Schweinfurth *et al.* (1996)	5
	unspecified algae	EC50	0.84	Kopf (1995)	4
	Daphnia spp.	EC50 (reproduction)	0.105	Kopf (1995)	4
	Daphnia spp.	EC50 (acute test)	5.7	Kopf (1995)	4
	Daphnia spp.	48 hr EC50	6.4	Schweinfurth *et al.* (1996)	5

Compound	Test organism	Toxic effect	Concentration (mg l^{-1})	Reference	Review code
	Daphnia spp.	NOEC (immobilisation)	3	Schweinfurth *et al.* (1996)	5
	Daphnia spp.	21 d NOEC (number of offspring)	>0.387	Schweinfurth *et al.* (1996)	5
	Daphnia spp.	21 d NOEC (immobilisation)	>0.387	Schweinfurth *et al.* (1996)	5
	O. mykiss	96 hr EC50	1.61	Schweinfurth *et al.* (1996)	5
	P. promelas (larvae)	28 d LOEC (changes to kidney/liver)	0.00001	Schweinfurth *et al.* (1996)	5
	P. promelas (larvae)	28 d LOEC (decreased growth)	≥0.0001	Schweinfurth *et al.* (1996)	5
	P. promelas (larvae)	28 d LOEC (mortality)	≥0.001	Schweinfurth *et al.* (1996)	5
	P. promelas (juvenile)	28 d LOEC (changes to kidney/liver)	0.00001	Schweinfurth *et al.* (1996)	5
	P. promelas (juvenile)	28 d LOEC (mortality)	≥0.001	Schweinfurth *et al.* (1996)	5
	P. promelas (adult)	28 d LOEC (inhibited egg production)	≥0.00001	Schweinfurth *et al.* (1996)	5
	P. promelas (adult)	28 d LOEC (mortality)	≥0.001	Schweinfurth *et al.* (1996)	5
	P. promelas	9 mth reproduction NOEC (growth retardation LOEC 4 ng l^{-1})	0.000001	Reported in Webb (2001)	5
	Rutilus rutilus	10 d plasma vitellogenin NOEC (9°C)	0.000001	Reported in Webb (2001)	5
				Reported in Webb (2001)	5
	O. mykiss	10 d plasma vitellogenin NOEC (9°C)	0.000001	Reported in Webb (2001)	5
	O. mykiss	28 wk plasma vitellogenin LOEC	0.0000003	Reported in Webb (2001)	5
	O. mykiss	10 d plasma vitellogenin LOEC (16.5°C)	0.0000001	Reported in Webb (2001)	5
	Lymnaea stagnalis	50-60 d LOEC (growth)	0.00000125	Reported in Webb (2001)	5
Fenbendazole	*Pseudodactylogyrus*	population decrease over 24 hr	1-10	US EPA (2001)	5
	Anguilla anguilla	24 hr (physiology and growth effect) 48 hr EC50	1-10	US EPA (2001)	5
	D. magna	96 hr LC50	1000	Lewis and Bardon (1998)	5
	Unspecified fish		500	Lewis and Bardon (1998)	5
Fenchlorphos	Unspecified shrimp	48 hr LC50	0.005	Reported in Lewis *et al*. (1993)	5
	I. punctatus (juvenile)	24 hr LC50	1.76	Reported in Lewis *et al*. (1993)	5
	I. punctatus (juvenile)	48 hr LC50	1.26	Reported in Lewis *et al*. (1993)	5
	L. macrochirus (juvenile)	24 hr LC50	2.5	Reported in Lewis *et al*. (1993)	5
	L. macrochirus (juvenile)	48 hr LC50	1	Reported in Lewis *et al*. (1993)	5

Compound	Test organism	Toxic effect	Concentration (mg l^{-1})	Reference	Review code
	O. mykiss (juvenile)	24 hr LC50	1.17	Reported in Lewis *et al*. (1993)	5
	O. mykiss (juvenile)	48 hr LC50	0.74	Reported in Lewis *et al*. (1993)	5
	S. trutta (juvenile)	24 hr LC50	0.53	Reported in Lewis *et al*. (1993)	5
	S. trutta (juvenile)	48 hr LC50	0.39	Reported in Lewis *et al*. (1993)	5
	S. fontinalis (juvenile)	24 hr LC50	0.59	Reported in Lewis *et al*. (1993)	5
	S. fontinalis (juvenile)	48 hr LC50	0.39	Reported in Lewis *et al*. (1993)	5
	S. namaycush (juvenile)	24 hr LC50	0.73	Reported in Lewis *et al*. (1993)	5
	S. namaycush (juvenile)	48 hr LC50	0.62	Reported in Lewis *et al*. (1993)	5
Flumequine	*M. aeruginosa*	EC50	0.159	Holten Lützhøft *et al*. (1999)	2
	S. capricornutum	EC50	5.0	Holten Lützhøft *et al*. (1999)	2
	R. salina	EC50	18	Holten Lützhøft *et al*. (1999)	2
	Lythrum salicaria	Growth	<100	Migliore *et al.* (2000)	2
	Vibrio fischeri	24 hr EC50	0.019	Backhaus *et al*. (2000)	1
	A. salina (nauplii)	24 hr EC50	477	Migliore *et al*. (1997)	2
	A. salina (nauplii)	48 hr EC50	308	Migliore *et al*. (1997)	2
	A. salina (nauplii)	72 hr EC50	96.4	Migliore *et al*. (1997)	2
	A. salina(nauplii)	22% mortality	6.31	Migliore *et al*. (1997)	2
	A. salina (nauplii)	Transparency induced		Migliore *et al*. (1997)	2
	S. vacuolatus	EC50	3.7	Backhaus *et al.* (2001)	3
Furazolidone	*A. salina*	LC50	250	Reported in Holten Lützhøft *et al*. (1999)	5
	D. magna	LC50	60	Reported in Holten Lützhøft *et al*. (1999)	5
	C. pipiens (larvae)	LC50	40	Reported in Holten Lützhøft *et al*. (1999)	5
Griseofulvin	*D. magna*	24 hr EC50 (physiology)	>1000	US EPA (2001)	5
	D. magna	48 hr EC50 (physiology)	>1000	US EPA (2001)	5
	D. magna	72 hr EC50 (physiology)	>1000	US EPA (2001)	5
	Mercenaria mercenaria	48 hr EC50 (developmental)	<0.25	US EPA (2001)	5
	M. mercenaria	14 d LC50	<1	US EPA (2001)	5
Halothane	*Lymnaea stagnalis*	Behavioural effects	0.5%	US EPA (2001)	5
Hydrogen peroxide	*D. magna*	24 hr EC50	2.3	US EPA (2001)	5
	A. salina	24 hr LC50	918	US EPA (2001)	5
	L. macrochirus	96 hr LC50	26.7	US EPA (2001)	5

