Targeted monitoring study for veterinary medicines in the environment

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Executive Summary

Veterinary medicines are widely used to treat disease and to protect the health of animals. Dietary additives may be incorporated into the feed of animals to improve animal productivity. During their use, both types of substances have the potential to be released to the environment.

Consequently, the marketing authorisation holder provides an environmental assessment to the licensing authorities as part of the authorisation process. A product is authorised for sale only where the licensing authority is satisfied that the environmental risk is sufficiently low. This study was performed to gain a greater understanding of the actual concentrations of approved veterinary medicines in the environment once they are in use. The project built upon a previous study funded by the Environment Agency, which brought together data on the usage, routes of entry, and the fate and effects of veterinary medicines in use in the UK. The information was used to prioritise these veterinary medicines in use in the UK in terms of their potential to be released to the environment and their ecotoxicity. A list of priority compounds was developed for further consideration.

In the current study, this priority list was refined. A pragmatic and scientifically sound risk-based ranking approach was developed and applied to each of the compounds on the priority list in order to gain a greater understanding of the risks they pose to the environment (soil, surface water and groundwater) relative to others on the list.

Using this approach, 18 compounds were deemed worthy of monitoring. A monitoring study was performed over an 11-month period to determine concentrations of seven of the 18 compounds in the UK environment. With the exception of enrofloxacin and its metabolite ciprofloxacin, all the study compounds were detected in one or more environmental compartments (see table below).

Concentrations of antibacterials in soils ranged from 0.5 $\mu g\ kg^{-1}$ (trimethoprim) to 305 (oxytetracycline) $\mu g\ kg^{-1}$. Maximum concentrations of antibacterials in water ranged from 0.02 $\mu g\ kg^{-1}$ (trimethoprim) to 21.1 (lincomycin) $\mu g\ l^{-1}$; the parasiticides (doramectin and ivermectin) were not detected. Concentrations of antibacterials in sediment were 0.5–813 $\mu g\ kg^{-1}$ and those for doramectin and ivermectin were 2.7 and 4.9 $\mu g\ kg^{-1}$ respectively.

Maximum measured concentrations were generally lower than predicted no effect concentrations derived from available ecotoxicity data. It is probable that the average concentrations across the broader UK agricultural landscape will be lower still for many of the determinands. This is because the monitoring programme:

- considered the highest ranked compounds and scenarios;
- selected sites with characteristics that would enhance environmental contamination;
- focused on occasions when the compounds were likely to be released to the environment.

The results therefore indicate that, in general, concentrations of these veterinary medicines in the UK environment are likely to be below those that could affect aquatic and terrestrial organisms

However, the study did identify some areas where future work is warranted, including:

- further assessment of the potential impacts of selected medicines on the soil environment;
- investigations into the fate and effects of parasiticides in sediment;
- assessment of those compounds that could not be studied in this project due to insufficient data;
- further assessment of the potential impacts of the other 11 (of the 18) selected veterinary medicines on the environment;
- monitoring of groundwater.

Maximum measured environmental concentrations of study veterinary medicines

	Faeces/litter ($\mu g\ kg^{-1}$)	**Soil ($\mu g\ kg^{-1}$)**	**Water ($\mu g\ l^{-1}$)**	**Sediment ($\mu g\ kg^{-1}$)**
ciprofloxacin	0.28	ND	-	-
doramectin	112	-	ND	2.69
enrofloxacin	2.92	ND	-	-
ivermectin (pigs)	-	46[$] (1,985^)	ND	-
ivermectin (cattle)	1,850	-	ND	4.91
lincomycin	-	8.5	21.1	8.9
oxytetracycline	-	305	4.49	813
sulfadiazine	-	0.8*	4.13	0.8*
trimethoprim	-	0.5*	0.02*	0.5*

* Values are indicative values only.
[$] The treatment dose and duration at study site were significantly higher than recommended, so concentrations under typical treatment regimes are likely to be more than an order of magnitude lower.
^ Concentration around/below feeding stations

Contents

List of figures

List of tables

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1 Introduction

Veterinary medicines are widely used to treat disease and to protect the health of animals. Some dietary additives are also incorporated into the feed of animals reared for food in order to improve their productivity. Compounds used include parasiticides, antibiotics and antifungals. Feed additives are not veterinary medicines and are authorised under different legislation. Most of the compounds considered in this study are authorised as veterinary medicines, but a few are authorised as feed additives. For simplicity, the term 'veterinary medicine' is used in this report to cover both.

Through its chemicals strategy *Managing Chemicals for a Better Environment* (Environment Agency 2003), the Environment Agency aims to focus its activities on those chemicals most likely to affect the environment. This can only be achieved if the release and subsequent potential effects of these chemicals are understood.

During their use, veterinary medicines have the potential to be released to the environment. Consequently, the marketing authorisation holder provides an environmental assessment to the licensing authorities as part of the authorisation process. A product is authorised for sale only where the licensing authority is satisfied that the environmental risk is sufficiently low. This study was performed to gain a greater understanding of the actual concentrations of approved veterinary medicines in the environment once they are in use.

Releases of veterinary medicines to the environment may occur directly (e.g. where they are used in fish farms) and indirectly via the application of animal manure containing excreted products to land. A number of groups of veterinary medicines have been well studied and their risks to the environment are relatively well understood; these are primarily:

- sheep dip chemicals (Environment Agency 1998, 2000, 2001; SEPA 2000)
- fish farm medicines (Jacobsen and Berglind 1988, Davies *et al.* 1998);
- anthelmintics (Wall and Strong 1987, McCracken 1993, Ridsill-Smith 1993, Strong 1993, McKellar 1997).

However, there are scant data available in the public domain on the potential environmental impacts of other groups of veterinary medicines.

To gain a greater understanding of the impacts on the environment arising from the use of veterinary medicinal products, the Environment Agency commissioned a review of all available information on veterinary medicines in the environment (Boxall *et al*. 2002, 2004). The review considered:

- current regulatory mechanisms
- current usage
- likely exposure routes
- environmental fate and behaviour
- environmental effects.

This review highlighted the large number and wide variety of veterinary medicines in use and found that, with the exception of a few groups of compounds, limited information is available in the public domain on potential environmental impacts.

To identify compounds of possible concern, a prioritisation scheme was developed as part of this earlier study to assess the relative potential for veterinary medicines and feed additives to cause environmental harm. The scheme was based on the potential for the compound to reach the environment in significant amounts and a simple assessment of hazard using the toxicity data given by Boxall *et al.* (2002, 2004).

This scheme enabled those compounds likely to be of greatest potential concern to be identified; using this approach, a total of 55 compounds were assigned to a 'high risk' category. However, there was only sufficient data available to fully characterise the potential risk for the 11 compounds listed in Table 1.1.

Table 1.1 'High risk' compounds subjected to full risk characterisation

Compound	Treatment scenario(s) that pose a 'high risk'
Amoxicillin	herd and aquaculture
Apramycin	herd
Chlortetracycline	herd
Cypermethrin	herd
Diazinon	herd
Dihydrostreptomycin	herd
Oxytetracycline	herd and aquaculture
Sarafloxacin	aquaculture
Sulfadiazine	aquaculture
Tetracycline	herd
Tylosin	herd

The 44 remaining compounds identified as potentially high priority but requiring further data are listed in Table 1.2.

Table 1.2 'High risk' compounds requiring further data for full risk characterisation§

Trimethoprim	Morantel	Enrofloxacin
Baquiloprim*	Flumethrin	Dimethicone
Amprolium	Triclabendazole	Poloxalene
Clopidol*	Fenbendazole	Toltrazuril
Lasalocid sodium	Levamisole	Decoquinate
Maduramicin*	Ivermectin	Diclazuril
Nicarbazin	Cephalexin	Phosmet*
Robenidine hydrochloride*	Florfenicol	Piperonyl butoxide
Procaine penicillin	Tilmicosin	Amitraz
Procaine benzylpenicillin	Oxolinic acid*	Deltamethrin
Clavulanic acid	Lido/lignocaine	Cyromazine
Monensin	Tiamulin	Emamectin benzoate
Salinomycin sodium	Lincomycin	Immunological products
Flavophospolipol	Clindamycin	
Neomycin	Nitroxynil	

§ Ranked in column form on the basis of annual usage.
* No longer marketed.

This prioritisation scheme was designed as a screening tool and was therefore simplistic in nature; for example, it did not consider dissipation and transport in the

environment and no information was provided on which environmental compartments (e.g. soil, surface water, groundwater and air) were most likely to be exposed.

The Environment Agency therefore commissioned this follow-on study in order to:

- refine the prioritisation exercise;
- investigate further those compounds identified as being of greatest potential to cause harm to gain greater understanding of the risks they pose to the environment (soil, surface water and groundwater) relative to other compounds on the priority list;
- develop and perform a targeted environmental monitoring programme to ascertain whether those compounds identified as posing the greatest risk are present in the environment at ecologically significant levels.

This work will inform the Environment Agency's approach to these compounds. It will help to ensure that the monitoring programme is effectively targeted, identify the need (if any) for pollution prevention measures and guide future research initiatives.

Section 2 of this report describes the refinement of the prioritisation exercise and the development and application of a ranking scheme to identify the relative risks posed to the environment following the use of the priority compounds as either livestock or aquaculture treatments.

Section 3 describes the performance of a targeted monitoring study to generate information on concentrations of seven of the highest ranked compounds in the UK environment. Section 4 offers a general discussion of the results, while the overall conclusions are drawn in Section 5.

2 Ranking of priority compounds

The screening-based approach described in Section 1 prioritised compounds based on information on usage and available ecotoxicity data. However, the approach was qualitative and did not consider how a compound is likely to behave in the environment.

This study was therefore undertaken to refine the previous approach by developing a ranking scheme that incorporated information on:

- different treatment scenarios for an active substance;
- environmental fate and effects

The aim was to identify those medicines and treatment scenarios with the greatest potential to cause harm and which thus warrant further study. The scenarios and compounds identified were considered of interest for inclusion in a targeted risk-based monitoring programme (see Section 3).

2.1 Method

The ranking was performed in a number of discrete stages (Figure 2.1).

In the first stage, the priority list from the previous Environment Agency project (Boxall *et al.* 2002) was reviewed and refined to ensure that it was up-to-date, accurate and reflected current regulatory concerns. Information on the usage, fate and effects of each of the compounds on the refined priority list was then collated and used to estimate their concentrations in the main environmental compartments. Predicted no-effect concentrations were calculated from available ecotoxicity data.

By comparing predicted environmental concentrations (PECs) with predicted no-effect concentrations (PNECs), it was possible to rank compounds and treatment types in terms of their potential to cause harm for the environmental compartments soil, surface water and sediment. Impacts on groundwaters were assessed solely on the basis of concentration, i.e. compounds of potential environmental concern were those with maximum environmental concentrations predicted to exceed 0.1 $\mu g\ l^{-1}$, the current limit for pesticides in drinking water. An outline of the scheme is given in Figure 2.2.

The aim of the scheme was not to characterise the risks posed by each compound individually (this is already done during the authorisation of its use), but to determine the level of risk associated with the use of a particular compound in relation to others on the priority list. This approach allowed those compounds with a higher potential to cause harm to be identified.

The process is outlined below. Detailed descriptions of the exposure calculations are given in Appendix 1. The results from each stage are given in Section 2.2 and summarised in Section 2.3.

2.1.1 Refinement of priority list

The priority list from the previous project was reviewed to take account of:

- changes in marketing authorisation status;
- revised treatment information;
- usage information provided by the industry;
- current knowledge on the fate and effects of each compound;
- concerns of Environment Agency staff and representatives of the Veterinary Medicines Directorate (VMD).

The priority list included a number of groups of compounds that were similar, i.e. they were from the same chemical class and would be expected to be used and act in a similar way. In such cases, one representative substance was selected for further assessment.

The results of the review were used to adjust the priority list for further assessment; some compounds were removed and some were added (see Section 2.2.1).

2.1.2 Collation of data on usage, fate and ecotoxicity

Data on typical treatment scenarios, environmental fate and persistence, and the ecotoxicological effects of each of the priority compounds were obtained from a range of sources.

Information on the typical treatment scenarios (dosage used for each substance, treatment durations, metabolism and the frequency of treatments over a year) was collated for each substance from a number of sources including:

- *Veterinary Applied Pharmacology and Therapeutics* (4th edn.) (Brander *et al.* 1977);
- *The Veterinary Formulary* (1st edn.) (Debuf 1991);
- *Diseases of Poultry* (10th edn.) (Calneck *et al.* 1997)
- *Veterinary Medicine* (9th edn.) (Radostis *et al.* 2000);
- *Compendium of Data Sheets for Veterinary Products* (NOAH 2002);
- personal communications with a number of veterinary surgeons in large animal practice;
- personal communications with veterinary pharmaceutical companies.

As many of the compounds on the priority list are used in a number of different products, it was necessary to obtain typical scenarios for each species and each product type. Scenarios were developed for group treatments using information from the National Office of Animal Health (NOAH) Compendium and were selected to represent a ‘worst case’ (i.e. where a range of doses was given, the highest was selected and where a range of treatment durations was possible, the longest was selected). All scenarios developed were circulated to NOAH members for comment

and many were revised based on feedback received during this consultation exercise.

Information on physico-chemical properties (octanol–water partition coefficients, soil sorption coefficients and dissociation constants), persistence in soils and surface waters, and ecotoxicity to both aquatic and terrestrial species were collated from a number of sources. These included:

- the initial Environment Agency review of veterinary medicines in use in the UK (Boxall *et al*. 2002, 2004);
- recently published data in scientific journals;
- environmental assessments for veterinary medicines available from the US Food and Drink Administration (FDA) website (www.fda.gov/cvm/default.html)
- data provided in confidence by manufacturers of compounds on the priority list.

Data on sorption were required in the ranking scheme to determine movement to surface waters and groundwaters, but experimental values for sorption were rarely available. Therefore, an indication of the sorption potential of these compounds in soil was obtained using quantitative structure–property relationships. Previous work (Boxall A B A and Tolls J, unpublished data) indicated that, while the estimates were poor, they would generally underestimate sorption and hence would provide a conservative estimation of movement of a substance to groundwaters or to surface waters. Estimations were obtained using the Syracuse Research Corporation (SRC) PCKOC package (SRC 1996) and structures were input to the program using SMILES notation.

2.1.3 Exposure assessment

Simple modelling approaches were used to estimate exposure concentrations arising from the use of compounds to treat pasture animals, housed animals and in aquaculture. These are outlined below and full details of the methods and the equations used are provided in Appendix 1.

Pasture animals

Veterinary medicines may be used to treat a range of animal types that are kept on pasture. For medicines applied orally or by injection, the medicine may be released directly to soils or surface waters in urine or faeces. Topical treatments may be washed off.

In this study, veterinary medicines used in the treatment of cattle, pigs, horses and sheep at pasture were considered.

Figure 2.1 Approach used to identify priority veterinary medicines for monitoring

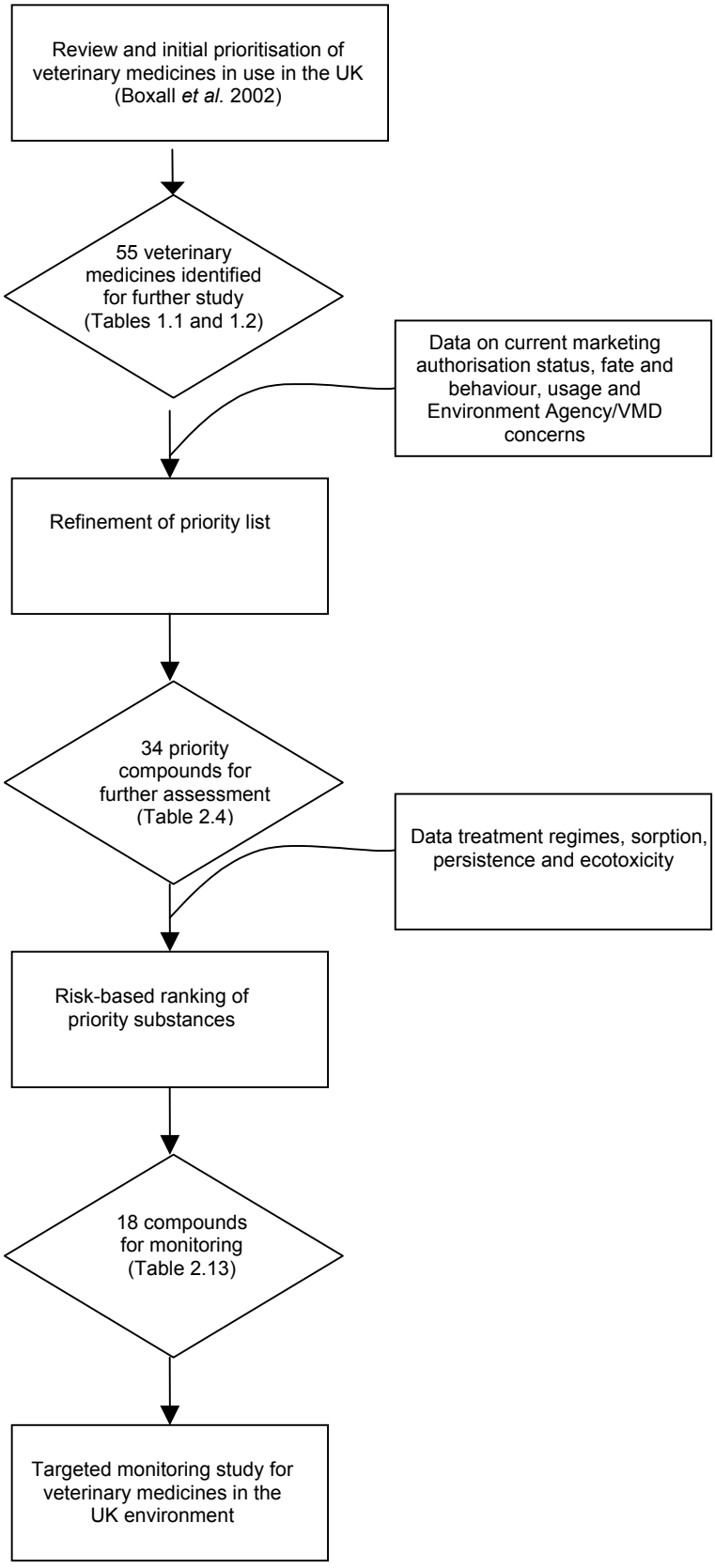
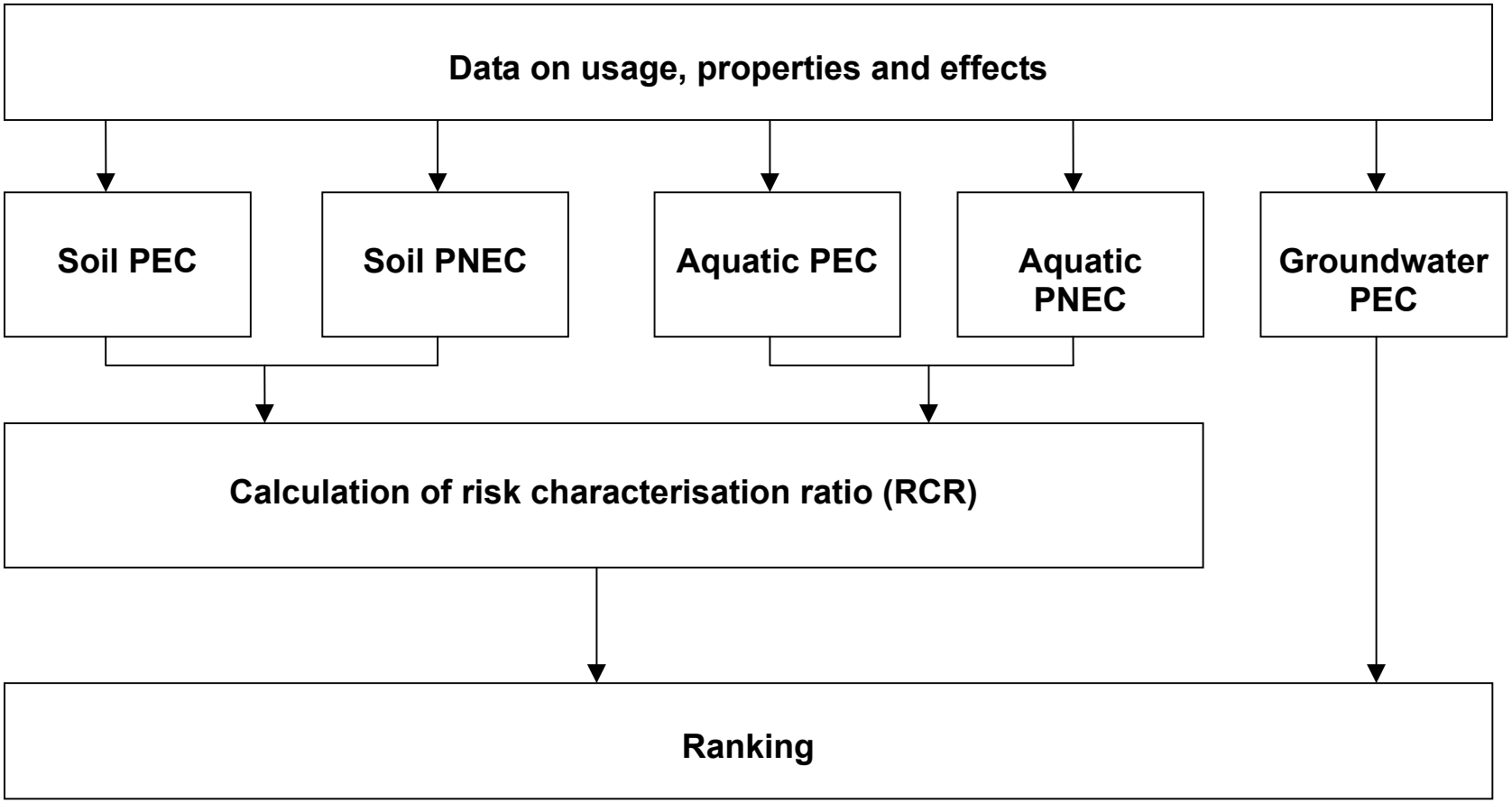


Figure 2.2 Schematic of the ranking scheme



Concentrations of each of the priority compounds in soil, surface water and groundwater arising from the treatment of animals on pasture were obtained using a combination of exposure assessment models. The methods were based on approaches developed specifically for veterinary medicines (e.g. Montforts 1999); where methods developed for veterinary medicines were not available, methods developed for pesticides were used.

The modelling approach assumed that all of the administered medicine was excreted and that this was then released directly to soil, where it mixed with the top 5-cm layer, or to a surface water body of set dimensions. Subsequent movement of the medicine from soil to groundwater was estimated using information on sorption and persistence in soils.

All models were run in Microsoft® Excel.

Intensively reared livestock

Intensively reared livestock are typically housed for long periods of time. Manure, slurry or litter arising from these animals is collected and stored before being spread onto land, as fertiliser, at relatively high application rates (ADAS 1997 and 1998).

Veterinary medicines used to treat intensively reared animals may be released to soils during the slurry/manure application process and may subsequently be transported to surface water (via runoff and drainage) and/or groundwater. The modelling approach for intensively reared livestock (cattle, pigs, poultry) (Spaepen *et al*. 1997) therefore considered estimates of:

- concentrations in manure and slurry at the time of application to land using information on treatment regime, manure storage and persistence in manure;
- concentrations in soil using information on the concentration of the medicine in slurry, typical slurry application rates for the UK and a soil mixing depth of 5 cm;
- concentrations in surface waters assuming that the main route of entry is in drainflow;
- groundwater concentrations using a soil leaching model and information on sorption and persistence in soils.

Aquaculture treatments

Aquaculture treatments are employed in aquaculture systems to treat:

- eggs in hatcheries;
- free-living stock within pond or tank-based systems.

Two modelling scenarios were therefore used:

- a trout hatchery (for the egg treatment);
- a land-based trout farm (for fish treatments).

The hatchery scenario assumed a farm with a continuous flow egg hatchery system, with treatment applied into the water supply to ensure a fixed concentration of the

chemical for a specified time period (30 minutes). It was assumed that the farm had a settlement pond, which ultimately discharged into a river.

The stocked fish scenario assumed a farm consisting of ten raceways (concrete tanks) operating at a high stocking density, and discharging into a river via a settlement pond. Although the stocking density used was high, the scenario was considered representative of a large commercial land-based aquaculture facility in England and Wales.

Models used for the simulations were based on plug flow of the medicine through the farm system over a 24-hour period, and were implemented as a Microsoft Excel spreadsheet.

2.1.4 Effects assessment

PNECs were derived from available ecotoxicity data. The 'base set' data (i.e. daphnids, fish, alga, earthworms, plants, soil microbes) were used to derive PNECs and appropriate uncertainty factors were applied. Uncertainty factors for the aquatic studies were based on those used in the Committee for Veterinary Medicinal Products (CVMP) guidance document (CVMP 1997). The terrestrial values were selected to reflect the type and amount of data available. The factors used are given in Tables 2.1 and 2.2.

Table 2.1 Assessment factors used to derive aquatic PNECs

Information available	Assessment factor
<3 standard test endpoints (one from each taxonomic group)	1000
Three standard test endpoints	100

Table 2.2 Assessment factors used to derive terrestrial PNECs

Information available				
Lowest end-point is an EC50	YES	NO	YES	NO
Lowest end-point is a NOEC from a chronic study	–	YES	NO	YES
Three tests from earthworms, plants and microbes	YES	YES	NO	NO
<3 tests have been performed	NO	NO	YES	YES
Assessment factor	100	10	1000	100

2.1.5 Ranking procedure

Risk characterisation ratios (RCRs) were calculated for both soil and surface water for each compound and treatment scenario. These ratios were obtained from the time weighted averaged (TWA) PEC and the PNEC using Equation 2.1.

$$\mathrm{RCR} = \frac{\mathrm{TWA\ PEC}}{\mathrm{PNEC}} \qquad \text{Equation 2.1}$$

The RCRs were then used to rank compounds and scenarios. For groundwater, compounds and scenarios were ranked purely on the basis of the maximum predicted concentration.

Those compounds and scenarios with a RCR >1 or which had a predicted concentration in groundwater of 100 ng l^{-1} were identified for further assessment during the monitoring phase of the project.

2.2 Results

2.2.1 Refinement of priority list

Following the review of the priority list developed during the previous project, 27 compounds were removed (Table 2.3). An additional six compounds were added to the list either because they had received a marketing authorisation since the previous project was completed or because of concerns over their high toxicity to aquatic and terrestrial organisms.

The final priority list (Table 2.4) for further assessment contained 34 compounds from the antibacterial, ectoparasiticide and feed additive groups.

2.2.2 Data on usage, fate and effects

In total, 211 scenarios were developed covering the use of each of the study compounds to treat intensively reared livestock and pasture animals. These scenarios are detailed in Appendix 2.

Data obtained from the public domain on the environmental fate and ecotoxicity of the final list of priority compounds are presented in Appendices 3–6. Additional data on a number of priority compounds were provided by their manufacturers. These data were used along with the public domain data to estimate PECs and PNECs but, due to their confidential nature, the values are not presented in the report.

Tables 2.5, 2.9 and 2.10 show that experimental or predicted data on sorption, persistence and ecotoxicity (i.e. allowing an assessment of potential risks to at least one of the environmental compartments) were available for 22 of the 34 compounds on the refined priority list.

For 13 of the compounds (amprolium, chlorhexidine, clavulanic acid, decoquinate, dicyclanil, lasalocid, levamisole, morantel, nicarbazin, nitroxynil, poloxalene, procaine penicillin, and salinomycin), insufficient data were available for ranking purposes in either the terrestrial or aquatic compartments.

Table 2.3 Veterinary medicines removed from or added to the priority list

Compound	Reason
Removed from the priority list	
amitraz	Very rarely used as an ectoparasiticide.
baquiloprim	No longer has marketing authorisation.
cephalexin	Used only on companion animals.
chlortetracycline, tetracycline	Use characteristics and properties are very similar to oxytetracycline, which is also on the priority list.
clopidol	No longer has marketing authorisation.
diazinon, cypermethrin, deltamethrin	Environmental risks are well understood and a number of Environment Agency projects were already investigating these compounds.
dihydrostreptomycin, neomycin, clindamycin, flavophospholipol	Use characteristics and/or properties are very similar to apramycin, which is also on the priority list.
dimethicone	An excipient.
emamectin benzoate	Used as a marine aquaculture treatment so outside the scope of the current study.
flumethrin	Substance used only to treat bees.
immunological products	Vaccines, etc. so chemical assessment inappropriate.
lidocaine and lignocaine	Both are highly volatile so unlikely to enter aquatic or terrestrial systems.
maduramicin	No longer has marketing authorisation.
oxolinic acid	No longer has marketing authorisation.
phosmet	No longer has marketing authorisation.
piperonyl butoxide	Used only in non-food producing animals.
procaine benzylpenicillin	Use characteristics and properties are very similar to procaine penicillin, which is also on the priority list.
robenidine	No longer has marketing authorisation.
sarafloxacin	Used only rarely as an aquaculture treatment.
toltrazuril	Use characteristics and properties are very similar to diclazuril, which is also on the priority list.
Added to the priority list	
bronopol	Compound used in aquaculture, which received market authorisation since the previous project was completed.
chlorhexidine	Believed to be widely used.
dicyclanil	New active substance expected to be used in large amounts with high potential to enter the environment.
doramectin, eprinomectin, moxidectin	Highly toxic to aquatic and terrestrial organisms.

Table 2.4 List of priority compounds for further assessment

amoxicillin	eprinomectin	nitroxynil
amprolium	fenbendazole	oxytetracycline
apramycin	florfenicol	poloxalene
bronopol	ivermectin	procaine penicillin
chlorhexidine	lasalocid	salinomycin
clavulanic acid	levamisole	sulfadiazine
cyromazine	lincomycin	tiamulin
decoquinate	monensin	tilmicosin
diclazuril	morantel	triclabendazole
dicyclanil	moxidectin	trimethoprim
doramectin	nicarbazin	tylosin
enrofloxacin		

Table 2.5 Sorption and persistence data used in the ranking process[§]

Compound	Lowest Koc	Highest Koc	Manure DT50 (d)	Soil DT50 (d)	Sediment DT50 (d)
amoxicillin	866*	866*	4	0.29	nd
amprolium	nd	nd	nd	nd	nd
apramycin			nd		nd
bronopol			nd	nd	nd
chlorhexidine	nd	nd	nd	nd	nd
ciprofloxacin[£]	35,342	134,465	nd	nd	nd
clavulanic acid	nd	nd	nd	nd	nd
cyromazine	21*	21*	nd	142	nd
decoquinate	nd	nd	nd	nd	nd
diclazuril			nd	303	nd
dicyclanil			nd		nd
doramectin	7,520	86,900	nd	79	nd
enrofloxacin			nd	696	nd
eprinomectin			126 (cow pats)	150	nd
fenbendazole			nd		nd
florfenicol	24	52	nd		nd
ivermectin			nd	56	nd
lasalocid	323*	323*	nd	nd	nd
levamisole	8,652*	8,652*	nd	nd	nd
lincomycin	59*	59*	nd	nd	nd
monensin			nd		nd
morantel	13,100*	13,100*	nd	nd	nd
moxidectin	18,000	41,000	nd	62	nd
nicarbazin	nd	nd	nd	nd	nd
nitroxynil	nd	nd	nd	nd	nd
oxytetracycline	27,792	93,317	nd	18	70
poloxalene	nd	nd	nd	nd	nd
procaine penicillin	421*	421*	nd	nd	nd
salinomycin	nd	nd	nd	64	nd
sulfadiazine			nd		nd
tiamulin	nd	nd	nd	nd	nd

Compound	Lowest Koc	Highest Koc	Manure DT50 (d)	Soil DT50 (d)	Sediment DT50 (d)
tilmicosin			nd	nd	nd
triclabendazole			nd		nd
trimethoprim	1,680	3,990	nd	110	nd
tylosin		7,988			nd

§ Confidential data provided by industry are not shown. The shaded entries indicate where confidential data were available.
* Predicted sorption coefficient obtained using the PCKOC program.
nd = data not available
£ Enrofloxacin is metabolised to ciprofloxacin, which also has antibiotic activity. Therefore properties for this molecule were also obtained.

2.2.3 Exposure assessment

Pasture animals

Concentrations in soil, surface water and groundwater arising from the treatment of a range of pasture animals (cattle, pigs, horses and sheep) were obtained for 22 of the study compounds and for a wide range of treatment types.

The highest concentrations in soil and surface water were observed for the aminoglycosides lincomycin, apramycin and tilmicosin. The lowest concentrations were observed for the milbemycins (moxidectin) and macrocyclic lactones (ivermectin and doramectin) (Table 2.6).

Predicted groundwater concentrations for a large proportion (17 out of 22) of the compounds were <100 ng l^{-1}. However, concentrations for five compounds (apramycin, florfenicol, lincomycin, tilimicosin and tylosin) in groundwater exceeded 100 ng l^{-1}, with lincomycin having a predicted maximum concentration of >2.5 μg l^{-1}.

The concentrations given in Table 2.6 have been generated for ranking purposes only and should not be interpreted as expected environmental concentrations. The simple modelling approaches applied and the assumptions used to develop the values are likely to greatly overestimate concentrations in the environment.

Table 2.6 Predicted TWA concentrations in soil and surface water and maximum predicted groundwater concentrations for the study compounds used to treat pasture animals

Compound	Soil (mg kg^{-1})	Aquatic (mg l^{-1})	Groundwater (μg l^{-1})
amoxicillin	0.0001–0.0009	0.0012–0.040	0.000
apramycin	0.14–1.51	0.035–0.38	0.072–0.469
chlorhexidine	0.0076	0.0019	0.000
cyromazine	0.019	0.0044	0.035
doramectin	0.00038–0.0035	0.00010–0.00094	0.000
enrofloxacin	0.012–0.19	0.0029–0.047	0.004–0.059
eprinomectin	0.0036	0.00094	0.001
fenbendazole	0.0041–0.03	0.002–0.004	0.000
florfenicol	0.057	0.019	0.124
ivermectin	0.00025–0.0088	6.9×10^{-5}–0.0051	0.000–0.002
levamisole	0.010–0.075	0.0026–0.019	0.003–0.023
lincomycin	0.010–1.07	0.0019–0.27	0.239–2.505
morantel	0.0083–0.14	0.0021–0.036	0.000
moxidectin	2.5×10^{-6}–3.4×10^{-5}	6.9×10^{-7}–3.7×10^{-6}	0.000
nitroxynil	0.014–0.076	0.0035–0.019	0.000
oxytetracycline	0.019–0.18	0.007–0.044	0.000–0.001
poloxalene	0.0083	0.0021	0.000
sulfadiazine	0.0069–0.124	0.004–0.068	0.003–0.039
tiamulin	0.0076–0.23	0.002–0.058	0.000
tilmicosin	0.0014–0.56	0.00035–0.14	0.002–0.173
trimethoprim	0.0026–0.086	0.0007–0.0089	0.001–0.018
tylosin	0.002–0.26	0.00058–0.073	0.003–0.297

Intensively reared livestock

Concentrations arising from the treatment of intensively reared livestock with 28 veterinary medicines were obtained for a range of treatment types (Table 2.7). No data were available for clavulanic acid for all three environmental compartments.

As with the pasture results, some of the highest soil concentrations were observed for lincomycin and tilmicosin. However, amprolium, enrofloxacin, monensin, oxytetracycline, trimethoprim, sulfadiazine and salinomycin were also predicted to result in high soil concentrations. Concentrations of the milbemycins and macrocyclic lactones were generally much lower. Predicted concentrations of amoxicillin and tylosin in soils were much lower than those obtained for the pasture scenario.

The highest concentrations for surface water and groundwater were observed for treatments with sulfadiazine, florfenicol or lincomycin. Concentrations of other compounds in surface water were much lower. None of the other compounds were predicted to leach to groundwater.