Compound	Test organism	Toxic effect	Concentration (mg l^{-1})	Reference	Review code
	O. mykiss	96 hr LC50	22	US EPA (2001)	5
	Siganus fuscescens	24 hr LC50	224	US EPA (2001)	5
	Trachurus japonicus	24 hr LC50	89	US EPA (2001)	5
	Tridentiger trigonocephalus	24 hr LC50	155	US EPA (2001)	5
Ivermectin	*Asterias rubens* (sediment test)	10 d LC50	23.6 mg kg^{-1}	Davies *et al*. (1998)	1
	C. volutator (sediment test)	10 d LC50	0.18 mg kg^{-1}	Davies *et al*. (1998)	1
	A. marina	10 d LC50	0.018 mg kg^{-1}	Thain *et al.* (1997)	2
	A. marina	Effects on feeding	<0.005 mg kg^{-1}	Thain *et al.* (1997)	2
	A. marina	Adverse effect on burrowing	>0.008 mg kg^{-1}	Thain *et al.* (1997)	2
	S. gardneiri	96 hr LC50	3.0	Halley *et al.* (1989)	2
	L. macrochirus	96 hr LC50	4.8	Halley *et al.* (1989)	2
	Crangon septemspinosa	96 hr LC50	>21.5	Reported in Davies *et al.* (1997)	5
	Neomysis integer	96 hr LC50	0.07	Davies *et al.* (1997)	1
	N. integer	48 hr LC50	0.026	Grant and Briggs (1998)	3
	Gammarus spp.	96 hr LC50	0.033	Grant and Briggs (1998)	3
	Palaemonectes varians	96 hr LC50	54	Grant and Briggs (1998)	3
	A. salina	24 hr LC50	>300	Grant and Briggs (1998)	3
	Sphaeroma rugicauda	96 hr LC50	348	Grant and Briggs (1998)	3
	Carcinus maenas	96 hr LC50	957	Grant and Briggs (1998)	3
	Crassostrea gigas (larvae)	96 hr LC50	80-100	Davies and Rodger (2000)	5
	C. gigas (spat)	96 hr LC50	460	Davies and Rodger (2000)	5
	Mytilus edulis	96 hr LC50	400	Davies and Rodger (2000)	5
	Tapes semidecassata (larvae)	96 hr LC50	380	Davies and Rodger (2000)	5
	Tapes semidecassata (spat)	96 hr LC50	600	Davies and Rodger (2000)	5
	Pecten maximus	96 hr LC50	300	Davies and Rodger (2000)	5
	Monodonta lineata	96 hr LC50	780	Davies and Rodger (2000)	5
	Nucella lapillus	96 hr LC50	390	Davies and Rodger (2000)	5
	Littorina littorea	96 hr LC50	580	Davies and Rodger (2000)	5
	Hydrobia ulvae	96 hr LC50	>10000	Grant and Briggs (1998)	3
	Potamopyrgus jenkinsii	96 hr LC50	<9000	Grant and Briggs (1998)	3
	Nereis diversicolor	96 hr LC50	7.75	Grant and Briggs (1998)	3
	A. marina	10 d LC50 (sediment)	0.023 mg kg-1	Grant and Briggs (1998)	3
	Biomphalaria glabrata	24 hr LC50	30	Matha and Weiser (1988)	3
	D. magna	48 hr LC50	0.025	Halley *et al.* (1989)	2
	Chlorella pyrenoidosa	14 d LC50	>10000	Halley *et al.* (1989)	2

Compound	Test organism	Toxic effect	Concentration (mg l^{-1})	Reference	Review code
Levamisole	*A. anguilla*	88% physiology effect over 25 hr	10	US EPA (2001)	5
Lincomycin	*D. magna*	48 hr EC50	379.4	Reported in Holten Lützhøft *et al*. (1999)	5
	D. magna	Phototactic behaviour decreased	5	Reported in Holten Lützhøft *et al*. (1999)	5
	Artemia spp.	72 hr EC50	283	Migliore *et al.* (1997)	2
Lomefloxacin	*Daphnia* spp.	EC50	130	Reported in Webb (2001)	5
	O. mykiss	LC50	170	Reported in Webb (2001)	5
	Unspecified green algae	EC50	2.4	Reported in Webb (2001)	5
	Unspecified green algae	NOEC	2	Reported in Webb (2001)	5
	V. fischeri	24 hr EC50	0.022	Backhaus *et al*. (2000)	1
	S. vacuolatus	EC50	58	Backhaus *et al.* (2001)	3
Metronidazole	*S. capricornutum*	72 hr EC50	39.1-40.4	Lanzky and Halling-Sørensen (1997)	2
	S. capricornutum	72 hr EC10	19.9	Reported in Webb (2001)	5
	D. magna	48hr LOEC	1000	Wollenberger *et al*. 2000	2
	Chlorella spp.	72 hr EC50	12.5 – 45.1	Lanzky and Halling-Sørensen (1997)	2
	Chlorella spp.	72 hr EC10	2.03	Reported in Webb (2001)	5
	Acartia tonsa	72 hr EC50	>100	Lanzky and Halling-Sørensen (1997)	2
	Brachydanio rerio	96 hr NOEC	>500	Lanzky and Halling-Sørensen (1997)	2
	P. putida	EC50 (growth inhibition)	>64	Kummerer *et al.* (2000)	3
	O. mykiss	48 hr LC50	>100	Reported in Webb (2001)	5
	S. trutta	48 hr LC50	>100	Reported in Webb (2001)	5
	S. fontinalis	48 hr LC50	>100	Reported in Webb (2001)	5
	I. punctatus	48 hr LC50	>100	Reported in Webb (2001)	5
	L. machrochirus	48 hr LC50	>100	Reported in Webb (2001)	5
	S. namaycush	48 hr LC50	>100	Reported in Webb (2001)	5
Naladixic acid	*V. fischeri*	24 hr EC50	0.200	Backhaus *et al*. (2000)	1
	S. vacuolatus	Inhibition of reproduction	21.9	Meyer *et al*. (2001)	3
	S. vacuolatus	EC50	22.9	Backhaus *et al*. (2001)	3
Neomycin	*A. japonica*	LC50	2829	US EPA (2001)	5
Norfloxacin	*V. fischeri*	24hr EC50	0.022	Backhaus *et al*. (2000)	1
	S. vacuolatus	EC50	69.6	Backhaus *et al*. (2001)	3

Compound	Test organism	Toxic effect	Concentration (mg l^{-1})	Reference	Review code
Ofloxacin	*V. fischeri*	24 hr EC50	0.014	Backhaus *et al*. (2000)	1
	S. vacuolatus	EC50	82.8	Backhaus *et al.* (2001)	3
	P. putida	EC50 (growth inhibition)	0.01	Kummerer *et al.* (2000)	3
Olaquindox	*D. magna*	48 h LOEC	1000	Wollenberger *et al*. (2000)	2
	M. aeruginosa	7 d EC50	5.1	Halling-Sørensen (2000)	2
	S. capricornutum	72 hr EC50	40	Halling-Sørensen (2000)	2
Oxolinic acid	*M. aeruginosa*	EC50	0.18	Holten Lützhøft *et al*. (1999)	2
	S. capricornutum	EC50	16	Holten Lützhøft *et al*. (1999)	2
	R. salina	EC50	10	Holten Lützhøft *et al*. (1999)	2
	D. magna	48 hr EC50	4.6	Wollenberger *et al*. (2000)	2
	V. fischeri	24 hr EC50	0.023	Backhaus *et al*. (2000)	1
	S. vacuolatus	EC50	>26	Backhaus *et al.* (2001)	3
Oxytetracycline	*M. aeruginosa*	EC50	0.207	Holten Lützhøft *et al*. (1999)	2
	S. capricornutum	EC50	4.5	Holten Lützhøft *et al*. (1999)	2
	R. salina	EC50	1.6	Holten Lützhøft *et al*. (1999)	2
	D. magna	48 hr LOEC	100	Wollenberger *et al*. (2000)	2
	D. magna	48 hr EC50 intoxication	>102 ppm	US EPA (2001)	5
	L. macrochirus	96 hr LC50	>100 ppm	US EPA (2001)	5
	Morone saxatilis (larvae)	24 hr LC50	62.5	Reported in Webb (2001)	5
	M. saxatilis (larvae)	48 hr LC50	62.5	Reported in Webb (2001)	5
	M. saxatilis (larvae)	72 hr LC50	62.5	Reported in Webb (2001)	5
	M. saxatilis (larvae)	96 hr LC50	62.5	Reported in Webb (2001)	5
	M. saxatilis (fingerling)	24 hr LC50	150	US EPA (2001)	5
	M. saxatilis (fingerling)	48 hr LC50	125	US EPA (2001)	5
	M. saxatilis (fingerling)	72 hr LC50	100	US EPA (2001)	5
	M. saxatilis (fingerling)	96 hr LC50	75	US EPA (2001)	5
	O. mykiss	96 hr LC50	>116 ppm	US EPA (2001)	5
	Panneus vannamei	24 hr EC50 intoxication	0.16	US EPA (2001)	5
	P. vannamei	48 hr EC50 intoxication	0.0611-0.2141	US EPA (2001)	5
	P. vannamei	24 hr LC50	0.16	US EPA (2001)	5
	P. vannamei	48 hr LC50	0.16-0.2384	US EPA (2001)	5
	P. vannamei	24 hr LOEC intoxication	0.1609	US EPA (2001)	5
	P. vannamei	48 hr LOEC intoxication	0.1089-0.3778	US EPA (2001)	5

Compound	Test organism	Toxic effect	Concentration (mg l^{-1})	Reference	Review code
	P. vannamei	24 hr NOEC intoxication	0.1609	US EPA (2001)	5
	P. vannamei	48 hr NOEC intoxication	0.0549-0.1609	US EPA (2001)	5
	S. namaycush	24 hr LC50	<200	Reported in Webb (2001)	5
Pipemidic acid	*V. fischeri*	24 hr EC50	1.019	Backhaus *et al*. (2000)	1
	S. vacuolatus	EC50	>151	Backhaus *et al.* (2001)	3
Pirimidic acid	*V. fischeri*	24 hr EC50	0.121	Backhaus *et al*. (2000)	1
Phosmet	*D. magna*	48 hr EC50	0.0056	Lewis and Bardon (1998)	5
	D. magna	Unspecified chronic test	0.0016	Lewis and Bardon (1998)	5
	Unspecified fish	96 hr LC50	0.07	Lewis and Bardon (1998)	5
Procaine HCL	*L. macrochirus*	4 d (physiology)	77-101	US EPA (2001)	5
	Ptychocheilus spp.	24 hr (mortality)	10	US EPA (2001)	5
Propetamphos	*D.magna*	24 hr EC50	0.0147	Reported in Lewis (1998)	5
	D.magna	48 hr EC50	0.00878	Reported in Lewis (1998)	5
	Photobacterium phosporeum	30 min EC50	21.4	Reported in Lewis (1998)	5
Sarafloxicin	*M. aeruginosa*	EC50	0.015	Holten Lützhøft *et al*. (1999)	2
	R. salina	EC50	24	Holten Lützhøft *et al*. (1999)	2
	S. capricornutum	EC50	16	Holten Lützhøft *et al*. (1999)	2
Spiramycin	*M. aeruginosa*	7 d EC50	0.005	Halling-Sørensen (2000)	2
	S. capricornutum	72 hr EC50	2.3	Halling-Sørensen (2000)	2
Streptomycin	*M. aeruginosa*	MIC	0.3	Holten Lützhøft *et al*. (1999)	2
	S. capricornutum	MIC	2.1	Holten Lützhøft *et al*. (1999)	2
	D. magna	48 hr EC50	487	Wollenberger *et al.* (2000)	2
	M. aeruginosa	7 d EC50	0.007	Halling-Sørensen *et al.* (2000)	2
	S. capricornutum	72 hr EC50	0.133	Halling-Sørensen *et al.* (2000)	2
	V. fischeri	24 hr EC50	8.21	Backhaus and Grimme (1999)	3
	S. vacuolatus	inhibition of reproduction	17.4	Meyer *et al.* (2001)	3

Compound	Test organism	Toxic effect	Concentration (mg l^{-1})	Reference	Review code
Sulfadiazine	*M. aeruginosa*	EC50 population	0.135	Holten Lützhøft *et al*. (1999)	2
	S. capricornutum	EC50	7.8	Holten Lützhøft *et al*. (1999)	2
	R. salina	EC50	403	Holten Lützhøft *et al*. (1999)	2
	D. magna	48 hr EC50	221	Wollenberger *et al.* (2000)	2
	D. magna	24 hr EC50 physiology	112	US EPA (2001)	5
	D. magna	48 hr EC50 physiology	88	US EPA (2001)	5
	D. magna	72 hr EC50 physiology	57	US EPA (2001)	5
	Cirrhinus mrigala	effect on growth	20 mg/100g	US EPA (2001)	5
Sulfachloropyridazine	*D. magna*	48 hr EC50	250	Novartis (1999)	5
	Zebra fish	96 hr LC50	>1000	Novartis (1999)	5
Sulfadimethoxine	*A. salina* (nauplii)	24 hr LC50	1866	Reported in Webb (2001)	5
	A. salina (nauplii)	48 hr LC50	851	Reported in Webb (2001)	5
	A. salina (nauplii)	72 hr LC50	537	Reported in Webb (2001)	5
	A. salina (nauplii)	96 hr LC50	19.5	Reported in Webb (2001)	5
Teflubenzuron	Fish (trout and carp)	96 hr LC50	>500	Tomlin (1997)	5
Tetracycline	*D. magna*	48 hr NOEC	340	Wollenberger *et al.* (2000)	2
	M. aeruginosa	7 d EC50	0.09	Halling-Sørensen (2000)	2
	S. capricornutum	72 hr EC50	2.2	Halling-Sørensen (2000)	2
	Nitzschia closterium	72 hr EC50	16	Reported in Webb (2001)	5
	V. fischeri	24 hr EC50	0.0251	Backhaus and Grimme (1999)	3
	C. gigas	48 hr EC50 developmental	81-89	US EPA (2001)	5
	C. gigas	48 hr LC50	520-579	US EPA (2001)	5
	Culex quinquefasciatus	48 hr LC50	127.8	US EPA (2001)	5
	C. quinquefasciatus	effect on reproduction	127.8	US EPA (2001)	5
	C. quinquefasciatus	100% mortality	300	US EPA (2001)	5
Tiamulin	*D. magna*	48 hr EC50	40-67	Boxall *et al*. (2000)	5
	Unspecified fish	96 hr LC50	5.2	Boxall *et al*. (2000)	5
	Unspecified algae	96 hr EC50	>0.62	Boxall *et al*. (2000)	5
	M. aeruginosa	7 d EC50	0.003	Halling-Sørensen (2000)	2
	S. capricornutum	72 hr EC50	0.165	Halling-Sørensen (2000)	2

Compound	Test organism	Toxic effect	Concentration (mg l^{-1})	Reference	Review code
Triclabendazole	Unspecified algae	72 hr EC50	45	Lewis and Bardon (1998)	5
	D. magna	48 hr EC50	133	Lewis and Bardon (1998)	5
	Unspecified fish	96 hr EC50	117	Lewis and Bardon (1998)	5
Trimethoprim	*M. aeruginosa*	EC50	112	Holten Lützhøft *et al.* (1999)	2
	S. capricornutum	EC50	130	Holten Lützhøft *et al.* (1999)	2
	R. salina	EC50	16	Holten Lützhøft *et al.* (1999)	2
Tylosin	*D. magna*	48 hr EC50	680	Wollenberger *et al*. (2000)	2
	M. aeruginosa	7 d EC50	0.034	Halling-Sørensen (2000)	2
	S. capricornutum	72 hr EC50	1.38	Halling-Sørensen (2000)	2
Valnemulin	*D. magna*	48 hr EC50	44.7	Boxall *et al*. (2000)	5
	Fish (yellowtail)	28 d NOEC	>15 mg kg^{-1} d^{-1}	Boxall *et al*. (2000)	5
	Unspecified aerobic microorganisms		> 2	Boxall *et al*. (2000)	5