Table 2.7 Predicted TWA concentrations in soil and surface water and maximum predicted groundwater concentrations for the study compounds used to treat intensively reared livestock

Compound	Soil (mg kg^{-1})	Aquatic (mg l^{-1})	Groundwater ($\mu g\ l^{-1}$)
amoxicillin	8.3×10^{-6}–0.00016	6×10^{-6}–0.00011	0.00
amprolium	1.34	nd	0.00
chlorhexidine	0.0044	nd	0.00
decoquinate	0.24	nd	0.00
diclazuril	0.02	2.3×10^{-7}	0.00
doramectin	0.0016–0.0040	8.8×10^{-8}–$2.2. \times 10^{-7}$	0.00
enrofloxacin	0.072–1.42	3.9×10^{-7}–7.6×10^{-6}	0.00
eprinomectin	0.0034	1.1×10^{-6}	0.00
fenbendazole	0.037–0.063	2.1×10^{-6}–3.6×10^{-6}	0.00
florfenicol	0.27	0.144	0.717
ivermectin	0.00038–0.024	1.3×10^{-7}–8×10^{-6}	0.00
levamisole	0.064–0.086	2.9×10^{-6}–3.8×10^{-6}	0.00
lincomycin	0.64–6.7	0.23–2.45	1.82–19.1
monensin	0.78–1.24	3.4×10^{-7}–2.3×10^{-6}	0.00
morantel	0.05–0.86	1.5×10^{-6}–2.5×10^{-5}	0.00
moxidectin	1.54×10^{-5}–3.8×10^{-5}	3.7×10^{-10}–9.3×10^{-10}	0.00
nicarbazin	0.90	nd	0.00
nitroxynil	0.086	0.040	0.00
oxytetracycline	0.088–3.00	1.8×10^{-6}–6×10^{-5}	0.00
poloxalene	0.19	0.09	0.00
procaine penicillin	1.17	1.9×10^{-4}	0.00
salinomycin	0.78–1.24	nd	0.00
sulfadiazine	0.037–1.59	0.026–1.14	0.121–5.20
tiamulin	0.70–1.39	0.042–0.085	0.00
tilmicosin	0.09–3.48	4.1×10^{-6}–0.00016	0.00
triclabendazole	0	0	0.00
trimethoprim	0.072–8.07	4.0×10^{-5}–0.0044	0.00
tylosin	1.3×10^{-7}–9.5×10^{-6}	1.2×10^{-8}–8.9×10^{-7}	0.00

Aquaculture treatments

Predicted maximum concentrations in receiving waters for the three priority compounds used as aquaculture treatments are presented in Table 2.8.

Highest peak concentrations were predicted for amoxicillin, followed by oxytetracycline and bronopol. Model predictions indicated that, within 24 hours of treatment, all three compounds would have dissipated and would be undetectable.

Table 2.8 Predicted maximum concentrations in receiving waters for the three priority compounds used in aquaculture during and 24-hours after treatment

Compound	Treatment dose or concentration	Peak concentration ($\mu g\ l^{-1}$)	Concentration after 24 h ($\mu g\ l^{-1}$)	Number of repeat doses
amoxicillin	160 mg kg^{-1}	531	0	10
bronopol	50 mg l^{-1}	9.5	0	1
oxytetracycline	75 mg kg^{-1}	236	0	8

2.2.4 Effect assessment

Using the collated ecotoxicity data (public domain data are given in Appendices 5 and 6), it was possible to derive PNECs for the terrestrial environment for 21 of the study compounds (Table 2.9).

The number of terrestrial data points for these study compounds was variable, with only eprinomectin and fenbendazole having a full dataset, i.e. earthworms, plants and microbes and chronic no observable effect concentration (NOEC) data. Many of the compounds had only one or two standard endpoints and hence an uncertainty factor of 100 or 1,000 was applied.

In addition to the results of the standard studies, some data were available on the effects on other organisms; a comparison of effect concentrations from these studies with the calculated PNECs indicated that the PNECs were generally much lower. The highest PNECs (i.e. least toxic compounds) were for cyromazine, diclazuril, fenbendazole, salinomycin and tiamulin; these all exceeded 1 mg kg^{-1}. Lowest PNECs (i.e. most toxic compounds) were observed for enrofloxacin and tilmicosin, with PNECs for both compounds being <1 $\mu g\ kg^{-1}$.

It was possible to determine an aquatic PNEC for a total of 22 of the study compounds (Table 2.10). The aquatic datasets were more complete than the terrestrial datasets with full datasets (i.e. fish 96 h LC50, daphnid 48 h EC50 and algae 96 h EC50) being available for 14 of the study compounds.

The highest PNECs were observed for amoxicillin, lincomycin and enrofloxacin; these all exceeded 100 $\mu g\ l^{-1}$. The lowest aquatic PNECs were observed for the macrocyclic lactones and milbemycins, with PNECs for ivermectin, doramectin, eprinomectin and moxidectin all being in the low ng l^{-1} range. This probably reflects the insecticidal mode of action of these compounds.

2.2.5 Risk characterisation

Risk characterisation ratios and predicted groundwater concentrations for each of the pasture and intensively reared animal scenarios investigated are given in Appendices 7–12.

Because of a lack of data on the ecotoxicity and physico-chemical properties of many of the study compounds, it was not possible to determine either a risk characterisation ratio or a groundwater concentration for them. Consequently, it was not possible to rank these compounds in one or more of the environmental compartments. Compounds with insufficient data were:

- amprolium
- chlorhexidine
- clavulanic acid
- decoquinate
- dicyclanil
- lasalocid
- levamisole
- morantel
- nicarbazin
- nitroxynil
- poloxalene
- procaine penicillin
- salinomycin.

Pasture animals

For those veterinary medicines used to treat pasture animals, a total of 15 compounds were identified that had a RCR >1 (Table 2.11). These included:

- antimicrobial agents (from the sulfonamide, macrolide, fluoroquinolone, pleuromutilin, chloramphenicol and aminoglycoside groups);
- compounds used as endoparasiticides (from the macrocyclic lactone, milbemycin and benzimidazole groups).

Treatments for pigs and cattle were generally ranked higher (i.e. posed a greater risk) than treatments for sheep and horses.

Seven compounds (apramycin, enrofloxacin, florfenicol, lincomycin, sulfadiazine, tilmicosin, tylosin) had an RCR ≥1 for the soil compartment with 12 compounds (apramycin, doramectin, eprinomectin, fenbendazole, ivermectin, moxidectin, oxytetracycline, sulfadiazine, tiamulin, tilmicosin, trimethoprim, tylosin) having an RCR >1 in the aquatic environment. Four compounds (apramycin, florfenicol, lincomycin, tylosin) were identified as having the potential to leach to groundwater.

Intensively reared animals

For those compounds used to treat intensively reared animals, a total of 10 compounds were identified that had an RCR >1 (Table 2.12). These included:

- antibacterial agents (from the tetracycline, amidine, sulfonamide, fluoroquinolone, chloramphenicol and aminoglycocide groups);
- an endectocide (ivermectin).

In terms of the different environmental compartments, eight compounds (enrofloxacin, florfenicol, lincomycin, monensin, oxytetracycline, sulfadiazine, tilmicosin, trimethoprim) had an RCR >1 for the soil compartment and five compounds (florfenicol, ivermectin, lincomycin, sulfadiazine, tiamulin) had an RCR >1 for the aquatic environment. Only three compounds (florfenicol, lincomycin, sulfadiazine) would be expected to leach to groundwater.

Sulfadiazine, florfenicol and lincomycin were ranked highest in terms of their risk to all three environmental compartments.

Aquaculture treatments

All of the aquaculture compounds had an RCR >1. In terms of ranking, bronopol was ranked highest, followed by oxytetracycline and amoxicillin.

Table 2.9 Terrestrial ecotoxicity data and PNECs for the study compounds

Compound	Trophic levels covered (std)	Most sensitive endpoint	Concentration (mg kg^{-1})	Uncertainty factor	PNEC (mg kg^{-1})	Most sensitive non standard endpoint	Concentration (mg kg^{-1})
amoxicillin	nd	nd	nd	nd	nd	nd	nd
amprolium	nd	nd	nd	nd	nd	*nd*	nd
apramycin	2	tomato seedling growth NOEC	36	100	0.36	*A. chroococcum*	0.1
bronopol	nd	nd	nd	nd	nd	nd	nd
chlorhexidine	nd	nd	nd	nd	nd	nd	nd
clavulanic acid	nd	nd	nd	nd	nd	nd	nd
cyromazine	1	earthworm 14 d LC_{50}	1000	1000	1	nd	nd
decoquinate	nd	nd	nd	nd	nd	nd	nd
diclazuril	2	plant emergence NOEC	100	100	1	*Candida albins* - no growth	100
dicyclanil						nd	nd
doramectin	2	ryegrass root elongation NOEC	1.6	100	0.016	*E. foetida* 28 d NOEC	2
enrofloxacin	2	wheat NOEC growth	<0.13	100	<0.00013	nd	nd
eprinomectin	3	plant NOEC	0.47	10	0.047	nd	nd
fenbendazole	3	tomato seedling growth NOEC	36	10	3.6	*L. terrestris* 28 d NOEC	56
florfenicol	1	microbes MIC/NOEC	0.4	100	0.004	nd	nd
ivermectin						nd	nd
lasalocid	nd	nd	nd	nd	nd	nd	nd
levamisole	nd	nd	nd	nd	nd	nd	nd
lincomycin	2	microbes MIC/NOEC	0.78	100	0.0078	nd	nd
monensin	3	radish LC_{50} emergence	9.8	100	0.098	nd	nd
morantel	nd	nd	nd	nd	nd	nd	nd
moxidectin	1	plant NOEC	4	100	0.04	earthworm 28 d LC50	37.2
nicarbazin	nd	nd	nd	nd	nd	nd	nd
nitroxynil	nd	nd	nd	nd	nd	nd	nd
oxytetracycline	1	*Phaseolus vulgaris* LC50	<160	100	<1.6	*Enchytraeus cryptucus* EC50 reproduction	2701
poloxalene	nd	nd	nd	nd	nd	nd	nd
procaine penicillin	nd	nd	nd	nd	nd	nd	nd
salinomycin	1	microbes NOEC	100	100	1	nd	nd
sulfadiazine						nd	nd
tiamulin	1	microbes NOEC	500	100	5	nd	nd
tilmicosin	2	microbes MIC	0.024	100	0.00024	nd	nd

Compound	Trophic levels covered (std)	Most sensitive endpoint	Concentration (mg kg^{-1})	Uncertainty factor	PNEC (mg kg^{-1})	Most sensitive non standard endpoint	Concentration (mg kg^{-1})
triclabendazole						*A. aegypiti* NOEC	10
trimethoprim						nd	nd
tylosin	1	*A. chroococcum*	5	1000	0.05	nd	nd

Confidential data provided by industry are not shown. The shaded entries indicate where confidential data were available.

Table 2.10 Aquatic ecotoxicity data and PNECs for study compounds

Compound	Trophic levels covered	Most sensitive endpoint	EC50 (mg l^{-1})	Proposed uncertainty factor	Calculated PNEC (mg l^{-1})	Most sensitive non standard endpoint	Effect concentration (mg l^{-1})
amoxicillin	1	*S. capricornutum* 72 h EC50	250	1000	0.25	*M. aeruginosa* 72 h EC50	0.0037
amprolium	nd	nd	nd	nd	nd	nd	nd
apramycin						nd	nd
bronopol							
clavulanic acid	nd	nd	nd	nd	nd	nd	nd
cyromazine	2	*Lepomis machrochirus* 96 h LC50	89.7	1000	0.0897	*Gambusa affinis* 72 h LC50	0.037
decoquinate	nd	nd	nd	nd	nd	nd	nd
diclazuril	2	*Lepomis machrochirus* 96 h LC50	0.5	1000	0.0005	*Daphnia magna* 21 d reproduction NOEL	0.16
dicyclanil							
doramectin	3	*Daphnia magna* 48 h EC50	0.0001	100	0.000001	nd	nd
enrofloxacin	3	*Lepomis machrochirus* 96h LC50	79.5	100	0.795	*Daphnia magna* chronic NOEL	9.8
eprinomectin	3	*Daphnia magna* 48 h EC50	0.00045	100	0.0000045	nd	nd
fenbendazole	2	*Daphnia magna* 48 h EC50	0.012	1000	0.000012	nd	nd
florfenicol	3	*S. capricornutum* 72 h EC50	>2.9	100	>0.029	*S. capricornutum* 72 h NOEC	2.9
ivermectin	3	*Daphnia magna* 48 h EC50	0.000025	100	0.00000025	Gammarus 96 h LC50	0.00003
lasalocid	nd	nd	nd	nd	nd	nd	nd
levamisole	nd	nd	nd	nd	nd	nd	nd
lincomycin	1	*Daphnia magna* 48 h EC50	379.4	1000	0.3794	*Daphnia magna* - phototactic behaviour decreased	5
monensin	2	*Onchorhynchus mykiss* 96 h LC50	9	1000	0.009	*Onchorhynchus mykiss* behaviour	>1.12
morantel	nd	nd	nd	nd	nd	nd	nd

Compound	Trophic levels covered	Most sensitive endpoint	EC50 (mg l^{-1})	Proposed uncertainty factor	Calculated PNEC (mg l^{-1})	Most sensitive non standard endpoint	Effect concentration (mg l^{-1})
moxidectin	3	*Daphnia magna* 48 h EC50	0.00003	100	0.0000003	*Daphnia magna* chronic NOEL	0.000011
nitroxynil	nd	nd	nd	nd	nd	nd	nd
oxytetracycline	3	*S. capricornutum* 72 h EC50	4.5	100	0.045	*P. vannamei* 48 h NOEC intoxication	0.055
poloxalene	nd	nd	nd	nd	nd	nd	nd
procaine penicillin	nd	nd	nd	nd	nd	nd	nd
salinomycin	nd	nd	nd	nd	nd	*Oryzias latipes*	63.5
sulfadiazine						*M. aeruginosa* 72 h EC50	0.135
tiamulin	3	*S. capricornutum* 72 h EC50	0.165	100	0.00165	*M. aeruginosa* 72 h EC50	0.003
tilmicosin	2	*Daphnia magna* 48 h EC50	57.3	1000	0.0573	nd	nd
triclabendazole						Trout non-standard	0.14
trimethoprim	2	*S. capricornutum* 72 h EC50	16	1000	0.016	*M. aeruginosa* 72 h EC50	112
tylosin						*M. aeruginosa* 72 h EC50	0.034

Confidential data provided by industry are not shown. The shaded entries indicate where confidential data were available.
NOEL = no observed effect level

Table 2.11 Priority compounds and scenarios identified for pasture animals (i.e. those compounds and scenarios with an RCR >1 or a concentration in groundwater > 0.1 μg l^{-1}, listed in order of increasing RCR or $PEC_{groundwater}$).

Soil			Surface water			Groundwater		
Compound	**Animal type**	**Treatment type**	**Compound**	**Animal type**	**Treatment type**	**Compound**	**Animal type**	**Treatment type**
sulfadiazine	pigs	injection	doramectin	sheep	injection	apramycin	pigs	premix
sulfadiazine	pigs	suspension	sulfadiazine	pigs	suspension	apramycin	pigs	powder
sulfadiazine	sheep	injection	sulfadiazine	horse	granules	florfenicol	cattle	injection
tylosin	cattle	soluble	trimethoprim	pigs	powder	tilmicosin	horse	injection
apramycin	cattle	powder	doramectin	pigs	injection	tylosin	pigs	premix
sulfadiazine	horse	injection	sulfadiazine	cattle	injection	lincomycin	cattle	soluble
tilmicosin	sheep	injection	moxidectin	sheep	injection	tylosin	pigs	soluble
sulfadiazine	horse	granules	moxidectin	sheep	liquid oral	apramycin	cattle	injection
lincomycin	pigs	soluble	tilmicosin	pigs	premix	lincomycin	cattle	powder
sulfadiazine	cattle	injection	doramectin	cattle	injection	lincomycin	pigs	premix
florfenicol	cattle	injection	oxytetracycline	pigs	feed			
tylosin	pigs	soluble	tylosin	sheep	injection			
tilmicosin	cattle	injection	tylosin	pigs	soluble			
enrofloxacin	pigs	piglet doser	doramectin	cattle	pour on			
tylosin	pigs	feed	apramycin	sheep	oral			
lincomycin	pigs	premix	tylosin	cattle	soluble			
enrofloxacin	pigs	injection	apramycin	pigs	premix			
enrofloxacin	cattle	oral	apramycin	pigs	powder			
enrofloxacin	cattle	injection	moxidectin	cattle	pour on			

Soil			Surface water			Groundwater		
Compound	**Animal type**	**Treatment type**	**Compound**	**Animal type**	**Treatment type**	**Compound**	**Animal type**	**Treatment type**
tilmicosin	pigs	premix	tylosin	pigs	feed			
			tiamulin	pigs	premix			
			apramycin	cattle	powder			
			fenbendazole	sheep	liquid oral			
			eprinomectin	cattle	pour on			
			fenbendazole	pigs	powder			
			ivermectin	sheep	injection			
			ivermectin	sheep	liquid oral			
			fenbendazole	pigs	liquid oral			
			fenbendazole	horse	liquid oral			
			ivermectin	horse	paste			
			ivermectin	pigs	injection			
			fenbendazole	cattle	powder			
			fenbendazole	cattle	liquid oral			
			fenbendazole	cattle	feed pellets			
			ivermectin	cattle	injection			
			fenbendazole	cattle	bolus			
			ivermectin	cattle	pour on			

Table 2.12 Priority compounds and scenarios identified for intensively reared animals (i.e. those compounds and scenarios with an RCR >1 or a concentration in groundwater > 0.1 μg l^{-1}, listed in order of increasing RCR or $PEC_{groundwater}$).

Soil			Surface water			Groundwater		
Compound	**Animal type**	**Treatment type**	**Compound**	**Animal type**	**Treatment type**	**Compound**	**Animal type**	**Treatment type**
oxytetracycline	cattle	topical	ivermectin	cattle	pour on	sulfadiazine	cattle	bolus
trimethoprim	poultry	powder	ivermectin	pigs	injection	sulfadiazine	cattle	injection
trimethoprim	pigs	powder	sulfadiazine	cattle	injection	florfenicol	cattle	injection
oxytetracycline	pigs	injection	florfenicol	cattle	injection	sulfadiazine	pigs	injection
oxytetracycline	pigs	topical	sulfadiazine	pigs	injection	sulfadiazine	pigs	suspension
oxytetracycline	pigs	soluble	sulfadiazine	pigs	suspension	lincomycin	pigs	soluble
monensin	cattle	premix	sulfadiazine	poultry	soluble	sulfadiazine	poultry	soluble
trimethoprim	poultry	soluble	sulfadiazine	pigs	powder	sulfadiazine	pigs	powder
sulfadiazine	cattle	bolus	tiamulin	pigs	premix	sulfadiazine	poultry	powder
monensin	poultry	premix	sulfadiazine	poultry	powder	lincomycin	pigs	premix
sulfadiazine	cattle	injection	tiamulin	poultry	soluble			
oxytetracycline	pigs	feed additive	tiamulin	pigs	injection			
trimethoprim	cattle	bolus	lincomycin	pigs	premix			
sulfadiazine	pigs	injection						
sulfadiazine	pigs	suspension						
florfenicol	cattle	injection						
sulfadiazine	poultry	soluble						
sulfadiazine	pigs	powder						

Soil			Surface water			Groundwater		
Compound	**Animal type**	**Treatment type**	**Compound**	**Animal type**	**Treatment type**	**Compound**	**Animal type**	**Treatment type**
sulfadiazine	poultry	powder						
tilmicosin	cattle	injection						
enrofloxacin	pigs	piglet doser						
enrofloxacin	cattle	oral						
lincomycin	pigs	premix						
enrofloxacin	cattle	injection						
enrofloxacin	pigs	injection						
tilmicosin	poultry	soluble						
enrofloxacin	poultry	soluble						
tilmicosin	pigs	premix						

2.3 Summary of the ranking process

The ranking scheme has allowed those treatment scenarios that pose the highest risk to the environment along with the environmental compartments most at risk to be identified for each compound. A total of 18 compounds (Table 2.13) were identified as potential determinands for the targeted risk-based monitoring study.