APPENDIX K TERRESTRIAL ECOTOXICITY

Compound	Test organism	Toxic effect	Concentration (mg kg^{-1})	Reference	Review code
Abamectin	*Onthophagus binodis*	Effect on reproduction and mortality	dose 200 µg kg^{-1} body weight	Ridsdill-Smith (1993)	3
	Onthophagus ferox	Effect on reproduction and mortality	dose 200 µg kg^{-1} body weight	Ridsdill-Smith (1993)	3
Apramycin	Earthworm	NOEC	100	VICH (unpublished)	5
	Microbes	MIC or NOEC	0.100	VICH (unpublished)	5
	Unspecified plant	NOEC	160	VICH (unpublished)	5
Amitraz	Earthworm	14 d LC50	1000	Lewis and Bardon (1998)	5
Amprolium	nitrification rate of soil	NOEC	>3.06	Warman (1980)	3
Aureomycin	nitrification rate of soil	NOEC	>0.34	Warman (1980)	3
Bactiracin	Microbes	MIC or NOEC	10	VICH (unpublished)	5
Benzimidazole	Earthworm	-	>1000	Greiner and Ronnefarth (2001)	4
	Dung beetle	-	>10	Greiner and Ronnefarth (2001)	4
Ceftiofur	Microbes	MIC or NOEC	0.250	VICH (unpublished)	5
Chlortetracycline	Soil respiration rate	NOEC	>0.6	Warman and Thomas (1981)	3
Clorsulon	Microbes	MIC or NOEC	2	VICH (unpublished)	5
Cypermethrin	Collembola	-	non-toxic	Tomlin (1997)	5
	Bees	24 hr LD50	highly toxic in laboratory tests = 0.035 µg/bee (oral); 0.02 µg/bee (topical)	Tomlin (1997)	5

Compound	Test organism	Toxic effect	Concentration ($mg\ l^{-1}$)	Reference	Review code
Cypromazine	Mallard duck	14 d LD50	>2510	US EPA (2001)	5
	Mallard duck	8 d LC50	>5620	US EPA (2001)	5
	Honey bee	48 hr LD50	>25 µg/bee	US EPA (2001)	5
	Northern bobwhite	14 d LD50	1785	US EPA (2001)	5
	Northern bobwhite	8 d LC50	>5620	US EPA (2001)	5
	Earthworm	14 d LC50	1000	Lewis and Bardon (1998)	5
Deltamethrin	Bees	LD50 (oral)	79 ng/bee	Tomlin (1997)	5
	Bees	LD50 (contact)	51 ng/bee	Tomlin (1997)	5
	Earthworms	14 d LC50	28.6	Tomlin (1997)	5
	Mallard duck	8 d LC50	>4640	US EPA (2001)	5
	Honey bee	48 hr LD50 (topical exposure)	0.067 µg/bee	US EPA (2001)	5
	Honey bee	24 hr LD50 (dermal exposure)	+0.186	US EPA (2001)	5
	Honey bee	1 d LOEL (dermal exposure)	+0.11 µ/bee	US EPA (2001)	5
	Northern bobwhite	14 d LD50	>2250	US EPA (2001)	5
	Northern bobwhite	8 d LC50	>10000	US EPA (2001)	5
Diazinon	*Lumbricus terrestris*	48 h LC50 (aqueous exposure)	0.0258	Reported in Larkin and Tjeerdema (2000)	5
	Saprotrophic isopods	LC50 (ingestion)	74.15	Vink *et al*., (1995)	1
	Saprotrophic isopods	LC50	3.03	Vink *et al*., (1995)	1
	Honeybee	Single-dose LD50	0.00045 mg/individual	Reported in Larkin and Tjeerdema (2000)	5
Dichlorvos	Bees	oral LD50	0.29 µg/bee	Tomlin (1997)	5
Doramectin	Earthworms	NOEC	2	VICH (unpublished)	5
	Microbes	MIC or NOEC	40	VICH (unpublished)	5
	Plants	NOEC	1.6	VICH (unpublished)	5
	Onthophagus gazella	LC90	38.3	Taylor (1999)	5
	O. gazella	LC50	12.5	Taylor (1999)	5
	Haematobia irritans	LC90	3	Taylor (1999)	5

Compound	Test organism	Toxic effect	Concentration (mg l^{-1})	Reference	Review code
Efrotomycin	Earthworms	NOEC	1,000	VICH (unpublished)	5
	Microbes	MIC or NOEC	20	VICH (unpublished)	5
	Plants	NOEC	0.40	VICH (unpublished)	5
Emamectin benzoate	Mallard duck	LD50 (dietary)	570	CORDAH (1999)	1
	Northern Bobwhite	LD50 (dietary)	1318	CORDAH (1999)	1
Eprinomectin	Earthworm	NOEC	295	VICH (unpublished)	5
	Plants	MIC or NOEC	1,000	VICH (unpublished)	5
Fenbendazole	Earthworms	NOEC	56	VICH (unpublished)	5
	Microbes	MIC or NOEC	1,000	VICH (unpublished)	5
	Plants	NOEC	36	VICH (unpublished)	5
Florfenicol	Microbes	MIC or NOEC	0.4	VICH (unpublished)	5
Halofuginone	Microbes	MIC or NOEC	200	VICH (unpublished)	5
	Plants	NOEC	24	VICH (unpublished)	5
Halothane	*Vicia faba* (seedling)	Cell mitotic abnormalities over 0.17 d	1-2%	US EPA (2001)	5
	V. faba (seedling)	Cell mitotic abnormalities over 0.33 d	1-2%	US EPA (2001)	5
	Alleim cepa	60-83% reduction in root mitotic rate over 0.33d	0.5-2%	US EPA (2001)	5
Ivermectin	Earthworms	NOEC	12	VICH (unpublished)	5
	Eiseniia foetida	28 d LC50	18-100	Halley *et al.* (1989)	2
	Plants	NOEC	0.56	VICH (unpublished)	5
	N. cornicina	behaviour	0.125	Gover and Strong (1996)	2
	N. cornicina	47 % mortality over 7d (dung)	0.125	Gover and Strong (1996b)	2
	N. cornicina	77% mortality over 7d (dung)	0.25	Gover and Strong (1996b)	2
	N. cornicina	87% mortality over 7d (dung)	0.5	Gover and Strong (1996b)	2
	N. cornicina	100% mortality over 7 d (dung)	1	Gover and Strong (1996b)	2
	N. cornicina	LC50 (dung)	0.139	Gover and Strong (1995)	2
	Scatophaga stercoraria (larvae)	24 hr EC50	0.051	Strong and James (1993)	2
	S. stercoraria (larvae)	48 hr EC50	0.036	Strong and James (1993)	2
	S. stercoraria (adults)	developmental abnormalities	0.0005	Strong and James (1993)	2

Compound	Test organism	Toxic effect	Concentration (mg kg^{-1})	Reference	Review code
	S. stercoraria	50% reduction in pupariation	0.015	Strong and James (1993)	2
	S. stercoraria	50% reduction in emergence	0.001	Strong and James (1993)	2
Laidlomycin	Microbes	MIC or NOEC	0.4	VICH (unpublished)	5
	Plants	NOEC	0.16	VICH (unpublished)	5
Lasalocid	Microbes	MIC or NOEC	0.20	VICH (unpublished)	5
	Plants	NOEC	2.0	VICH (unpublished)	5
Lincomycin	Earthworms	NOEC	1,000	VICH (unpublished)	5
	Microbes	MIC or NOEC	0.78	VICH (unpublished)	5
	Phaseolus vulgaris (seedling)	Physiological damage to organelle over 1.17 d	100 µg ml^{-1}	US EPA (2001)	5
	P.vulgaris (seedling)	12% reduction to leaf chlorophyll over 0.12 d	100 µg ml^{-1}	US EPA (2001)	5
	P.vulgaris (seedling)	39% reduction to leaf chlorophyll over 0.25 d	100 µg ml^{-1}	US EPA (2001)	5
	P.vulgaris (seedling)	23% reduction to leaf chlorophyll over 0.79 d	100 µg ml^{-1}	US EPA (2001)	5
	P.vulgaris (seedling)	39% reduction to leaf chlorophyll over 0.92 d	100 µg ml^{-1}	US EPA (2001)	5
	P.vulgaris (seedling)	61% reduction to leaf chlorophyll over 2 d	100 µg ml^{-1}	US EPA (2001)	5
	P.vulgaris (seedling)	61% reduction to leaf chlorophyll over 2.67 d	100 µg ml^{-1}	US EPA (2001)	5
	P.vulgaris (seedling)	43% reduction in leaf photosynthesis over 0.25 d	100 µg ml^{-1}	US EPA (2001)	5
	P.vulgaris (seedling)	43% reduction in leaf photosynthesis over 0.92 d	100 µg ml^{-1}	US EPA (2001)	5
	P.vulgaris (seedling)	86% reduction in leaf photosynthesis over 1 d	100 µg ml^{-1}	US EPA (2001)	5
	P.vulgaris (seedling)	92% reduction in leaf photosynthesis over 2.67 d	100 µg ml^{-1}	US EPA (2001)	5
	P.vulgaris (seedling)	leaf pigmentation over 2.67 d	100 µg ml^{-1}	US EPA (2001)	
Maduramicin	Microbes	MIC or NOEC	0.25	VICH (unpublished)	5
	Plants	NOEC	0.1	VICH (unpublished)	5
Melengestrol acetate	Earthworms	NOEC	1.8	VICH (unpublished)	5
	Plants	NOEC	2	VICH (unpublished)	5
Monensin	Earthworms	NOEC	10	VICH (unpublished)	5
	Plants	MIC or NOEC	0.15	VICH (unpublished)	5