Table 2.13 Compounds identified as of potential concern for inclusion in the targeted monitoring programme

Compound	Treatment group	Scenario	Soil	Surface water	Groundwater
amoxicillin	f	A	X	√	X
apramycin	c,p	P	√	√	√
bronopol	f	A	X	√	X
doramectin	c,p,s	P	X	√	X
enrofloxacin	c,p, po	I,P	√	X	X
eprinomectin	c	P	X	√	X
fenbendazole	p,h,s, c	P	X	√	X
florfenicol	c,	I,P	√	√	√
ivermectin	c,p, s, h	I,P	√	√	X
lincomycin	p, c	I,P	√	√	√
monensin	po, c	I	√	X	X
moxidectin	c,s	P	X	√	X
oxytetracycline	p,f, c	I,P,A	√	√	√
sulfadiazine	c,h,s,p, po	I,P	√	√	√
tiamulin	p, po	I,P	X	√	X
tilmicosin	p,c, s, po	I,P	√	√	X
trimethoprim	p,c,po	I,P	√	√	X
tylosin	p,c, s	P	√	√	√

c = cattle, p = pigs, s = sheep, h = horse, po = poultry, f = fish
P = pasture, I = intensive, A = aquaculture

Only three compounds (triclabendazole, cyromazine and diclazuril) could be excluded from further consideration on the basis of the ranking procedure.

- Triclabendazole is extensively metabolised and released to the environment in amounts lower than detection limits (Novartis, personal communication).
- Cyromazine is used to treat sheep at low therapeutic doses; concentrations in soil and surface water were therefore considerably lower than PNECs.
- Diclazuril is used to treat poultry and sheep at low therapeutic doses; concentrations in soil and surface water were therefore considerably lower than PNECs.

Insufficient data meant it was not possible to rank a number of compounds, i.e.

- amprolium
- chlorhexidine
- clavulanic acid
- decoquinate
- dicyclanil
- lasalocid
- levamisole

- morantel
- nicarbazin
- nitroxynil
- poloxalene
- procaine penicillin
- salinomycin.

It is therefore recommended that attempts should be made to obtain data for these compounds. It may also be appropriate to include some of them in a future monitoring programme, selected on the basis of concentration alone.

3 Monitoring of veterinary medicines in the UK environment

A targeted monitoring programme was carried out between January and December 2004. Compounds and scenarios to be monitored were selected on the basis of the ranking results described in Section 2. In reviewing these results, the project board decided at this stage in the project, on the basis of the resources available, to target monitoring effort into the investigation of land-based livestock scenarios. No further investigation into fish farming medicines and scenarios was conducted.

3.1 Site selection

A number of sites were visited in January 2004 and assessed in terms of their suitability as potential monitoring sites. The following criteria were considered during site visits:

- **Soil and hydrological characteristics**. Ideally, the characteristics of the study sites should correspond to the characteristics used in the ranking process in order that they represent a potentially high exposure scenario. Consequently, for sites receiving manure application, preference was given to sites with underdrained clay soils and, for pasture treatments, preference was given to sites where small watercourses were present.

- **Area to which slurry or manure was applied**. Preference was given to sites where slurry or manure from treated animals was applied to a large proportion of the site.

- **Potential inputs of veterinary medicines from other sources**.

- **Type of animal treated and method of treatment**. Preference was given to sites using one of the top-ranked treatment scenarios identified for the compound.

- **Number of veterinary medicines used**. Preference was given to sites using a number of the highest ranked study compounds.

Four study sites were selected using these criteria. These were:

- an indoor intensive pig facility;
- a cattle farm where animals are kept on pasture from May to October/November;
- an outdoor pig unit;
- a turkey unit.

At the cattle farm, two sets of animals kept separately, were selected for study.

Using these scenarios, it was possible to monitor seven of the study compounds identified by the ranking process (see Table 2.13) as high priority when used to treat livestock. Details of the sites and compounds are given in Tables 3.1 and 3.2. Concentrations of ciprofloxacin, a metabolite of enrofloxacin, were also monitored at the turkey site.

Details of the sampling approaches, the sites and the specific monitoring routines applied at each site are given below.

3.2 Monitoring

3.2.1 Sampling approaches

At each site, different media (soil, faeces, sediment and water) appropriate to the site and treatment scenario were collected. The sampling procedures adopted for these media are described below.

Faeces

Samples from freshly deposited pats (at least nine) were collected and consolidated. A sub-sample (250 ml) was transferred to a plastic bottle (Nalgene) and sent for analysis to the Environment Agency National Laboratory Service (NLS) Llanelli. Any unused sample was transferred to freezer storage.

Soil

On each sampling occasion, duplicate soil samples were collected from the top 10 cm of the soil profile using a 30 mm i.d. gouge auger. Samples were chilled during transport back to the laboratory. A 300 g sub-sample taken from one of the field samples was sent for analysis and the second field sample was transferred to freezer storage.

Sediment

On each field visit, sediment (approximately a 1-litre composite sample) was collected from several points at each sampling station. A sub-sample (250 ml) was transferred to a plastic bottle (Nalgene) and sent for analysis to NLS Llanelli. Any unused sample was transferred to freezer storage.

Water

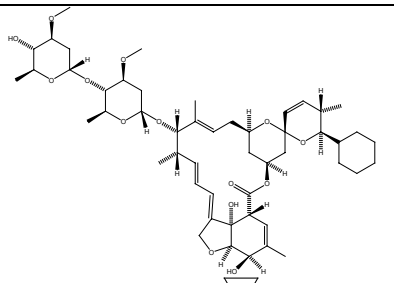
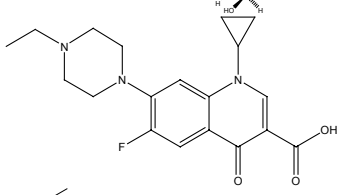
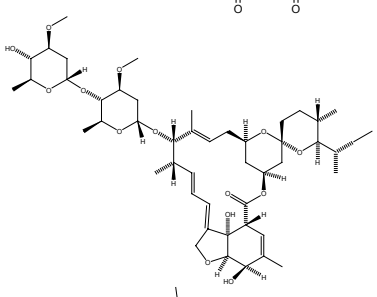
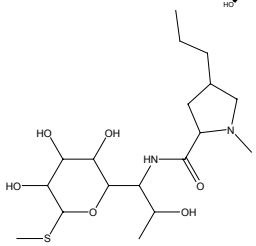
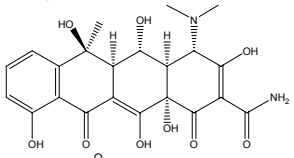
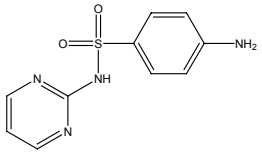
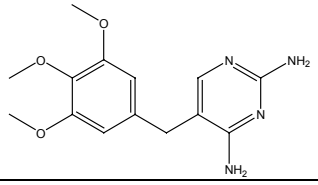
Continuous monitoring of waters was achieved using EPIC automatic water samplers configured to collect samples on a timed basis. A single composite sample of around 400 ml (comprising 8 $\times$ 50 ml samples taken every 3 hours) was collected on a daily basis. Samples were collected in borosilicate glass bottles and following collection were transferred to silanised glass bottles (Azlon) for shipping to NLS Llanelli for residue analysis.

Table 3.1 Treatment scenarios used at the monitoring sites

Scenario	Location	Medicines used	Active ingredient	Dose	Duration (days)	Frequency
Intensively reared pigs (indoor pigs)	Nottinghamshire /Lincolnshire	LincoSpectin	lincomycin*	33–44 mg/animal/day	35	1
			spectinomycin	33–44 mg/animal/day	35	1
		Tetramin 200	oxytetracycline*	1,800 mg/animal/day	35	1
		Trimediazine	sulfadiazine*	113 mg/animal/day	35	1
			trimethoprim*	23 mg/animal/day	35	1
Pigs at pasture (outdoor pigs)	Nottingham	Aurofac 100 Granular	chlortetracycline	8 g/sow/day	14	1
		Ivomec Premix	ivermectin*	75 mg/sow/day	14	1
Cattle at pasture	North Derbyshire	Dectomax Pour-on	doramectin*	25 ml/animal	NA	2
Cattle at pasture	North Derbyshire	Qualimintic Pour-on	ivermectin*	0.1 ml/kg	NA	2
Poultry	Northeast Yorkshire	Vetremox	amoxicillin**	15 mg/kg/day	3	1
		Baytril 10% Oral Solution	enrofloxacin*	10 mg/kg/day	3	1

NA = not applicable
* Study compound
** Priority compound but not investigated as it was only identified as being of potential risk when used in aquaculture.

Table 3.2 Veterinary medicines selected for monitoring

Veterinary medicine	Class	CAS No.	Structure
Doramectin	macrocyclic lactone	117704-25-3	
Enrofloxacin	fluoroquinolone	93106-60-6	
Ivermectin	macrocyclic lactone	70288-86-7	
Lincomycin	lincosamide	154-21-2	
Oxytetracycline	tetracycline	6153-64-6	
Sulfadiazine	sulphonamide	68-35-9	
Trimethoprim	pyrimidine	738-70-5	

CAS = Chemical Abstracts Service

3.2.2 Monitoring regimes employed at each site

Indoor pigs

The indoor pig scenario consisted of a 420 sow unit using:

- LincoSpectin (lincomycin) to treat weaners from 8 to 12 weeks of age;
- Trimediazine (sulfadiazine/trimethoprim) to treat weaners (3–7 weeks of age);
- Tetramin (oxytetracycline) on sows as a five-week treatment when necessary.

Weaners up to 12 weeks of age and about 140 sows were kept on slats; from 12 weeks of age, the pigs were fattened on straw. Slurry from slats was transferred to and stored in an earth bank lagoon, which was emptied twice a year. Solid manure from sow yards and fattening yards was also spread onto land (set-aside).

An umbilical system was used to spread the slurry onto a 29.4 ha field between 9 and 16 March 2004. Slurry was applied at a rate of 78,600 l/ha. The field had a modern drainage system comprising plastic drains and gravel backfill (to within 40 cm of the surface). Laterals were spaced at 20 and 40 m, and the field was mole drained (about 10 years ago, to within 50 cm of the surface). There were six drain outfalls along the receiving ditch monitored during the experiment.

Following guidance provided by the farmer, one of the six drain outfalls (the one most likely to run) was fitted with a float switch to monitor the presence/absence of drainflow. A rain gauge and soil temperature probe were placed in the field margin to monitor hourly rainfall totals and soil temperature. An auto-sampler was positioned to collect water samples from the ditch at the furthest and most accessible point downstream.

Samples of soil were collected from across the field using a ‘W’ formation sampling strategy and combined. Samples of stream water were collected during periods of drainflow and following significant rainfall.

Outdoor pigs

The outdoor pig unit was located on arable land and consisted of 1,125 sows, 300 farrowing sows/gilts, 550 dry/serviced sows/gilts and 275 gilts and boars. All breeding stock were routinely wormed twice a year using Ivomec Premix for Pigs – a meal mixture containing 0.6% w/w ivermectin, which is incorporated into rations. The pigs also received Aurofac 100 Granular (premix containing 100 g per kg chlortetracycline) in the ration as a therapeutic antimicrobial treatment to maintain herd fertility and health.

The treatments were administered as a blanket programme and, during treatment, the unit operated a closed system. The breeding pigs received rations containing ivermectin and chlortetracycline for a period of 1–2 weeks. The farrowing sows received the medicated ration over the full 14-day period and were thus targeted for monitoring as they presented a worst case scenario. The ration, in the form of a compound paddock nut, was fed to the sows ad lib (average 10 kg/sow/day). Treatment began on 28 April 2004 and was completed by 10 May 2004. The ration was fed to the pigs via feeding stations.

The farrowing unit was situated on a single block of land split into 28 farrowing paddocks. Each paddock was approximately 0.4 ha in size and accommodated 8–12 sows. Average stocking density was 25 sows per ha.

Soil samples were collected from three paddocks occupied by sows that had received the medicated ration, and from beneath and around the feed stations. Soil samples were collected 1, 7, 14, 21, 28, 60 and 122 after the last day of the treatment period. In addition, an untreated soil sample was collected from an adjacent field.

Cattle at pasture

Monitoring of doramectin and ivermectin was performed using a mixed breed herd that consisted of 150 head suckler cows and 250 associated young stock. All cattle were housed over winter and turned out onto blocks of land in the first week of May. Once turned out, cattle typically stay outdoors until October/November.

Two groups of animals, having direct access to surface water (with no other source of drinking water), were identified for treatment with doramectin and ivermectin.

Doramectin

Twenty-five store cattle, 6-12 months old (average weight 250 kg) were treated on two occasions, eight weeks apart, with Dectomax Pour-On for Cattle (0.5% w/v pour-on solution containing 5 mg/ml doramectin). The first treatment was administered in the farmyard on 6 May 2004. The second treatment was administered in-field on 1 July 2004. On each occasion, each animal received a 25 ml topical application along the midline (base tail to withers). Following the first treatment, the cattle were transported to summer grazing – nine fields of permanent pasture (9.47 ha in total), approximately 2 miles from the farm. The cattle were initially turned out onto 4.54 ha (four fields) of grassland. The remaining five fields (4.93 ha) were made available for aftermath grazing after a cut of hay had been taken.

A stream ran along the boundary of the four fields in which the cattle were initially turned into. There were two sizeable access points for the livestock to obtain drinking water (stock access to the full length of a stream is not considered good farming practice). There was no other source of drinking water for this block of land and livestock entered the stream to drink frequently, particularly during warmer spells of weather.

Faeces samples were taken:

- 7, 14, 21, 28 and 35 days after treatment 1;
- immediately prior to treatment 2;
- 7, 15, 21, 28, 36 and 43 days after treatment 2.

A pretreatment sample of stream water was collected prior to cattle turnout and prior to the second treatment. Thereafter, daily samples (400 ml – obtained by taking 50 ml every three hours) were taken using an auto-sampler positioned immediately downstream of the second drinking access point to the stream. Water samples were bulked for analysis as follows:

- 1–7, 7–14, 14–21, 21–28, 28–35, 35–42 and 42–49 days after treatment 1;
- 1–7, 7–15, 15–21, 22–28, 28–36, 36–43, 43–50, 50–57, 57–61, 61–64 and 64–70 days after treatment 2.

Ivermectin

Calves were treated with the cattle wormer Qualimintic Pour-On, containing 5% w/v ivermectin (5 mg/ml) on two occasions.

The first treatment was administered in the farmyard on 25 June 2004. On this occasion, a total of 26 cattle were treated (25 calves and one newly calved heifer). Animals were treated with the recommended dose of 1 ml per 10 kg bodyweight (500 µg ivermectin per kg bodyweight).

The second treatment was administered in the farmyard on 6 August 2004. On this occasion, a total of 37 animals were treated. Additions of 'qualifying' individuals to the group and the removal of some of the larger animals since the first treatment resulted in more animals being treated on this occasion.

On each occasion, the formulation was administered topically along the midline of the back (base tail to withers). Following the first treatment, the calves were turned onto a block of grazing land consisting of seven individual fields (15.57 ha in total) adjacent to the farm. Grazing was restricted at this time and cattle had access to five fields (12.0 ha). Following treatment 2, the group was given access to the remaining two fields (2.29 ha).

A small brook bisected the fields and the cattle used this as a drinking water resource. The cattle had to traverse the brook to access half of the total grazing area.

Samples from freshly deposited pats were collected:

- 4, 7, 14, 21 and 28 days after treatment 1;
- 4, 7 and 14 days after treatment 2.

A sample of stream water was collected prior to cattle turnout following treatment 1. Additional water samples were taken daily (400 ml – obtained by taking a 50 ml sample every three hours). Samples collected were either analysed separately (1 and 2 days after treatment 1 and 1, 2 and 3 days after treatment 2) or consolidated (2–4, 4–7, 7–14, 14–21, 21–28, 28–34 and 34–42 days after treatment 1, and 7–10 and 10–14 days after treatment 2). Grab samples were also collected 7, 21 and 31 days after treatment.

Poultry

The poultry scenario consisted of a turkey unit of 60,000 birds. Birds were treated with Baytril 10% Oral Solution (enrofloxacin), administered via the drinking water at a rate of 1 litre per 10,000 kg bodyweight per day (10 mg kg^{-1} bodyweight equivalent) and Vetremox (amoxicillin trihydrate) where 150 g/day was administered for 3 days.

Litter from the unit was collected and transported to the field site between 21 and 27 July 2004. Litter was stored before being spread on a 18.6 ha field on 24 August

2004. Following this, the field was sprayed-off (Roundup), drag-tined (29 August 2004) and paraploughed. It was top-tilthed, drilled and rolled on 7 September 2004.

Samples of soil were taken from the treated field 21, 42, 64, 90 and 120 days after litter application.

3.2.3 Analysis

Avermectins

The target analytes (ivermectin and doramectin) were extracted from river water using solid phase extraction (SPE).

Target analytes were extracted from soils and sediments using an accelerated solvent extraction (ASE) system using 95 per cent methanol/5 per cent water as the extraction solvent. Extracts were evaporated to low volume prior to reverse phase clean-up using a semi-preparative liquid chromatography system with a fraction collector that allowed individual isolation of the target analytes. Clean-up proved essential for good ion ratio confirmation.

The extracts were analysed using a high performance liquid chromatography/mass spectrometry (HPLC/MS) system with an atmospheric pressure chemical ionisation (APCI) ion source. No derivatisation of the analytes was required prior to HPLC/MS. Confirmation of residues was achieved using ion trap MS/MS.

Recoveries in water ranged from 79 per cent (doramectin) to 103 per cent (eprinomectin), with limits of detection of 0.87, 0.21, 3.97 and 0.68 ng l^{-1} for doramectin, ivermectin, eprinomectin and moxidectin respectively.

Recoveries of ivermectin and doramectin in soil were 80 and 91 per cent respectively, with limits of detection of 3.9 $\mu g\ kg^{-1}$ for doramectin and 4.8 $\mu g\ kg^{-1}$ for ivermectin.

Recoveries in sediment were 75 per cent for doramectin and 87 per cent for ivermectin respectively, with limits of detection of 0.84 $\mu g\ kg^{-1}$ for doramectin and 0.2 $\mu g\ kg^{-1}$ for ivermectin.

Enrofloxacin

Enrofloxacin was extracted from soils using an ASE system using acidified methanol as the extraction solvent. Extracts were evaporated to low volume prior to clean-up on a SPE column. Clean-up proved essential for good ion ratio confirmation.

Analysis of extracts was carried out using a HPLC/MS system with an APCI ion source. Confirmation of residues was achieved using ion trap MS/MS. Recoveries from spiked soil were 86–91 per cent, with a limit of detection of 0.97 $\mu g\ kg^{-1}$. Concentrations of ciprofloxacin (a major metabolite of enrofloxacin) were also determined.

Lincomycin

Lincomycin was extracted from river water using SPE.

Lincomycin was extracted from soils and sediments using an ASE system using 70 per cent acetonitrile/30 per cent water as the extraction solvent. Extracts were evaporated to low volume prior to clean-up on an SPE column. Clean-up proved essential for good ion ratio confirmation.

Analysis of extracts was carried out using a HPLC/MS system equipped with an electrospray ionisation (ESI) source. Confirmation of residues was achieved using ion trap MS/MS.

Recoveries in water ranged from 75 to 79 per cent with a limit of detection of 27.5 ng l^{-1}.

Recoveries in soil ranged from 60 to 80 per cent with a limit of detection of 1.26 μg kg^{-1}.

Recoveries in sediment ranged from 58 to 74 per cent with a limit of detection of 1.48 μg kg^{-1}.

Oxytetracycline, trimethoprim, sulfadiazine

Spike recovery tests were performed alongside each set of samples using pretreatment stream water. Recoveries for oxytetracyline, sulfadiazine and trimethoprim were 17–85 per cent, 9–16 per cent and 56–69 per cent respectively.

The National Laboratory Service performed a review of the performance testing and results arising from the analytical methods for oxytetracycline, trimethoprim and sulfadiazine. The review concluded that:

- concentrations of oxytetracycline in water samples were significantly above the limit of detection (LOD) and spiking studies resulted in an acceptable recovery of 85 per cent. Measurements of oxytetracycline in water were therefore likely to provide a true reflection of actual values.

- concentrations of oxytetracycline in soil samples and sulfadiazine in water samples were significantly above the LOD. Spiking studies resulted in recoveries below 50 per cent but with low relative standard deviations. It was therefore recommended that a correction factor be applied to correct for recovery.

- concentrations of sulfadiazine in soil and sediment and trimethoprim in water, soil and sediment were close to the LOD. Spike recoveries for these samples were low. Results for trimethoprim and sulfadiazine in these matrices should therefore only be considered as indicative values.

As a result of the review, a correction factor was applied to measurements of oxytetracycline in soil and sulfadiazine in water samples.

3.2.4 Soil characterisation

Soil properties were determined at each site in accordance with the United States Department of Agriculture (USDA) and UN Food and Agriculture Organization (FAO) guidelines.

A composite sample was taken from the top soil horizon and a sub-sample (500 g) was analysed for:

- percentage sand
- percentage silt
- percentage clay (six fractions)
- pH (in water and potassium chloride)
- organically bound carbon
- cation exchange capacity (CEC).

Properties are given in Appendix 13.

3.3 Results

3.3.1 Indoor pigs

There was a total of 123 mm of rainfall during the study period (9 March to 7 May 2004) (Figure 3.1), compared with average rainfall data for the Nottingham area for March and April of 92 mm (45.3 mm in March, 46.6 mm in April). The monitored field drain was flowing throughout the logging period.

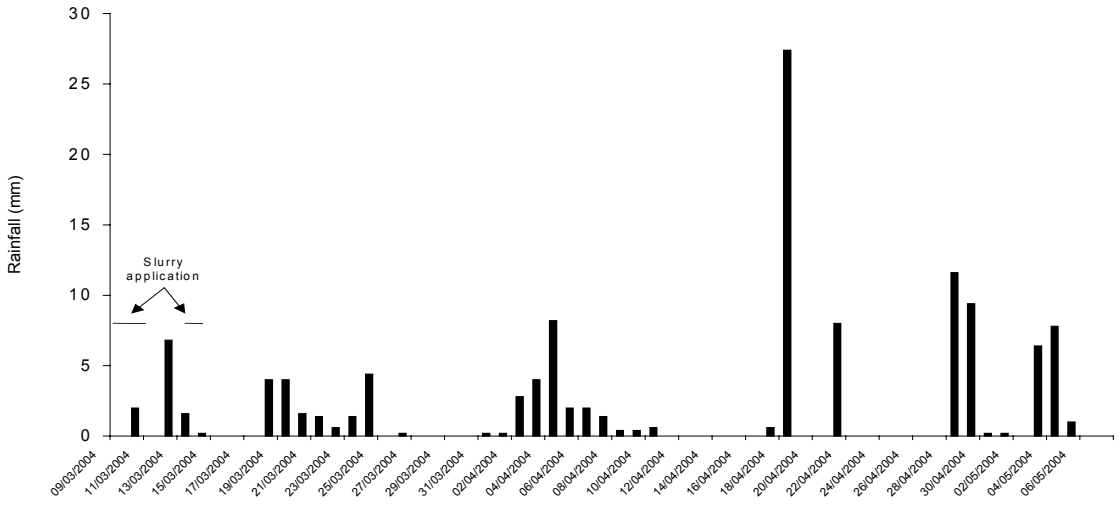
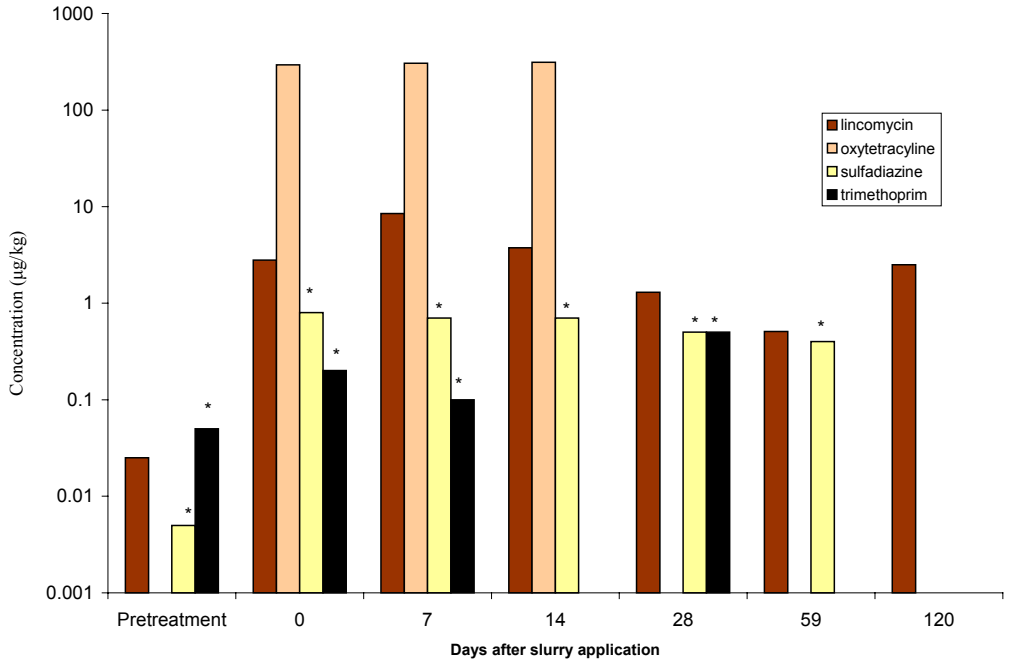


Figure 3.1 Measured daily rainfall at the indoor pig monitoring site

Soil

Before the slurry was applied, concentrations of lincomycin, oxytetracyline, trimethoprim and sulfadiazine in soil were at or below LODs (Figure 3.2). The highest concentrations of lincomycin, oxytetracycline and sulfadiazine were then observed in samples taken within two weeks of slurry application. Concentrations of these had

declined in samples taken one and two months after treatment. Highest concentrations for trimethoprim were observed in a sample taken 28 days after treatment. Highest concentrations were observed for oxytetracycline followed by lincomycin, sulfadiazine and trimethoprim (Figure 3.2, Table 3.3).



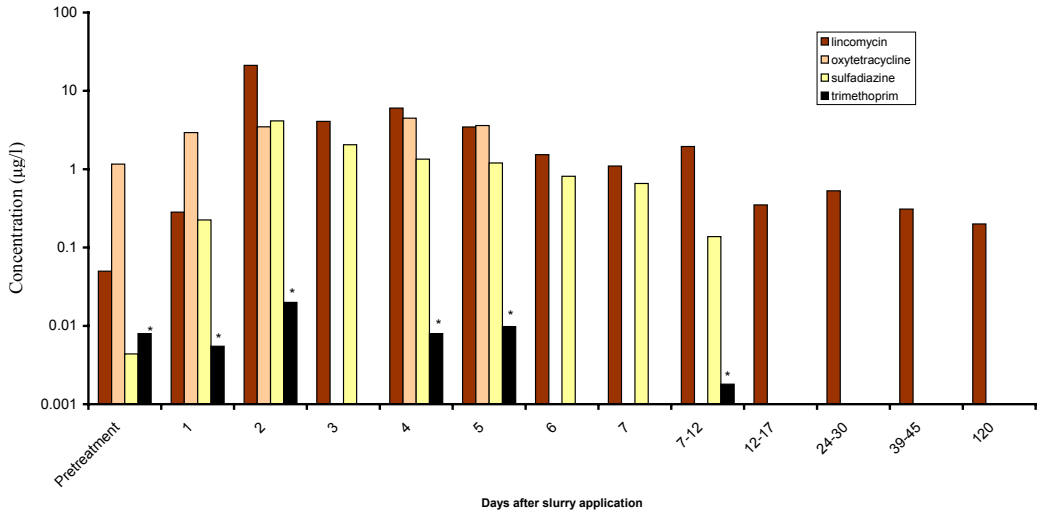
* Measurements are considered as indicative.

Figure 3.2 Concentrations of the study medicines in soil samples taken from a field treated with slurry from the intensively reared pigs

Water

Samples of stream water obtained during the first week following treatment of the field site with slurry were analysed individually. Subsequent samples were consolidated. In addition, a pretreatment sample was obtained immediately prior to slurry application.

Lincomycin, oxytetracycline and sulfadiazine were detected in pretreatment water, whereas the concentration of trimethoprim was close to the LOD (Figure 3.3). Following slurry application, concentrations of lincomycin, oxytetracycline and sulfadiazine increased, with the highest concentrations being observed in samples taken within seven days of treatment. After this time, concentrations in stream water declined. Concentrations of oxytetracycline and sulfadiazine were undetectable by the end of the study. Lincomycin concentrations remained relatively constant throughout the monitoring period. The rank order of maximum concentrations was lincomycin > oxytetracycline > sulfadiazine > trimethoprim (Table 3.3).

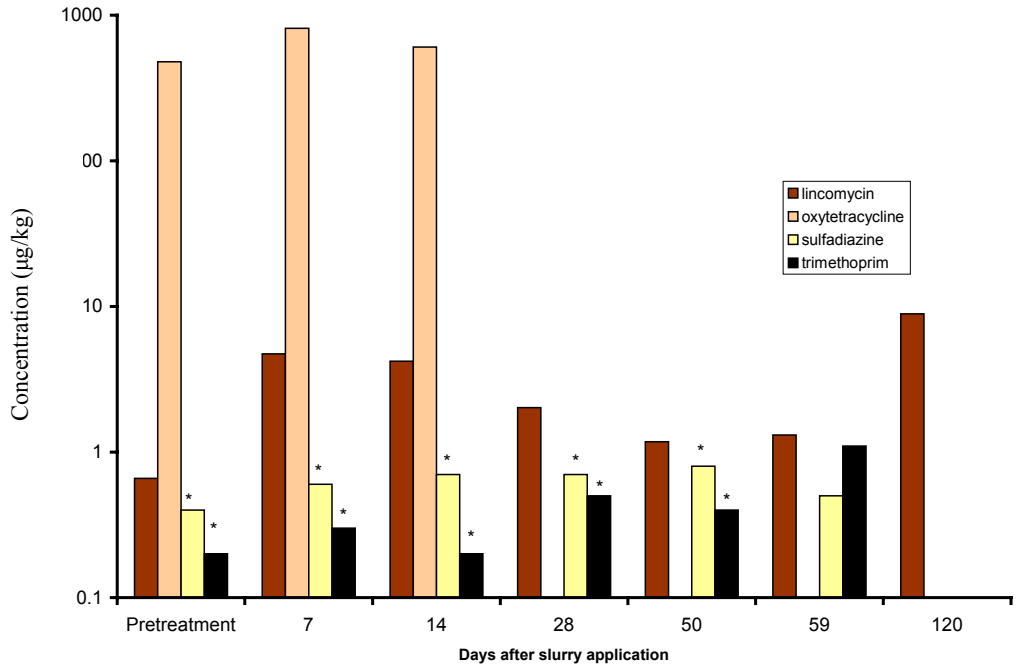


* Measurements are considered as indicative.

Figure 3.3 Concentrations of lincomycin, oxytetracycline, sulfadiazine and trimethoprim in stream water during the study period

Sediment

All the study compounds were detected in stream sediment prior to slurry application (Figure 3.4). Following slurry application, concentrations in sediment increased. Concentrations of lincomycin and oxytetracyline then declined over time, whereas those of sulfadiazine and trimethoprim remained relatively constant. The rank order of maximum concentrations was oxytetracycline > lincomycin > trimethoprim > sulfadiazine (Table 3.3).



* Measurements are considered as indicative.

Figure 3.4 Concentrations of the study medicines in sediment samples taken from a stream adjacent to a field treated with pig slurry

Table 3.3 Maximum measured concentrations of study compounds in soil, stream water and sediment

	Soil (μg kg^{-1})	Water (μg l^{-1})	Sediment (μg kg^{-1})
lincomycin	8.5	21.1	8.9
oxytetracycline	305	4.49	813
sulfadiazine	0.8*	4.13	0.8*
trimethoprim	0.5*	0.02*	1.1*

* Should be considered as indicative of actual concentrations.

3.3.2 Outdoor pigs

For the outdoor pig scenario, samples of soil (from the top 10 cm layer) were taken along a transect across the paddocks to assess the concentrations of veterinary medicines arising from excretion by animals. A second set of soil samples was obtained from areas immediately surrounding and underneath the feed stations to assess losses from spilt feed. In addition, grab samples of stream water were taken from a small stream that ran adjacent to the site. These samples were analysed for ivermectin.

Concentrations in control soil were around detection limits. High concentrations of ivermectin were observed in the samples taken from within the feed station (Figure 3.5), the highest concentration being observed one day after cessation of treatment (1,985 μg kg^{-1}). Concentrations then declined throughout the remainder of the study and were at 237 μg kg^{-1} on the last monitoring occasion. Concentrations outside the feeding station ranged from 5.9 to 46 μg kg^{-1}, and highest concentrations were observed 60 days after treatment had stopped. Ivermectin was not detected in any of the stream water samples (LOD 0.0002 μg l^{-1}).

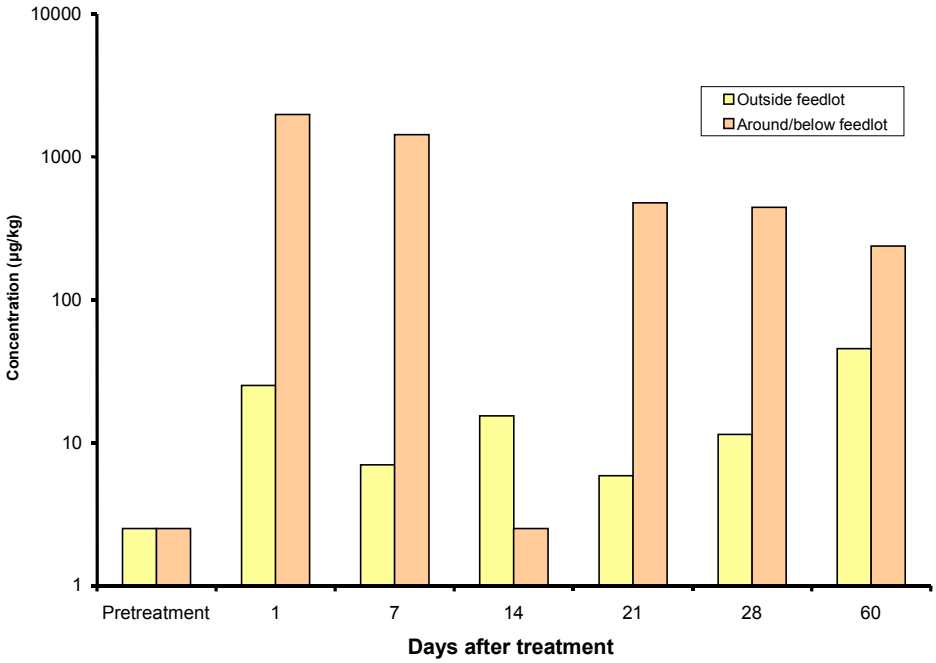


Figure 3.5 Concentrations of ivermectin in soil samples obtained from outside the feeding stations and around/below the feeding stations at the outdoor pig farm

3.3.3 Cattle at pasture

Doramectin

Faeces

Samples of faecal material, stream water and sediment were taken from the outdoor cattle site. The cattle were found to drink from the stream at two access points. Observations made during site visits indicated that they had a preference for the downstream site. Cattle were observed standing in the stream and its margins on several site visits, particularly during warm weather. Poaching and damage to the area leading down to the stream were evident and there was a lot of faecal material present in and around the stream.