Compound	Test organism	Toxic effect	Concentration (mg kg^{-1})	Reference	Review code
Morantel	Microbes	MIC or NOEC	50	VICH (unpublished)	5
Narasin	Earthworms	NOEC	0.5	VICH (unpublished)	5
	Microbes	MIC or NOEC	0.1	VICH (unpublished)	5
	Plant	NOEC	0.15	VICH (unpublished)	5
Oxfendazole	Earthworm	NOEC	971	VICH (unpublished)	5
	Microbes	MIC or NOEC	9	VICH (unpublished)	5
	Plants	NOEC	0.9	VICH (unpublished)	5
Oxytetracycline	Mallard duck	8 d LC50	>5620 ppm	US EPA (2001)	5
	Northern bobwhite	8 d LC50	>5620 ppm	US EPA (2001)	5
	Northern bobwhite	14 d LD50	>2000	US EPA (2001)	5
	Folsomia. fimetaria	LC50	>5000 mg kg-1	Baguer *et al*. (2000)	2
	F. fimetaria	EC50 reproduction	>5000 mg kg-1	Baguer *et al*. (2000)	2
	Enchytraeus. crypticus	LC50	>5000 mg kg-1	Baguer *et al*. (2000)	2
	E. crypticus	EC50 reproduction	2701 mg kg-1	Baguer *et al*. (2000)	2
	Aporrectodea caliginosa	LC50	>5000 mg kg-1	Baguer *et al*. (2000)	2
	A. caliginosa	EC50 reproduction	4420 mg kg-1	Baguer *et al*. (2000)	2
	A. caliginosa	EC50 growth	>5000 mg kg-1	Baguer *et al*. (2000)	2
	A. caliginosa	EC50 hatchability	>5000 mg kg-1	Baguer *et al*. (2000)	2
Pirlimycin	Earthworm	NOEC	1000	VICH (unpublished)	5
	Microbes	MIC or NOEC	0.13	VICH (unpublished)	5
	Plants	NOEC	0.4	VICH (unpublished)	5
Procaine penicillin	*Lactus sativa*	Effect on root mitotic rate and hypocotyl size over 2.5 d	0.5%	US EPA (2001)	5
Salinomycin	Microbes	MIC or NOEC	0.78	VICH (unpublished)	5
	Plants	NOEC	0.4	VICH (unpublished)	5
Sarafloxicin	Earthworm	NOEC	1000	VICH (unpublished)	5
	Microbes	MIC or NOEC	0.03	VICH (unpublished)	5
	Plants	NOEC	1.3	VICH (unpublished)	5

Compound	Test organism	Toxic effect	Concentration (mg kg^{-1})	Reference	Review code
Sendramicin	Microbes	MIC or NOEC	100	VICH (unpublished)	5
	Plants	NOEC	0.31	VICH (unpublished)	5
Sulfadiazine	*Lupinus albus*	13% reduction in root size over 1 day	100 ppm	US EPA (2001)	5
Sulfadimethoxine	*Amaranthus retroflexus*	development	<300 mg l^{-1}	Migliore *et al.* (1997a)	2
	Plantago major	development	<300 mg l^{-1}	Migliore *et al.* (1997a)	2
	Rumex acetosella	development	<300 mg l^{-1}	Migliore *et al.* (1997a)	2
	Paniceum miliaceum	development	<300 mg l^{-1}	Migliore *et al.* (1995)	2
	Pisum sativum	development	<300 mg l^{-1}	Migliore *et al.* (1995)	2
	Zea mays	development	<300 mg l^{-1}	Migliore *et al.* (1995)	2
	Hordeum disthicum	development and growth	<300 mg l^{-1}	Migliore *et al.* (1996)	2
Teflubenzuron	Bees	Non toxic at recommended rates	-	Tomlin (1997)	5
	Other	Low toxicity to predatory arthropods	-	Tomlin (1997)	5
Tiamulin	Wheat	plant vigour/germination	no effect	Boxall *et al*. (2000)	5
	Lettuce	plant vigour/germination	no effect	Boxall *et al*. (2000)	5
	Microbes	MIC or NOEC	500	VICH (unpublished)	5
Tylosin	*F. fimetaria*	LC50	>5000 mg kg^{-1}	Baguer *et al.* (2000)	2
	F. fimeteria	EC50 reproduction	2520 mg kg^{-1}	Baguer *et al.* (2000)	2
	E. crypticus	LC50	3381 mg kg^{-1}	Baguer *et al.* (2000)	2
	E. crypticus	EC50 reproduction	3109 mg kg^{-1}	Baguer *et al.* (2000)	2
	A. caliginosa	LC50	>5000 mg kg^{-1}	Baguer *et al.* (2000)	2
	A. caliginosa	EC50 reproduction	4530 mg kg^{-1}	Baguer *et al.* (2000)	2
	A. caliginosa	EC50 growth	>5000 mg kg^{-1}	Baguer *et al.* (2000)	2
	A. caliginosa	EC50 hatchability	4823 mg kg^{-1}	Baguer *et al.* (2000)	2
Virginiamycin	Microbes	MIC or NOEC	10	VICH (unpublished)	5

APPENDIX L

Table L- 1 Results of stage 1 assessment procedure for veterinary medicines

Usage rank	Therapeutic Group	Chemical group	Chemical group usage class	Major usage products (where data available)	Target group	Metabolism	Potential to reach environment	Hazard assess?
1	Antimicrobials	tetracyclines	H	oxytetracycline	C	na	L	x
					H	L	H	✔
					A	na	H	✔
				chlortetracycline	C	na	L	x
					H	L	H	✔
				tetracycline	C	na	L	x
					H	L	H	✔
2	Antimicrobials	potentiated sulphonamides	H	sulphadiazine	C	na	L	x
					H	H	L	x
					A	na	H	✔
				sulphadimidine	C	na	L	x
					H	H	L	x
				trimethoprim	C	na	L	x
					H	H	L	x
					A	na	H	✔
				baquiloprim	C	na	L	x
					H	U	U	✔

[a]Specific usage data unavailable, however compound considered to be potentially major usage within therapeutic group [b]Usage data incomplete
Target group abbreviations: A = aquaculture; C = companion animals: H = herd animals; I = individual food production animals

Table L-1 cont-d

Usage rank	Therapeutic Group	Chemical group	Chemical group usage class	Major usage products (where data available)	Target group	Metabolism	Potential to reach environment	Hazard assess?
3	Endoparasiticides - coccidiostats	-	H[b]	amprolium[a]	H	M	M	✔
				clopidol[a]	H	U	U	✔
				dimetridazole	H	H	L	x
				lasalocid sodium[a]	H	U	U	✔
				maduramicin[a]	H	M	M	✔
				narasin[a]	H	H	L	x
				nicarbazin[a]	H	U	U	✔
				robenidine hydrochloride[a]	H	U	U	✔
4	Antimicrobials	β-lactams	H	amoxicillin	C H A	na U na	L U H	x ✔ ✔
				procaine penicillin	C H	na U	L U	x ✔
				procaine benzylpenicillin	C H	na U	L U	x ✔
				clavulanic acid	C H	na U	L U	x ✔