Faecal material was collected weekly. The highest concentration (112 µg kg^{-1}) was observed in a sample obtained seven days after the first treatment (Figure 3.6). Concentrations then declined and were at 11 µg kg^{-1} 35 days after treatment. A similar pattern was observed for the second treatment. The maximum concentration (56 µg kg^{-1}) was observed seven days after treatment; this then declined throughout the monitoring period to 2.5 µg kg^{-1} 43 days after treatment.

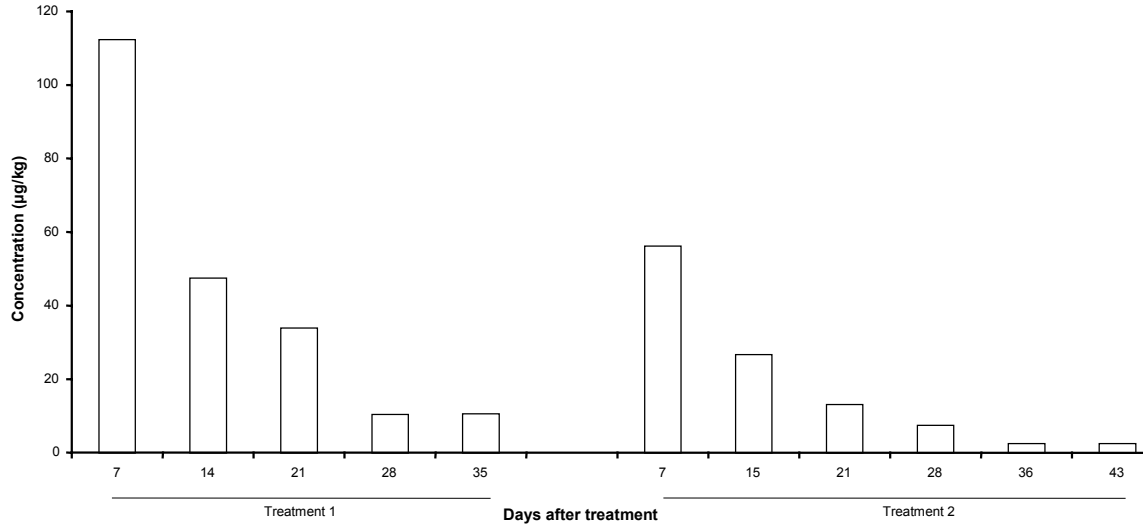


Figure 3.6 Concentrations of doramectin in faecal material collected from the outdoor cattle farm

Water

Water samples were obtained from the stream over time. Concentrations of doramectin in these samples were all below the LOD (0.001 µg l^{-1}).

Concentrations in sediment obtained prior to and within four weeks of the first cattle treatment were all below the LOD (0.84 mg kg^{-1}) (Figure 3.7). Doramectin was then detected in samples taken 35 days after treatment 1 and samples taken immediately before the second doramectin treatment. Subsequently, doramectin was detected in all samples taken within four weeks of the second treatment. Doramectin concentrations were below the limit of quantification thereafter.

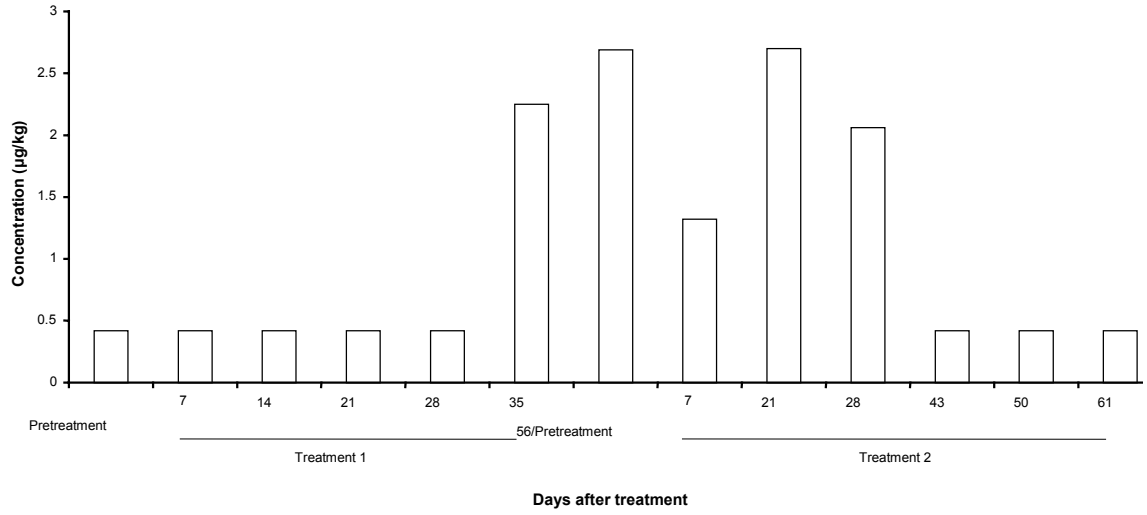


Figure 3.7 Concentrations of doramectin in stream sediment

Ivermectin

Cattle treated with ivermectin were kept on an area of pasture bisected by a small brook that was the sole source of drinking water. During site visits, cattle were observed either standing in (drinking or defecating) or crossing the brook. The area

around the brook was steep and covered in faecal material. There was visual evidence of transport of faecal material from the slope to the brook through walking in and runoff.

Maximum concentrations of ivermectin in faecal material were observed in samples obtained 4 and 7 days after treatment (Figure 3.8). Concentrations in subsequent samples were more than an order of magnitude lower and were below the LOD (0.005 mg kg^{-1}) four weeks after treatment.

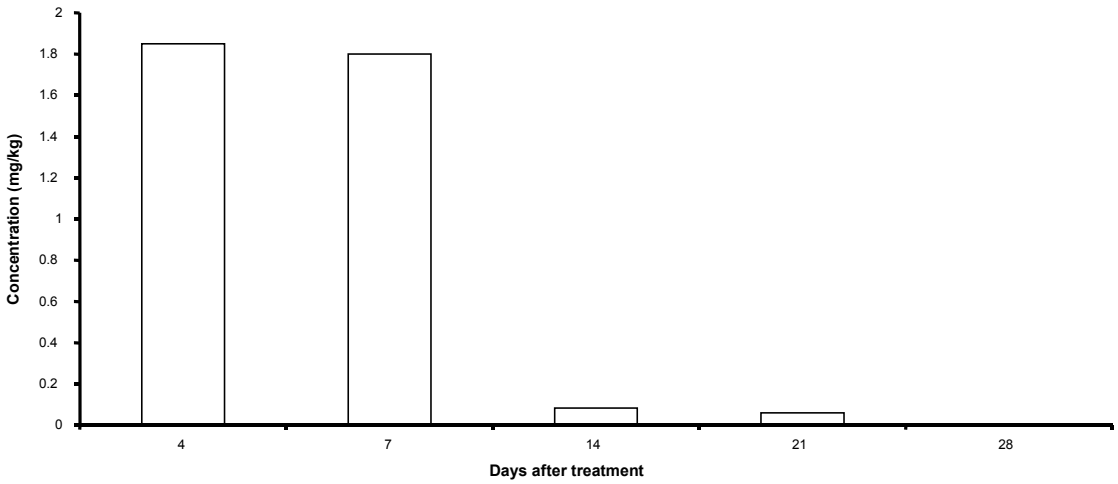


Figure 3.8 Concentrations of ivermectin in faecal material obtained from the outdoor cattle site

Concentrations of ivermectin in water samples taken from the brook over time were all lower than the LOD (0.0002 μg l^{-1}). Before the first treatment, ivermectin was detected in sediment at a level of 0.78 μg kg^{-1}. Concentrations in sediment samples taken following treatment ranged from 0.82 to 4.9 μg kg^{-1} (Figure 3.9). There was no relationship between the concentration in sediment and time after treatment.

The maximum concentration (1.5 μg kg^{-1}) following the second treatment was observed in a sediment sample obtained four days after treatment. Concentrations in sediment then declined to below the LOD (0.2 μg kg^{-1}) 14 days after treatment.

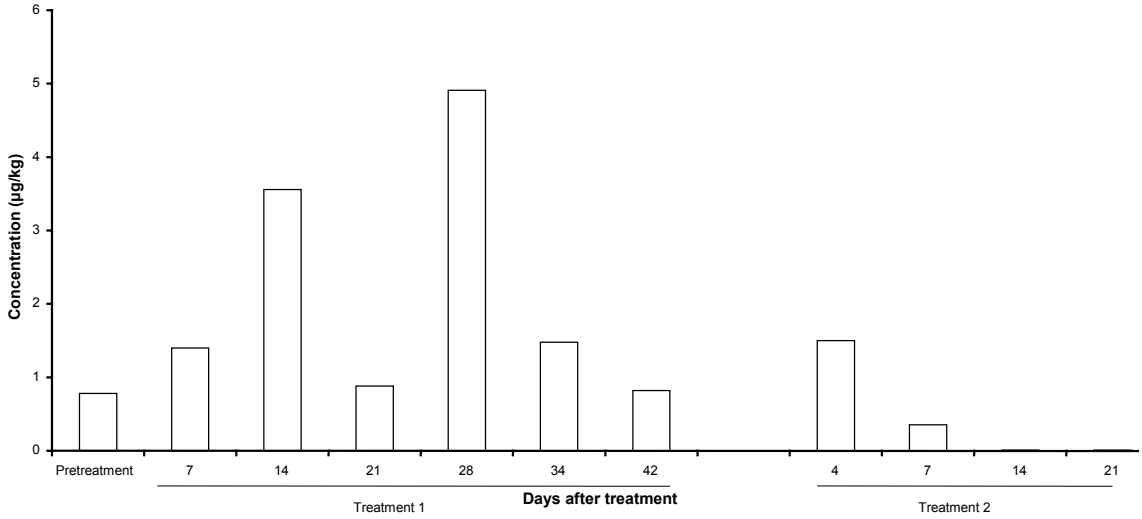


Figure 3.9 Concentrations of ivermectin in sediment obtained from the outdoor cattle site

3.3.4 Poultry

Litter from the turkey unit was analysed for enrofloxacin and its major metabolite ciprofloxacin. Samples were also taken from a field treated with the litter over a three month period.

Both enrofloxacin and ciprofloxacin were detected in the turkey litter at concentrations of 2.92 and 0.28 $\mu g\ kg^{-1}$ respectively. Enrofloxacin and ciprofloxacin were not detected in any of the soil samples (LOD 1 $\mu g\ kg^{-1}$).

3.4 Summary of field results

Eighteen veterinary medicines were identified for inclusion in a monitoring programme using the risk-based ranking approach described in Section 2. Four study sites were selected that used one or more of the highest ranked compounds and treatment scenarios.

Using these four study sites, it was possible to investigate the exposure to seven veterinary medicines (doramectin, enrofloxacin, ivermectin, lincomycin, oxytetracycline, sulfadiazine and trimethoprim) from four different scenarios (indoor pigs, outdoor pigs, cattle at pasture and poultry).

The ranking process also considered a number of environmental scenarios that would be expected to promote the transport of veterinary medicines to surface water bodies. Aquatic exposure assessments for compounds applied to land in slurry or manure were based on a heavy underdrained soil scenario, whereas assessments for pasture animals focused on the situation where a small stream is present in a pasture field. Both study sites where surface waters were monitored were similar to the associated model scenario. Slurry from the indoor pig site was applied to a large

field of heavy soil that drained via mole drains to a small stream. Outdoor cattle were kept on fields where small bodies of water were present.

At each study site, the monitoring was targeted to detect the highest exposure concentrations arising from the treatment. Hence, stream water was monitored continuously at the indoor pig and outdoor cattle study sites, and samples of soil and sediment were taken on a number of occasions following either application of slurry or litter or the cessation of treatment.

The maximum concentrations measured for each determinand across the different sites are summarised in Table 3.3. These are likely to provide an indication of 'worst' case maximum concentrations for the scenarios studied.

Table 3.3 Maximum measured environmental concentrations of study veterinary medicines

	Faeces/litter ($\mu g\ kg^{-1}$)	Soil ($\mu g\ kg^{-1}$)	Water ($\mu g\ l^{-1}$)	Sediment ($\mu g\ kg^{-1}$)
ciprofloxacin	0.28	nd	-	-
doramectin	112	-	nd	2.69
enrofloxacin	2.92	nd	-	-
ivermectin (pigs)	-	46 (1,985^)	nd	-
ivermectin (cattle)	1,850	-	nd	4.91
lincomycin	-	8.5	21.1	8.9
oxytetracycline	-	305	4.49	813
sulfadiazine	-	0.8*	4.13	0.8*
trimethoprim	-	0.5*	0.02*	0.5*

* Indicative values only.
$ The treatment dose and duration at study site were significantly higher than recommended, so concentrations under typical treatment regimes are likely to be more than an order of magnitude lower.
^ Concentration around/below feeding stations.

4 Discussion

A previous Environment Agency study (Boxall *et al.* 2002) reviewed information on the usage, fate and ecotoxicity of veterinary medicines in use in the UK. Using this information, compounds were prioritised in terms of their potential to enter the environment and cause harm in order to identify compounds of potential concern. A total of 55 compounds were assigned to a 'high risk' category but sufficient data were only available to fully characterise the potential risk of 11 compounds. This prioritisation approach was designed as a simple screening tool and did not provide any information on which environmental compartments were at most risk from a particular compound and on the level of risk associated with it.

This study was therefore performed to:

- refine the prioritisation results using newly available data;
- rank compounds in terms of their relative environmental risks using 'worst case' estimates of environmental exposure and available ecotoxicological data;
- perform targeted monitoring for compounds with a 'high risk' ranking to establish whether veterinary medicines are present in the environment at ecologically significant concentrations.

Following advice from the Veterinary Medicines Directorate and veterinary medicine manufacturers, a number of compounds were removed from the initial priority list (some no longer held a marketing authorisation and some were used very rarely or only in small quantities). Conversely, a number of compounds were added to the list, either because they were considered highly toxic to aquatic or terrestrial organisms (e.g. the macrocyclic lactone endectocides) or they had recently been granted marketing authorisations (bronopol, dicyclanil) and were expected to be used in significant amounts. Following a review of the priority list, 34 compounds were selected for further assessment.

A pragmatic and scientific approach was developed and adopted to enable the identification of those compounds and scenarios that warranted further study by the Environment Agency. The scheme used a risk-based approach to identify those compounds with the highest potential relative to other veterinary medicines to impact the environment. It allowed the identification of those treatment scenarios for each compound that pose the highest relative risk to the environment along with the environmental compartments most likely to be exposed.

A total of 18 priority compounds were identified as potential determinands for a targeted monitoring study. The risk-based ranking procedure allowed three compounds (triclabendazole, cyromazine and diclazuril) to be excluded from the monitoring programme. Due to insufficient data, it was not possible to rank a number of compounds given on the initial priority list, namely amprolium, chlorhexidine, clavulanic acid, decoquinate, dicyclanil, lasalocid, levamisole, morantel, nicarbazin, nitroxynil, poloxalene, procaine penicillin, and salinomycin. The relative risks of these to the environment, compared with the compounds for which full datasets were

available, are unknown. It is therefore recommended that attempts should be made to obtain data for these compounds in the future.

The ranking scheme used assumptions that are likely to overestimate true environmental concentrations. In addition, the risk characterisation ratios used are, in general, unlikely to reflect actual risks in the environment. Some of the reasons for this are given below.

- The treatment scenarios used represent 'worst case' treatments. For many compounds, these scenarios may only apply to a small proportion of animals each year.

- The assessments considered group treatments. For some compounds, it is likely that, at the whole farm scale, the concentrations in the different environmental compartments (soil, surface water, groundwater, etc.) will be diluted by the presence of untreated animals in a herd.

- Apart from a few compounds, metabolism was not considered in the assessments.

- Surface water simulations assume that a substance is released to a static ditch. Removal by flowing waters or partitioning to sediment material was not considered. In the 'real' environment, medicines applied in slurry will enter surface water in short-lived pulses (Kay *et al.* 2004), which are likely to dissipate rapidly.

- Groundwater simulations were based on vulnerable soil types. They assumed a groundwater depth of 1 m and used maximum predicted concentrations of veterinary medicines. In the 'real' environment, these concentrations are likely to be significantly diluted.

- Aquaculture simulations were based on a simplified scenario, which was likely to overestimate receiving water concentrations for compounds strongly sorbing to soil (e.g. oxytetracycline). In all cases, substances would likely exist in surface waters for less than 24 hours (in many cases, considerably shorter).

The calculated RCRs therefore probably overestimate risk and are not intended to be used for risk assessment purposes. They are, however, appropriate for ranking purposes as required in this study.

The results of the ranking procedure were used to design a targeted risk-based monitoring programme. Four study sites were selected, which used one or more of the highest ranked compounds. Using the four study sites, it was possible to investigate:

- exposure to seven veterinary medicines (doramectin, enrofloxacin, ivermectin, lincomycin, oxytetracycline, sulfadiazine and trimethoprim);
- four scenarios (indoor pigs, outdoor pigs, cattle at pasture and poultry).

In order to draw conclusions on the potential environmental impacts of veterinary medicines in use in the UK, the treatment scenarios at the study sites needed to correspond to the realistic 'worst' case scenarios used in the risk ranking. With the exception of ivermectin in outdoor pigs, treatment scenarios used at each of the sites were similar to scenarios used in the modelling component of the project. At the pig farm, animals were treated with ivermectin at a higher dose and for a longer period than recommended, receiving more than 10 times the recommended amount of ivermectin. Therefore, measured concentrations for ivermectin in soil at this site are likely to be significantly higher than would be expected under recommended treatment regimes.

The characteristics (e.g. type of water body, animal density and manure application) of the study sites were selected to provide a high potential for environmental exposure to the veterinary medicines (Table 4.1).

The monitoring study was performed over an 11-month period during 2004.

- With the exception of enrofloxacin and its metabolite ciprofloxacin, all the study compounds were detected in one or more environmental compartment.

- Concentrations of antibacterials in soil ranged from 0.5 $\mu g\ kg^{-1}$ (trimethoprim) to 305 (oxytetracycline) $\mu g\ kg^{-1}$.

- Maximum measured concentrations for ivermectin in soil were 1,985 $\mu g\ kg^{-1}$ around the feeding stations and 46 $\mu g\ kg^{-1}$ elsewhere in the field. The amount of ivermectin given to the pigs was more than an order of magnitude higher than recommended, so concentrations of ivermectin arising from recommended treatment regimes are likely to be significantly lower.