[a]Specific usage data unavailable, however compound considered to be potentially major usage within therapeutic group [b]Usage data incomplete
Target group abbreviations: A = aquaculture; C = companion animals: H = herd animals; I = individual food production animals

Table L-1 cont-d

Usage rank	Therapeutic Group	Chemical group	Chemical group usage class	Major usage products (where data available)	Target group	Metabolism	Potential to reach environment	Hazard assess?
5	Ectoparasiticides - sheep dips	organophosphates	H	diazinon	H	na	H	✔
6	Antimicrobials	macrolides	H	tylosin	C H	na L	L H	x ✔
7	Growth promoters	-	H[b]	monensin	H	U	U	✔
				salinomycin sodium[a]	H	U	U	✔
				flavophospolipol[a]	H	U	U	✔
8	Antimicrobials	aminoglycosides	H	dihydrostreptomycin	C H	na L	L H	x ✔
				neomycin	C H	na L	M H	✔ ✔
				apramycin	C H	na L	L H	x ✔
				avilamycin[a]	H	H	L	x
				flavomycin[a]	H	U	U	✔
9	Neurological preparations - general anaesthetics	-	H	isoflurane	C	na	L	x
				halothane	C	na	L	x

[a]Specific usage data unavailable, however compound considered to be potentially major usage within therapeutic group [b]Usage data incomplete
Target group abbreviations: A = aquaculture; C = companion animals: H = herd animals; I = individual food production animals

Table L-1 cont-d

Usage rank	Therapeutic Group	Chemical group	Chemical group usage class	Major usage products (where data available)	Target group	Metabolism	Potential to reach environment	Hazard assess?
10	Endoparasiticides - wormers	pyrimidines	M[b]	morantel	H	M	M	✔
				pyrantel emboate	C	na	L	x
11	Ectoparasiticides - sheep dips	pyrethroids	M	cypermethrin	H	na	H	✔
				flumethrin	H	na	H	✔
12	Endoparasiticides - wormers	azoles	M[b]	triclabendazole	H	M	M	✔
				fenbendazole	C H	na U	L U	x ✔
				levamisole	H	U	U	✔
13	Endoparasiticides - wormers	macrolide endectins	M[b]	ivermectin	C H	na na	L H	x ✔
14	Antimicrobials - other antibiotics	-	M[b]	cephalexin	C H	na U	L U	x ✔
				florfenicol	A	na	H	✔
				tilmicosin	H	M	M	✔
				oxolinic acid[a]	A	na	H	✔

[a]Specific usage data unavailable, however compound considered to be potentially major usage within therapeutic group [b]Usage data incomplete
Target group abbreviations: A = aquaculture; C = companion animals: H = herd animals; I = individual food production animals

Table L-1 cont-d

Usage rank	Therapeutic Group	Chemical group	Chemical group usage class	Major usage products (where data available)	Target group	Metabolism	Potential to reach environment	Hazard assess?
15	Neurological preparations - euthanasia products	-	M	pentobarbitone sodium	C I	na na	L L	x x
16	Neurological preparations - local anaesthetics	-	M[b]	procaine hydrochloride	C H	na U	L U	x ✔
				lido/lignocaine hydrochloride	C H	na U	L U	x ✔
17	Antimicrobials	pleuromutilins	M[b]	tiamulin	H	U	U	✔
18	Antimicrobials	lincosamides	M	lincomycin	C H	na M	L M	x ✔
				clyndamycin	C H	na U	L U	x ✔
19	Antimicrobials - antifungals	azoles	M	miconazole	C	na	M	✔
20	Endoparasiticides - wormers	others	M[b]	nitroxynil	H	U	U	✔
21	Antimicrobials	fluoroquinolones	M	enrofloxacin	C H	na L	L H	x ✔
			M	sarafloxacin	A	na	H	✔

[a]Specific usage data unavailable, however compound considered to be potentially major usage within therapeutic group [b]Usage data incomplete
Target group abbreviations: A = aquaculture; C = companion animals: H = herd animals; I = individual food production animals

Table L-1 cont-d

Usage rank	Therapeutic Group	Chemical group	Chemical group usage class	Major usage products (where data available)	Target group	Metabolism	Potential to reach environment	Hazard assess?
22	Antimicrobials - antifungals	others	L	griseofulvin	C	na	L	x
23	Antimicrobials - antifungals	biguanide/gluconate	L[b]	chlorhexidine	C I	na U	M M	x x
24	Neurological preparation - tranquilisers	-	L	phenobarbitone	C I	na na	L L	x x
25	Anti-inflammatory preparations - NSAIDS	-	L	phenylbutazone	C I	na na	L L	x x
				caprofen	C H	na na	L L	x x
26	Neurological preparations - analgesics	-	L	metamyzole	C I	na na	L L	x x
27	Sex hormones	-	L	altrenogest	C H	na U	L U	x ✔
				progesterone	C H	na U	L U	x ✔
				medroxyprogesterone	C H	na U	L U	x ✔

[a]Specific usage data unavailable, however compound considered to be potentially major usage within therapeutic group [b]Usage data incomplete
Target group abbreviations: A = aquaculture; C = companion animals: H = herd animals; I = individual food production animals

Table L-1 cont-d

Usage rank	Therapeutic Group	Chemical group	Chemical group usage class	Major usage products (where data available)	Target group	Metabolism	Potential to reach environment	Hazard assess?
28	Enteric preparations	-	L[b]	dimethicone	C H	na U	L U	x ✔
				poloxalene	C H	na U	L U	x ✔
29	Endoparasiticides - antiprotozoals	-	L[b]	toltrazuril	H	L	H	✔
				decoquinate	H	U	U	✔
				diclazuril	H	L	H	✔
30	Endectocides	macrocyclic lactone injections	L	ivermectin	H	M	M	x
				doramectin	H	M	M	x
				moxidectin	H	U	U	✔
31	Ectoparasiticide - others	-	U/L[b]	phosmet	H	na	H	✔
				piperonyl butoxide	C	na	M	✔
32	Ectoparasiticide - sheep dips	amidine	U	amitraz	H	na	H	✔
33	Ectoparasiticide - spray and pour-ons for sheep	-	U	deltamethrin	H	na	H	✔
				cypromazine	H	na	H	✔

[a]Specific usage data unavailable, however compound considered to be potentially major usage within therapeutic group [b]Usage data incomplete
Target group abbreviations: A = aquaculture; C = companion animals: H = herd animals; I = individual food production animals

Table L-1 cont-d

Usage rank	Therapeutic Group	Chemical group	Chemical group usage class	Major usage products (where data available)	Target group	Metabolism	Potential to reach environment	Hazard assess?
34	Ectoparasiticide - aquaculture treatments	-	U	emamectin benzoate	A	na	H	✔
35	Antiseptics	-	U	?	C/I	na	M	✔
36	Anti-inflammatory preparations	steroids	U	?	C/I	na	L	x
37	Diuretics	-	U	?	C/I	na	L	x
38	Cardiovascular and respiratory treatments	-	U	?	C/I	na	L	x
39	Locomotor treatments	-	U	?	C/I	na	L	x
40	Immunological products	-	U	?	C H	na U	L U	x ✔

[a]Specific usage data unavailable, however compound considered to be potentially major usage within therapeutic group [b]Usage data incomplete
Target group abbreviations: A = aquaculture; C = companion animals: H = herd animals; I = individual food production animals

Table L- 2 Criteria used to assign score to indicate the extent of the data used in the aquatic and terrestrial hazard classifications

	Criteria	
Hazard classification score of extent of data*	**Aquatic**	**Terrestrial**
subscript 1	three trophic levels; algae, dapnia and fish chronic only tests	three trophic levels; microbes, invertebrates and plants
subscript 2	three trophic levels; algae, dapnia and fish mixture of acute and chronic tests	Any two of above three trophic levels
subscript 3	three trophic levels; algae, dapnia and fish acute tests only	Any one of above three trophic levels
subscript 4	less than three trophic levels; algae, daphnia or fish acute or chronic tests or mixture of both	-

* adaptation of assessment factors used to derive a PNEC (Technical guidance document in support of Commission Directive 93/67/EEC on risk assessment for new notified substances and Commission Regulation (EC) No. 1488/94 on risk assessment for existing substances, Part II)

Table L- 3 Prioritisation assessment for veterinary medicinal products that have the potential to enter the environment

Therapeutic group	Chemical group	Major usage products (where data available)	Potential to reach environment	Relevant target group(s)	Usage class	Hazard assessment		Priority classification
						Aquatic[c]	Terrestrial[d]	
Antimicrobials	tetracyclines	oxytetracycline	H	H, A	H	H_3	L_3	1
		chlortetracycline	H	H		VH_4	VH_3	1
		tetracycline	H	H		VH_4	U	1
Antimicrobials	potentiated sulphonamides	sulphadiazine	H	A	H	H_4	H_3	1
		trimethoprim	H	A		M_4	U	1
		baquiloprim	U	H		U	U	1
Endoparasiticides - coccidiostats	-	amprolium[a]	M	H	H[b]	U	VH_3	1
		clopidol[a]	U	H		U	U	1
		lasalocid sodium[a]	U	H		U	U	1
		maduramicin[a]	M	H		U	VH_2	1
		nicarbazin[a]	U	H		U	U	1
		robenidine hydrochloride[a]	U	H		U	U	1
Antimicrobials	β-lactams	amoxicillin	H	H, A	H	VH_4	U	1
		procaine penicillin	U	H		U	VH_3	1
		procaine benzylpenicillin	U	H		VH_4	U	1
		clavulanic acid	U	H		U	U	1
Ectoparasiticides - sheep dips	organophosphates	diazinon	H	H	H	VH_4	VH_3	1

[a] Specific usage data unavailable, however compound considered to be potentially major usage

[b] Usage data incomplete

[c] subscript$_1$ – 3 trophic levels, chronic test
subscript$_2$ – 3 trophic levels, acute or chronic test
subscript$_3$ – 3 trophic levels, acute test
subscript$_4$ – less than 3 trophic levels, acute or chronic test or both

[d] subscript$_1$ – 3 trophic levels; microbes, invertebrate and plants
subscript$_2$ – any two of 3 trophic levels
subscript$_3$ – any one of 3 trophic levels

Table L-3 cont-d

Therapeutic group	Chemical group	Major usage products (where data available)	Potential to reach environment	Relevant target group(s)	Usage class	Hazard assessment		Priority classification
						Aquatic[c]	Terrestrial[d]	
Antimicrobials	macrolides	tylosin	H	H	H	VH_4	L_3	1
Growth promoters	-	monensin	U	H	H[b]	U	VH_2	1
		salinomycin sodium[a]	U	H		U	VH_2	1
		flavophospolipol[a]	U	H		U	U	1
Antimicrobials	aminoglycosides	dihydrostreptomycin	H	H	H	VH_4	U	1
		neomycin	H	C, H		L_4	U	1
		apramycin	H	H		U	VH_1	1
		flavomycin[a]	U	H		U	U	1
Endoparasiticides - wormers	pyrimidines	morantel	M	H	M[b]	U	U	1
Ectoparasiticides - sheep dips	pyrethroids	cypermethrin	H	H	M	VH_4	U	1
		flumethrin	H	H		U	U	1
Endoparasiticides - wormers	azoles	triclabendazole	M	H	M[b]	U	U	1
		fenbendazole	U	H		U	U	1
		levamisole	U	H		U	U	1

[a] Specific usage data unavailable, however compound considered to be potentially major usage

[b] Usage data incomplete

[c] subscript$_1$ – 3 trophic levels, chronic test
subscript$_2$ – 3 trophic levels, acute or chronic test
subscript$_3$ – 3 trophic levels, acute test
subscript$_4$ – less than 3 trophic levels, acute or chronic test or both

[d] subscript$_1$ – 3 trophic levels; microbes, invertebrate and plants
subscript$_2$ – any two of 3 trophic levels
subscript$_3$ – any one of 3 trophic levels

Table L-3 cont-d

Therapeutic group	Chemical group	Major usage products (where data available)	Potential to reach environment	Relevant target group(s)	Usage class	Hazard assessment		Priority classification
						Aquatic[c]	Terrestrial[d]	
Endoparasiticides - wormers	macrolide endectins	ivermectin	M	H	M[b]	VH_3	VH_2	1
Antimicrobial - other antibiotics	-	cephalexin	U	H	M[b]	U	U	1
		florfenicol	H	A		U	VH_3	1
		tilmicosin	U	H		U	U	1
		oxolinic acid[a]	H	A		VH_4	U	1
Neurological preparations - local anaesthetics	-	procaine hydrochloride	U	H	M[b]	M_4	U	2
		lido/lignocaine hydrochloride	U	H		U	U	1
Antimicrobials	pleuromutilins	tiamulin	U	H	M[b]	VH_3	M_2	1
Antimicrobials	lincosamides	lincomycin	U	H	M	M_4	VH_1	1
		clyndamycin	U	H		U	U	1
Antimicrobials - antifungals	azoles	miconazole	M	C	M	U	U	2
Endoparasiticides - wormers	others	nitroxynil	U	H	M[b]	U	U	1

[a] Specific usage data unavailable, however compound considered to be potentially major usage

[b] Usage data incomplete

[c] subscript$_1$ – 3 trophic levels, chronic test
subscript$_2$ – 3 trophic levels, acute or chronic test
subscript$_3$ – 3 trophic levels, acute test
subscript$_4$ – less than 3 trophic levels, acute or chronic test or both

[d] subscript$_1$ – 3 trophic levels; microbes, invertebrate and plants
subscript$_2$ – any two of 3 trophic levels
subscript$_3$ – any one of 3 trophic levels

Table L-3 cont-d

Therapeutic group	Chemical group	Major usage products (where data available)	Potential to reach environment	Relevant target group(s)	Usage class	Hazard assessment		Priority classification
						Aquatic[c]	Terrestrial[d]	
Antimicrobials	fluoroquinolones	enrofloxacin	H	H	M	U	U	1
		sarafloxacin		A		VH_4	VH_1	1
Sex hormones	-	altrenogest	U	H	L	U	U	2
		progesterone	U	H		U	U	2
		medroxyprogesterone	U	H		U	U	2
Enteric preparations	-	dimethicone	U	H	L[b]	U	U	1
		poloxalene	U	H		U	U	1
Endoparasiticides - antiprotozoals	-	toltrazuril	U	H	L[b]	U	U	1
		decoquinate	U	H		U	U	1
		diclazuril	U	H		U	U	1
Endectocides	macrocyclic lactone injections	moxidectin	U	H	L	U	U	2
Ectoparasiticides - others	-	phosmet	H	H	U/L[b]	U	U	1
		piperonyl butoxide	M	C		U	U	1
Ectoparasiticides - sheep dips	amidines	amitraz	H	H	U	M_2	U	1

[a] Specific usage data unavailable, however compound considered to be potentially major usage

[b] Usage data incomplete

[c] $subscript_1$ – 3 trophic levels, chronic test
$subscript_2$ – 3 trophic levels, acute or chronic test
$subscript_3$ – 3 trophic levels, acute test
$subscript_4$ – less than 3 trophic levels, acute or chronic test or both

[d] $subscript_1$ – 3 trophic levels; microbes, invertebrate and plants
$subscript_2$ – any two of 3 trophic levels
$subscript_3$ – any one of 3 trophic levels