- Maximum concentrations of antibacterials in water ranged from 0.02 $\mu g\ l^{-1}$ (trimethoprim) to 21.1 (lincomycin) $\mu g\ l^{-1}$. The parasiticides (doramectin and ivermectin) were not detected.

- Concentrations of antibacterials in sediment ranged from 0.5 to 813 $\mu g\ kg^{-1}$ and the concentrations of doramectin and ivermectin were 2.7 and 4.9 $\mu g\ kg^{-1}$ respectively.

At the indoor pig farm, concentrations of the study compounds in soil prior to application of the slurry were around analytical limits of detection. At this point, however, oxytetracycline and sulfadiazine were detected in stream water and all the study compounds were detected in stream sediment. Discussions with the farm owner revealed that a field drain that discharges into the stream passes under the pig unit. The detections may therefore be explained by the leakage of slurry from the unit into the underlying field drain.

Following application of the slurry to the field, all the study compounds were detected in soils. The relative ranking of the compounds based on maximum concentrations was oxytetracycline > lincomycin > sulfadiazine > trimethoprim.

Table 4.1 Comparison of modelled treatment scenarios with actual treatments used on the monitored farms

	Modelled treatment scenario				Monitored treatment scenario			
	Dose (mg kg^{-1})	Duration (days)	Frequency	Total (mg)	Dose (mg kg^{-1})	Duration (days)	Frequency	Total (mg)
doramectin	0.2	1	3	0.6	0.5	1	2	1.0
enrofloxacin	10	10	1	100	10	14	1	140
ivermectin (pigs)	0.1	7	1	0.7	0.75	14	1	10.5
ivermectin (cattle)	0.5	1	3	1.5	0.5	1	2	1.0
lincomycin	22	21	1	462	2.2	35	1	77
oxytetracycline	20	15	1	300	18	35	1	630
sulfadiazine	25	3	1	75	5.7	35	1	200
trimethoprim	8	5	1	40	1.15	35	1	40

Concentrations of oxytetracycline were more than an order of magnitude greater than lincomycin and more than two orders of magnitude greater than sulfadiazine and trimethoprim. These differences in concentration cannot be explained by the differences in the animal treatment regimes and suggest that some of the study compounds are degraded during slurry storage.

Rainfall occurred soon after application of slurry to the field and measurements of concentrations in stream water samples indicated that all the compounds were transported from the soil to the adjacent stream in runoff. The highest concentrations were observed during the first week following slurry application. The rank order in terms of maximum concentrations was lincomycin > oxytetracycline > sulfadiazine > trimethoprim. After one week, concentrations of most of the study compounds declined and oxytetracycline, sulfadiazine and trimethoprim were undetectable in samples taken from 12 days after slurry application. A similar pattern was obtained in a recent field monitoring study where manure spiked with tetracyclines, sulfonamides and macrolides was applied to a tile drained field (Kay *et al*. 2004). A limited amount of published data is available on concentrations of tetracyclines, macrolides, sulfonamides and trimethoprim in surface waters in the US (Kolpin *et al*. 2002); maximum concentrations of macrolides and tetracyclines in these studies were significantly lower than in the present study.

The inputs of ivermectin and doramectin to surface waters were investigated at a farm where cattle are kept on pasture. A small water body was present on the two areas of grassland used for the study. For both compounds, monitoring was performed over two treatment cycles. Analysis of faecal material indicated that doramectin, applied as a pour on, was excreted to the pasture over a five-week period, with the highest faecal concentrations observed in samples taken in the first week following treatment. Ivermectin was excreted more quickly. These observations agree with previous studies into the excretion of ivermectin and doramectin (Sommer and Steffansen 1993, Pfizer 1996, Steel and Hennessey 2001). Neither of the compounds was detected in any of the surface water samples obtained. This probably reflects the high sorptive potential of both compounds (Koc values for ivermectin: 12,600–15,700; doramectin: 7,520–86,900), which means that any material entering streams will be particle-associated and that it will be transported to the stream sediment. Analysis of sediment samples supports this conclusion; both doramectin and ivermectin were detected in sediment at maximum concentrations of 2.69 and 4.91 $\mu g\ kg^{-1}$ respectively. The lack of any pattern in the analytical results for the sediment indicated that there might be significant variation in concentrations of both compounds in sediment across a small area.

Concentrations of ivermectin were also measured at a site where pigs were kept outdoors. Ivermectin was detected in all soil samples. Samples were taken from around and below the feeding stations as well as from outside the feeding stations. Highest concentrations were observed around the feeding stations in areas where there was evidence that feed had been spilt. Concentrations outside the feeding stations were generally much lower. As with the sediment data described above, there appeared to be considerable spatial variability in ivermectin concentrations. However, the data do indicate that the substance may persist in soil with an appreciable amount being observed both within and outside the feeding stations 60 days after treatment. As the amount of ivermectin given to the pigs was more than an

order of magnitude higher than recommended, concentrations arising from recommended treatment regimes are likely to be significantly lower. This is supported by previous studies where measured concentrations were significantly higher than those reported in previous monitoring studies (e.g. Nessel *et al.* 1989).

Inputs of enrofloxacin to soils were investigated at a large turkey unit where litter was spread on a nearby field; concentrations of enrofloxacin in the soil over time were measured. Although enrofloxacin was detected in the litter, it was not detected in any soil sample taken between 21 and 90 days after litter application. This suggested that the compound had degraded either during storage of the litter prior to application or following application to the soil. Concentrations of ciprofloxacin, a metabolite of enrofloxacin, were also measured. This substance was also detected in litter but not in any of the soil samples.

In order to put the monitoring data into some context, the maximum measured environmental concentrations (MECs) for each of the compounds studied in the monitoring study were compared with PNECs (Tables 4.2 and 4.3).

Comparison of MECs for surface waters with available data on environmental effects indicated that concentrations of the antibacterial compounds studied (oxytetracycline, sulfadiazine, trimethoprim and lincomycin) were at least an order of magnitude lower than their PNECs. It is therefore recommended that these compounds are not treated as a high priority for further study. Concentrations of the parasiticides in all water samples were below LODs. As the LODs were either the same as or lower than PNECs, these compounds are also unlikely to be a major concern in the water compartment.

Maximum MECs of oxytetracycline, sulfadiazine, trimethoprim, ivermectin and enrofloxacin in soils were also significantly lower than PNECs. These compounds should also not be treated as a priority in the future. In contrast, the maximum concentrations of lincomycin found in soil were higher than its PNEC. Although impacts from lincomycin cannot be ruled out, the endpoint used in deriving its PNEC was a no-observed effect concentration (NOEC) to which a conservative uncertainty factor of 100 was applied.

For the majority of compounds, no data were available on the toxicity to sediment-dwelling organisms. However, following release to surface waters, many of the compounds are likely to partition to sediment and hence may have the potential to affect benthic organisms. For pesticides, it has been proposed that compounds with a sorption coefficient (Koc) exceeding 1,000 could pose a risk to sediment dwellers and thus should be considered experimentally (Maund *et al.* 1997). Fifteen of the compounds assessed that would be expected to enter surface waters (i.e. amoxicillin, apramycin, doramectin, eprinomectin, fenbendazole, ivermectin, lasalocid, levamisole, morantel, moxidectin, oxytetracycline, procaine penicillin, tilmicosin, trimethoprim and tylosin) have Koc values greater than this trigger value. Sediment samples were therefore taken and analysed during the monitoring phase of the study.

All the compounds monitored for in sediment during this project (i.e. doramectin, ivermectin, lincomycin, oxytetracycline, sulfadiazine and trimethoprim) were detected.

However, due the absence of relevant ecotoxicological data, it was not possible to assess the significance of these measurements.

The only available data were for the effects of ivermectin on marine sediment dwellers. Effects of ivermectin on feeding of *Asterias rubens* have been reported at <5 $\mu g\ kg^{-1}$ (Thain *et al*. 1997). Because this value is similar to the maximum concentration of ivermectin measured in stream sediment in this study, impacts of ivermectin on sediment-dwelling invertebrates cannot be ruled out. Doramectin has a similar mode of toxic action and was observed at similar concentrations to ivermectin; this may also warrant further consideration.

While this study has identified some areas for concern, the overall results indicate that the concentrations of veterinary medicines measured are significantly lower than those that might cause environmental effects. It is probable that concentrations across the broader UK agricultural landscape will be lower still because:

- the monitoring study focused on sites with characteristics that would enhance environmental contamination (e.g. pasture land with small water bodies present, heavy underdrained soils);
- the monitoring regime focused on occasions when the compounds were likely to be released to the environment.

However, the study highlighted a number of areas where future work is warranted. These include:

- a more detailed assessment of the potential impacts of veterinary medicines on soil;
- an assessment of the potential fate and impacts of parasiticides in sediment;
- consideration of those compounds, which despite being identified as high priority, could not be assessed in the current study due to insufficient data;
- consideration of those compounds (11) where there were sufficient data to undertake ranking and where ranking placed them in the top 18, but for which monitoring was not pursued;
- monitoring studies to assess the potential to contaminate groundwater. A number of compounds were identified as being of potential concern to this environmental compartment.

There are also a number of broader issues that could not be addressed in this study, but which warrant further consideration.

- A number of workers are investigating the use of more subtle endpoints such as impacts on behaviour, physiology and biochemistry. Although highly conservative uncertainty factors were used in this study, it may be beneficial for the Environment Agency to review regularly the results arising from such studies.

- The current work focused on parent veterinary medicines, yet many compounds are metabolised in the treated animal or degraded to other substances in the environment. The potential impacts of these degradation products (and degradation products from other chemical classes) should be assessed.

- This study has shown that soil and aquatic systems can contain a mixture of veterinary medicines. When considering potential impacts, compounds are generally assessed on an individual basis. However, it would be beneficial to begin to develop an understanding of the potential interactions of veterinary medicines and other substances that might be present in the environment.

Table 4.2 Comparison of maximum measured concentrations in surface waters with PNECs

Compound	Most sensitive endpoint	EC50 (mg l^{-1})	Calculated PNEC (µg l^{-1})	Maximum measured concentration (µg l^{-1})	MEC:PNEC
oxytetracycline	*S. capricornutum* 72 h EC50	4.5	45	4.49	0.10
sulfadiazine	*S. capricornutum* 72 h EC50	3.49	34.9	4.13	0.12
trimethoprim	*S. capricornutum* 72 h EC50	16	16	0.02*	0.001*
ivermectin	*Daphnia magna* 48 h EC50	0.000025	0.00025	<0.0002	<0.8
doramectin	*Daphnia magna* 48 h EC50	0.0001	0.001	<0.001	<1
lincomycin	*Daphnia magna* 48 h EC50	379.4	379	21.1	0.056

Table 4.3 Comparison of maximum measured concentrations in soils with PNECs

Substance	Most sensitive endpoint	Effect concentration (mg kg^{-1})	PNEC (µg kg^{-1})	Maximum measured concentration (µg kg^{-1})	MEC:PNEC
oxytetracycline	*Phaseolus vulgaris* LC50	<160	<1600	305	<0.19
sulfadiazine	plant NOEC (red clover)	0.884	8.84	0.8*	0.090*
trimethoprim	red clover NOEC emergence	38.7	387	0.5*	0.001*
ivermectin	plant NOEC	0.56	56	45.5	0.81
lincomycin	microbes MIC/NOEC	0.78	7.8	8.49	1.088
enrofloxacin	wheat NOEC growth	<0.13	1.3	< 1	<0.76
ciprofloxacin				< 1	

* Measured concentrations were considered as indicative only (see section 3.2.3)

5 Conclusions

A pragmatic and scientifically sound risk-based ranking approach has been developed and applied to those veterinary medicines identified as high priority by a previous Environment Agency project.

Using the ranking scheme, 18 compounds were identified as worthy of monitoring in the environment. The procedure identified those treatment scenarios that are most likely to cause harm and the environmental compartments that should be monitored. Based on the results of the ranking work, a monitoring study was performed to determine concentrations in the UK environment of seven of the 18 compounds.

With a few exceptions, maximum measured environmental concentrations were lower than predicted no effect concentrations (PNECs). For many of the determinands, average concentrations across the broader UK agricultural landscape are likely to be lower still as the monitoring programme:

- considered the highest ranked compounds and scenarios;
- selected sites with characteristics that would enhance environmental contamination;
- focused on occasions when the compounds were likely to be released to the environment.

The results thus indicate that, in general, concentrations of these veterinary medicines in the UK environment are likely to be below those that could affect aquatic and terrestrial organisms.

However, the study identified some areas where future work is warranted. These include:

- a more detailed assessment of the potential impacts of veterinary medicines on soil;
- investigations into the fate and effects of parasiticides in sediment;
- assessment of those compounds that could not be studied in this project due to insufficient data, concentrating on issues arising from the environmental risk assessments submitted to gain marketing authorisation;
- further assessment of the potential impacts of the other 11 (of the 18) selected veterinary medicines on the environment;
- monitoring of groundwater.

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List of acronyms and abbreviations

APCI	atmospheric pressure chemical ionisation
ASE	accelerated solvent extraction
CEC	cation exchange capacity
CVMP	Committee for Veterinary Medicinal Products
DT50	Time taken to degrade to 50 per cent of original concentration of the compound
EC50	Concentration effective against 50 per cent of the organisms or animals tested
ESI	electrospray ionisation
FAO	Food and Agriculture Organization (of the United Nations)
FDA	Food and Drink Administration (in USA)
HPLC	high performance liquid chromatography
LC50	Concentration lethal to 50 per cent of the organisms or animals tested
LOD	limit of detection
MEC	measured environmental concentration
MIC	minimum inhibitory concentration
MS	mass spectrometry
nd	data not available
NLS	National Laboratory Service (of the Environment Agency)
NOAH	National Office of Animal Health
NOEC	no observable effect concentration
NOEL	no observed effect level
PEC	predicted environmental concentration
PNEC	predicted no-effect concentration
RCR	risk characterisation ratio
SPE	solid phase extraction
TLM	median tolerance limit
TWA	time weighted average
USDA	United States Department of Agriculture
VMD	Veterinary Medicines Directorate

Appendix 1 Prediction of environmental concentrations

Data on usage, sorption in soils and persistence in manure were used together with exposure assessment models to predict the concentrations of each of the study compounds in soil, surface water and groundwater.

The lowest reported sorption coefficient was used to estimate movement to surface water and groundwater, and the longest reported DT50 (time taken to degrade to 50 per cent of original concentration of the compound) was used to assess persistence. In the absence of information on the persistence of a substance in a particular medium, a degradation half-life of 1,000 days was assumed.

A discussion of methods and models used and the predicted concentrations obtained is provided below.

Pasture animals

Veterinary medicines are used to treat a range of animal types kept on pasture. For medicines applied orally or by injection, the medicine may be released directly to soil or surface water in urine or faeces. Topical treatments may be washed off. In this study, veterinary medicines used in the treatment of cattle, pigs, horses and sheep at pasture were considered.

Concentrations of each of the priority compounds in soil, surface water and groundwater arising from the treatment of animals on pasture were obtained using a combination of exposure assessment approaches. These included:

- methods developed specifically for veterinary medicines (e.g. Montforts 1999);
- methods developed for pesticides (where methods developed for veterinary medicines were not available).

The models were run in Microsoft® Excel. The approaches used are described in more detail below.

Concentrations in soil

The amount of each study compound released to soil by pasture animals was calculated using Equation A1.

$$A_{excreted} = M \times N \times D \times T \times F_{excreted} \qquad \text{Equation A1}$$

where:

$A_{excreted}$ (mg ha^{-1}) is the amount excreted (mg/animal);
M is the mass of the animal (kg);

N is the stocking density of animals (animals ha^{-1});
D is the dosage (mg kg^{-1});
T is the duration of the treatment (days);
F is the fraction of the administered dose excreted as the parent substance.

Data on the mass of individual animals used in the calculations are given in Table A1.1.

Table A1.1 Animal data used as the inputs to the pasture model (Montforts 1999)

	Cattle	Horses	Sheep	Pigs
Mass of animal (kg)	600	600	70	70
Stocking density (animals ha^{-1})	9.5	3	15	25

To obtain a concentration in soil, it was assumed that the excreted veterinary medicine is spread uniformly across a field and that it is evenly distributed in the top 5 cm layer of the soil. A soil bulk density of 1,500 kg m^{-3} was used in the calculations. This clearly will not happen in the real world, where faeces are likely to be excreted in distinct patches. However, this simple approach was considered sufficient for the ranking purposes of this study.

Where a substance was administered over a number of days and/or where there were multiple applications during a year, the amount of substance remaining at the time of the final application for each individual treatment was calculated using Equation A2.

$$A_t = A_{excreted} \times e^{-kt} \qquad \text{Equation A2}$$

where:

At is the amount left at the time of the final application (mg);
k is the first order rate of degradation (d^{-1});
t is the time between the earlier and the final application.

By summing the amounts left for each individual treatment at the end of the treatment period, it was possible to estimate a total amount released to soils.

Following release to soils, the veterinary medicine may be degraded. Therefore, to account for potential degradation of the study compounds in soil, a time weighted average predicted environmental concentration in soil (TWA PEC_{soil}) was calculated using Equation A3. The TWA PEC_{soil} was calculated for a period of 21 days following release to land. This time span was selected because it corresponds to the duration of typical terrestrial ecotoxicology tests (e.g. earthworm studies last for 14 days and plant studies for 28 days).

$$\text{TWA PEC}_{soil} = \frac{\text{PEC}_{soil} \text{ x DT50}_{soil} \text{ x } (1 - e^{(-\ln 2/\text{DT50}_{soil}) \text{ x } 21})}{\ln 2 \text{ x } 21}$$ Equation A3

Prediction of concentrations in groundwater

The guidance on the environmental risk assessment of veterinary medicines (CVMP 1997) recommends that exposure models used for pesticides are used for estimating concentrations of veterinary medicines leaching to groundwaters. When determining the potential for pesticides to contaminate groundwaters, current regulatory practice is to simulate average concentrations of a pesticide leaching through soil to 1 m depth and to use this value as a protective surrogate for concentrations in groundwater.