Table L-3 cont-d

Therapeutic group	Chemical group	Major usage products (where data available)	Potential to reach environment	Relevant target group(s)	Usage class	Hazard assessment		Priority classification
						Aquatic[c]	Terrestrial[d]	
Ectoparasiticides - spray and pour-ons for sheep	- 	deltamethrin cypromazine	H H	H H	U	VH_4 VH_4	H_3 U	1 1
Ectoparasiticides - aquaculture treatments	-	emamectin benzoate	H	A	U	VH_4	na	1
Antiseptics	-	?	H	C/I	U	U	U	1
Immunological products	-	?	U	C, H	U	U	U	1

[a] Specific usage data unavailable, however compound considered to be potentially major usage

[b] Usage data incomplete

[c] subscript$_1$ – 3 trophic levels, chronic test
subscript$_2$ – 3 trophic levels, acute or chronic test
subscript$_3$ – 3 trophic levels, acute test
subscript$_4$ – less than 3 trophic levels, acute or chronic test or both

[d] subscript$_1$ – 3 trophic levels; microbes, invertebrate and plants
subscript$_2$ – any two of 3 trophic levels
subscript$_3$ – any one of 3 trophic levels

Table L- 4 Matrix used to determine the priority classification of a substance

	Priority classification													
	1			**2**					**3**			**4**	**5**
Potential to enter environment	H/M/U	H/U	H/U	M	M	H/U	H/U	H/U	M	M	H/U	All other combinations	low potential to enter environment or medium potential to enter environment combined with low usage = **Stop at Stage I** or high, medium or low potential to enter environment combined with low usage and hazard
Usage	H/U/H[b]/M[b]/L[b]	H/U/H[b]/M[b]/L[b]	M/U/H[b]/M[b]/L[b]	M	H/U/H[b]/M[b]/L[b]	L	M/L	H/U/H[b]/M[b]/L[b]	M	H/U/H[b]/M[b]/L[b]	M		
Hazard	VH/U	H	VH/U	VH/U	H	VH/U	H	M	H	M	M		

[b] usage data incomplete
VH = very high
H = high
M = medium
L = low
U = unknown

Table L- 5 Prioritisation list – compounds considered to have the greatest potential for environmental impact (group 1)

				Data gap identified/further data required			
				Usage	Metabolism	Ecotox	
Prioritisation classification	Ranking (usage based)	Compound	Relevant target group(s)			Aquatic	Terrestrial
1	1	oxytetracycline	H, A				✔
1	2	chlortetracycline	H			✔	✔
1	3	tetracycline	H			✔	✔
1	4	sulphadiazine	A			✔	✔
1	5	trimethoprim*	A			✔	✔
1	6	baquiloprim*	H		✔	✔	✔
1	7	amprolium*	H	✔		✔	✔
1	8	clopidol*	H	✔	✔	✔	✔
1	9	lasalocid sodium*	H	✔	✔	✔	✔
1	10	maduramicin*	H	✔		✔	✔
1	11	nicarbazin*	H	✔	✔	✔	✔
1	12	robenidine hydrochloride*	H	✔	✔	✔	✔
1	13	amoxicillin	H, A		✔	✔	✔
1	14	procaine penicillin*	H		✔	✔	✔

* based on worst case assumption(s) made for potential to reach environment and/or usage and/or hazard

Table L-5 cont-d

				Data gap identified/further data required			
				Usage	Metabolism	Ecotox	
Prioritisation classification	Ranking (usage based)	Compound	Relevant target group(s)			Aquatic	Terrestrial
1	15	procaine benzylpenicillin*	H		✔	✔	✔
1	16	clavulanic acid*	H		✔	✔	✔
1	17	diazinon	H		na	✔	✔
1	18	tylosin	H			✔	✔
1	19	monensin*	H	✔	✔	✔	✔
1	20	salinomycin sodium*	H	✔		✔	✔
1	21	flavophospolipol*	H	✔	✔	✔	✔
1	22	dihydrostreptomycin	H			✔	✔
1	23	neomycin*	C, H			✔	✔
1	24	apramycin	H			✔	
1	25	flavomycin*	H		✔	✔	✔
1	26	morantel*	H	✔		✔	✔
1	27	cypermethrin	H		na	✔	✔
1	28	flumethrin*	H		na	✔	✔
1	29	triclabendazole*	H	✔		✔	✔
1	30	fenbendazole*	H	✔	✔	✔	✔

* based on worst case assumption(s) made for potential to reach environment and/or usage and/or hazard

Table L-5 cont-d

				Data gap identified/further data required			
				Usage	Metabolism	Ecotox	
Prioritisation classification	Ranking (usage based)	Compound	Relevant target group(s)			Aquatic	Terrestrial
1	31	levamisole*	H	✔	✔	✔	✔
1	32	ivermectin*	H	✔			✔
1	33	cephalexin*	H	✔	✔	✔	✔
1	34	florfenicol*	A	✔	na	✔	✔
1	35	tilmicosin*	H	✔		✔	✔
1	36	oxolinic acid*	A	✔	na	✔	✔
1	37	lido/lignocaine hydrochloride*	H	✔	✔	✔	✔
1	38	tiamulin*	H	✔	✔		✔
1	39	lincomycin*	H			✔	
1	40	clindamycin*	H			✔	✔
1	41	nitroxynil*	H	✔	✔	✔	✔
1	42	enrofloxacin*	H			✔	✔
1	43	sarafloxacin	A		na	✔	
1	44	dimethicone*	H	✔	✔	✔	✔
1	45	poloxalene*	H	✔	✔	✔	✔

* based on worst case assumption(s) made for potential to reach environment and/or usage and/or hazard

Table L-5 cont-d

				Data gap identified/further data required			
				Usage	Metabolism	Ecotox	
Prioritisation classification	Ranking (usage based)	Compound	Relevant target group(s)			Aquatic	Terrestrial
1	46	toltrazuril*	H	✔	✔	✔	✔
1	47	decoquinate*	H	✔	✔	✔	✔
1	48	diclazuril*	H	✔	✔	✔	✔
1	49	phosmet*	H	✔	na	✔	✔
1	50	piperonyl butoxide*	C	✔	na	✔	✔
1	51	amitraz*	H	✔	na		✔
1	52	deltamethrin*	H	✔	na	✔	✔
1	53	cypromazine*	H	✔	Na	✔	✔
1	54	emamectin benzoate*	A	✔	Na	✔	✔ ?
1	55	Antiseptics*	C/I	✔	✔	✔	✔
1	56	Immunological products*	C, H	✔	✔	✔	✔

* based on worst case assumption(s) made for potential to reach environment and/or usage and/or hazard

Table L-6 Prioritisation list – group 2 and 5 compounds

				Data gap identified/further data required			
				Usage	Metabolism	Ecotox	
Prioritisation classification	Ranking (usage based)	Compound	Relevant target group(s)			Aquatic	Terrestrial
2	57	procaine hydrochloride*	H	✔	✔	✔	✔
2	58	miconazole*	C		na	✔	✔
2	59	altrenogest*	H		✔	✔	✔
2	60	progesterone*	H		✔	✔	✔
2	61	medroxyprogesterone*	H		✔	✔	✔
2	62	moxidectin*	H		✔	✔	✔
5	63	sulphadimidine	Not applicable				
5	64	dimetridazole					
5	65	narasin					
5	66	avilamycin					
5	67	isoflurane					
5	68	halothane					
5	69	pyrantel emboate					
5	70	pentobarbitone sodium					
5	71	griseofulvin					
5	72	chlorhexidine					

* based on worst case assumption(s) made for potential to reach environment and/or usage and/or hazard

Table L-6 cont-d

				Data gap identified			
				Usage	Metabolism	Ecotox	
Prioritisation classification	Ranking (usage based)	Compound	Relevant target group(s)			Aquatic	Terrestrial
5	73	phenobarbitone	Not applicable				
5	74	phenylbutazone					
5	75	caprofen					
5	76	metamyzole					
5	77	doramectin					

* based on worst case assumption(s) made for potential to reach environment and/or usage and/or hazard