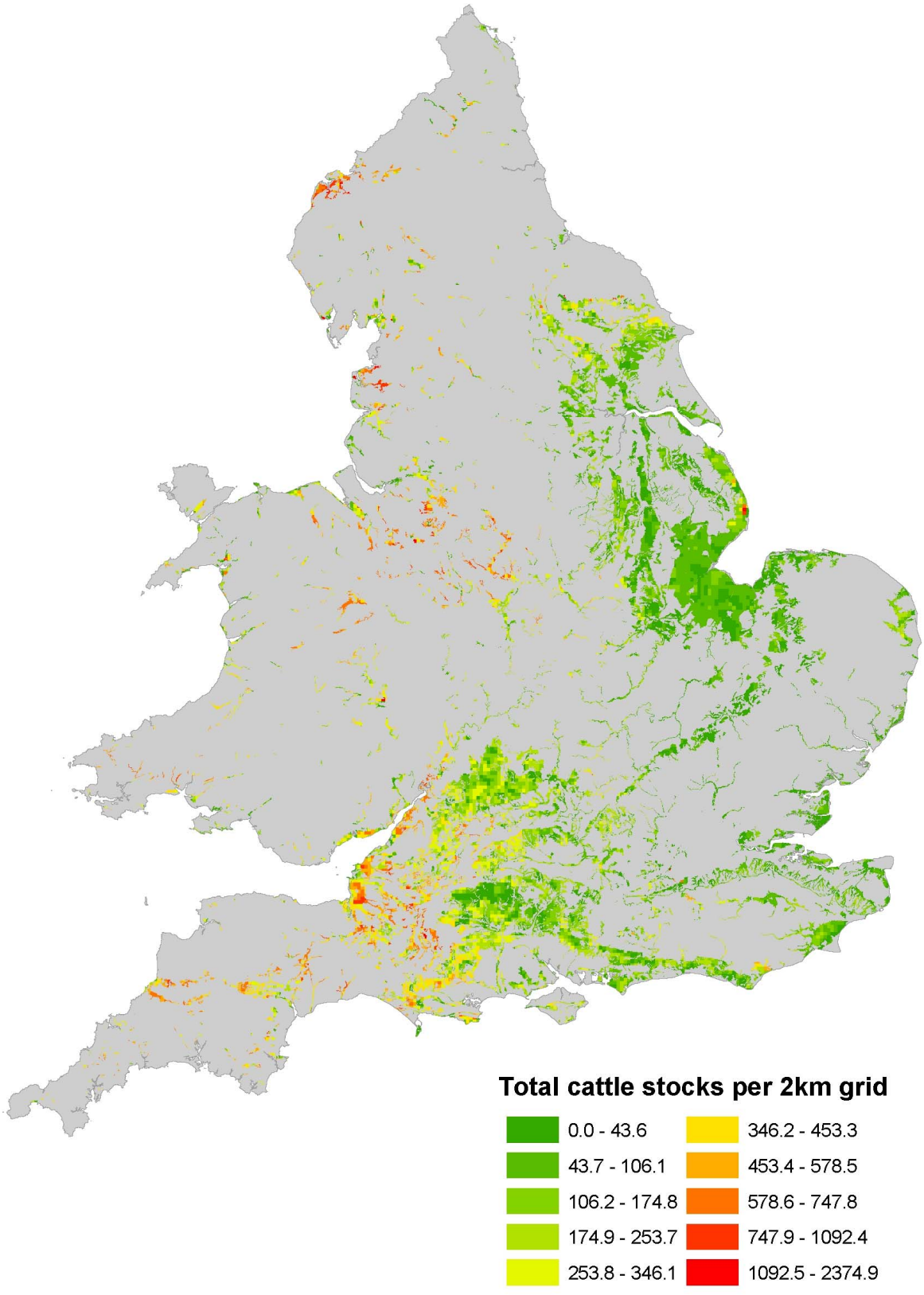
MACRO is one of the four leaching models recommended for European regulatory use for pesticides (FOCUS 1997). Unlike other models, it includes macropore flow – an important transport route in many UK soils. MACRO was therefore selected as the model to use in this study to assess the leaching of veterinary medicines to groundwater. As this model has a long running time, a meta-version of the model was used to determine maximum concentrations of each of the veterinary medicines. This meta-version was developed by running the model a number of times to generate look-up tables (Brown *et al.* 2003). In this study, the look-up table for vulnerable clay soil associated with shallow groundwater was selected (Table A1.2). This soil type (H1) corresponds to areas where livestock are typically reared (e.g. Figure A1.1).

The lowest Koc and longest DT50 value for each study compound were selected. These values were then used in conjunction with the look-up table to estimate the concentration leached. The DT50 for the compound was rounded up to the closest DT50 value in the table whereas the Koc value was rounded down. Values in the look-up table were corrected for the actual application rate.

Table A1.2 Look-up table for determining concentrations leaching to groundwater. Values are in µg l^{-1} and correspond to an application rate of 1 kg ha^{-1}

		Koc (ml g^{-1})								
		2	**5**	**10**	**20**	**50**	**100**	**200**	**500**	**1000**
Half-life (days)	2	0.0210	0.0154	0.0097	0.0045	0.0011	0.0003	0.0001	0.0000	0.0000
	5	0.1516	0.1239	0.0979	0.0760	0.0546	0.0333	0.0105	0.0001	0.0000
	10	0.5553	0.4941	0.4369	0.3879	0.3181	0.2111	0.0719	0.0012	0.0000
	20	1.3462	1.2467	1.1478	1.0476	0.8670	0.5966	0.2363	0.0126	0.0014
	50			2.4500	2.2421	1.8621	1.3729	0.6975	0.1476	0.0345
	100					2.5794	1.9805	1.1187	0.4342	0.1170
	200					3.0976	2.4345	1.4492	0.7694	0.2608
	350						2.6743	1.6273	0.9921	0.4118

Figure A1.1 Livestock densities corresponding to areas with HI soil type



Prediction of concentrations in surface water

Concentrations of each of the study compounds in surface water were predicted using the method described by Montforts (1999). This assumes that:

- livestock roam freely on pasture;
- excretion is as likely to occur in the stream as onto the pasture;
- a hectare of pasture contains a slow flowing stream 100 m long, 1 m wide and 0.3 m deep.

Consequently 1 per cent of the excreted dose of a substance will be released to the stream and this will be diluted in 30,000 litres of water.

To account for potential degradation of the study compounds in water, a time weighted average predicted environmental concentration in water (TWA PEC_{water}) was calculated using Equation A4. The TWA PEC_{water} was calculated for a period of 21 days following release to the surface water. This time span was selected as it corresponds to the duration of typical chronic aquatic ecotoxicology tests.

$$\text{TWA PEC}_{water} = \frac{PEC_{water} \text{ x } DT50_{water} \text{ x } (1 - e^{(-\ln 2/DT50_{water}) \text{ x } 21}}{\ln 2 \text{ x } 21} \quad \text{Equation A4}$$

Intensively reared livestock

Intensively reared livestock are typically housed for long periods of time. Manure, slurry or litter arising from these animals is collected and stored before being spread onto land, as fertiliser, at relatively high application rates (ADAS 1997, 1998). Veterinary medicines used to treat intensively reared animals may be released to soils during the slurry/manure application process and may subsequently be transported to surface water and groundwater.

The assessment scheme for livestock animals (cattle, pigs, poultry) considered:

- the effects of manure/slurry storage on the concentrations of veterinary medicines;
- releases of manure and slurry to land;
- the main transport routes for veterinary medicines to surface water and groundwater.

Concentrations in slurry/manure, soil, groundwater and surface water arising from the treatment of intensively reared livestock were predicted using a combination of:

- the Uniform Approach developed by Spaepen *et al.* (1997);
- approaches described by Montforts (1999)
- look-up tables developed by the UK Pesticides Safety Directorate for movement to surface waters;

- look-up tables used in the p-EMA computer-based decision support tool for leaching to groundwater (Brown *et al.* 2003).

The different approaches used are described below. Each is either already being used in the regulation of veterinary medicines or is used routinely in the regulation or management of pesticides. The models were run using Microsoft Excel.

Concentrations in slurry and manure

Initially the amount of substance excreted by an animal was calculated using Equation A5.

$$A_{excreted} = M \times D \times T \times F_{excreted} \quad \text{Equation A5}$$

where:

$A_{excreted}$ is the amount excreted (mg/animal);
M is the mass of the animal (kg);
D is the dosage (mg kg^{-1});
T is the treatment duration (days) (a maximum of 70 days was set);
F is the fraction of the administered dose excreted as the parent substance.

Data on the mass of individual animals and the manure/slurry production used in the calculations are given in Table A1.3.

Table A1.3 Manure/slurry production and animal mass data used in the calculations (Montforts 1999)

	Cattle	Pigs	Poultry
Manure/slurry production (kg $animal^{-1}$ d^{-1})	78.5	3.8	0.072
Mass of animal (kg)	600	70	2

Where data were available on persistence in slurry or manure, the rate constant for degradation in slurry and manure (RC_{slurry}) was calculated using Equation A6 and reported half-lives in manure or slurry ($DT50_{slurry}$ (d)). The rate constant was then used in Equation A7 to determine the fraction of compound in slurry or manure prior to application to land ($F_{application}$). It was assumed that storage time ($t_{storage}$) for manure or slurry is typically 70 days and that, on average, the residence time (t_E) of the study compound in the slurry or manure will be 35 days.

$$RC_{slurry} = \frac{\ln 2}{DT50_{slurry}} \quad \text{Equation A6}$$

$$F_{application} = e^{RC_{slurry} \times t_e} \quad \text{Equation A7}$$

The concentration of each study substance in slurry (PEC_{slurry} (mg kg^{-1})) was then determined from the amount excreted, the fraction remaining prior to application and

the slurry production for individual animals (P_{slurry} (kg animal^{-1} d^{-1}); Table A3) using Equation A8.

$$PEC_{slurry} = \left(\frac{A}{P_{slurry} \text{ x } t_{storage}} \right) \text{ x } F_{application} \qquad \text{Equation A8}$$

Concentrations in soil

Guidance limits exist on inputs of fertilising substances to land. The maximum recommended amount of manure or slurry that could be applied to land was therefore calculated using Equation A9 and data on:

- the concentrations of nitrogen or phosphorus in different manure/slurry types ($P_{N \text{ or } P}$ (kg place^{-1} year^{-1})
- recommended nitrogen or phosphate limits for the United Kingdom ($A_{N \text{ or } P}$ (kg ha^{-1} year^{-1});
- the typical manure/slurry output for an animal holding (P_E).

$$M = \frac{A_{N \text{ or } P}}{P_{N \text{ or } P}} \text{ x } P_E \qquad \text{Equation A9}$$

The amount of each study substance applied to land ($A_{applied}$ (mg ha^{-1})) was then calculated using Equation A10 from the predicted manure/slurry concentration and the amount of manure that can be applied.

$$A_{applied} = M \text{ x } PEC_{slurry} \qquad \text{Equation A10}$$

The concentration of each substance in soil was then calculated using Equation A11. It was assumed that all the manure/slurry is applied to a field on one occasion each year and that the mixing depth (D) is 5 cm. A soil bulk density (BD) of 1,500 kg m^{-3} was used.

$$PEC_{soil} = \frac{A_{applied}}{M + (((D/100) \text{ x} 100 \text{ x} 100) \text{ x BD})} \qquad \text{Equation A11}$$

To account for potential degradation of the study compounds in soil, a time weighted average predicted environmental concentration in soil (TWA PEC_{soil}) was calculated for a 21-day period using Equation A12.

$$TWA\ PEC_{soil} = \frac{PEC_{soil} \text{ x } DT50_{soil} \text{ x } (1 - e^{(-\ln 2/DT50_{soil}) \text{ x } 21})}{\ln 2 \text{ x } 21} \qquad \text{Equation A12}$$

Concentrations in surface waters

Up to 30 per cent of the UK's cereal crops may be grown on heavy clay soils (Callow 2000), as may significant proportions of other crops. Many of these soils require the use of sub-surface drainage systems to ensure that waterlogging does not occur. Such systems accelerate the passage of water through the soil profile and into surface waters. As the soils are used extensively to grow crops, it is likely that they will be fertilised with manure or slurry and hence veterinary medicines may be released to them. Recent work (Boxall *et al*. 2002, Kay *et al*. 2004) indicates that such systems are a major route for transport of veterinary medicines applied in slurry to surface waters.

The UK Pesticides Safety Directorate has proposed an approach for estimating the losses of pesticides to surface waters in drainflow (Callow 2000). The method is derived from results of research carried out at Brimstone Farm. Recent studies (Kay *et al*. 2004) indicate that the approach is appropriate for veterinary medicines. Hence, it was used in this study to estimate the proportion of a veterinary medicine moving to surface waters and to calculate the resulting surface water concentration.

It was assumed that a rainfall event occurs and that a percentage of the applied veterinary medicine per hectare is lost in 10 mm of drainflow (see Table A1.4). The percentage of veterinary medicine lost was determined from the lowest reported Koc value for a particular substance.

Table A1.4 Veterinary medicine loss in drainflow

	Koc (ml g^{-1})	Veterinary medicine transported in 10 mm of drain water (%)
very mobile	<15	1.9
mobile	15–74	1.9
moderately mobile	75–499	0.7
slightly mobile	500–1000	0.5
	1000–4000	0.02
non mobile	>4000	0.008

It is probable that dilution in the receiving water will occur and therefore an additional factor was included to account for this. It was assumed that the drain entered a ditch 100 m long, 1 m wide and 30 cm deep. This equates to a dilution of the drainflow in a further 30,000 litres of water (equivalent to the surface water body used in the pasture assessment).

To account for potential degradation of the study compounds in water, a time weighted average predicted environmental concentration in water (TWA PEC_{water}) was calculated for a period of 21 days following the drainflow event.

Concentrations in groundwater

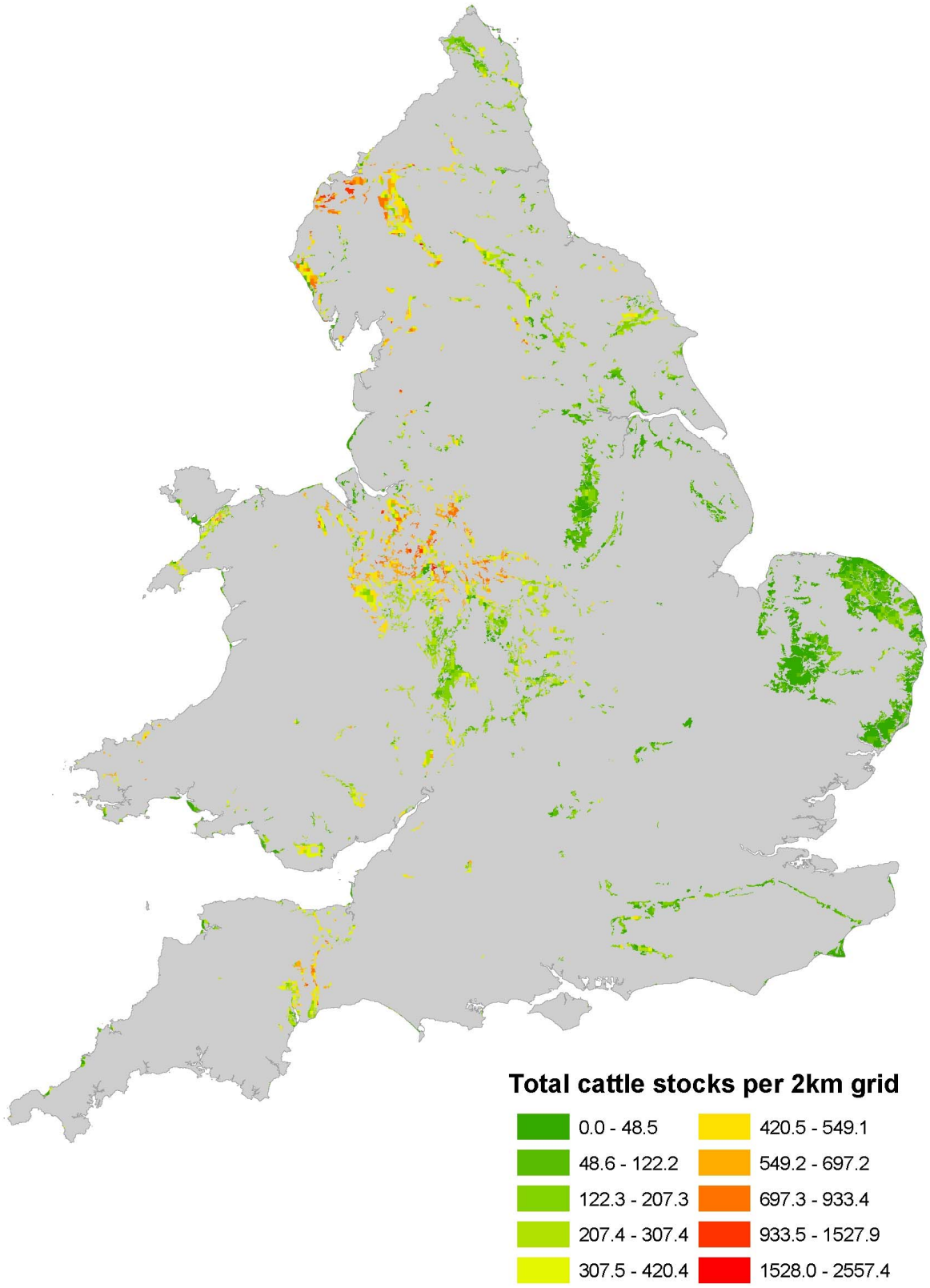
A similar approach to that used for pasture animals was used to estimate groundwater concentrations. However, as it is very unlikely that slurry or manure would be applied to the soil type investigated for the pasture animals (Hollis J, personal communication), a look-up table for a sandy soil where there will be high potential for leaching was used instead (Table A1.5). The soil type (H2) is found in areas where livestock are reared (Figure A1.2).

The lowest Koc and longest DT50 value for each study compound were used. These values were then used in conjunction with the look-up table to estimate the concentration leached; the DT50 for the compound was rounded up to the closest DT50 value in the table whereas the Koc value was rounded down. Values were corrected for the actual application rate ($A_{applied}$) of each study substance.

Table A1.5. Look-up table for determining concentrations leaching to groundwater. Values correspond to an application rate of 1 kg ha^{-1}

		Koc (ml g^{-1})								
		2	**5**	**10**	**20**	**50**	**100**	**200**	**500**	**1000**
Half-life (days)	2	0.0202	0.0085	0.0023	0.0003	0.0000	0.0000	0.0000	0.0000	0.0000
	5	0.4173	0.2557	0.1170	0.0272	0.0007	0.0000	0.0000	0.0000	0.0000
	10	1.6764	1.2301	0.7218	0.2396	0.0103	0.0002	0.0000	0.0000	0.0000
	20	3.7688	3.1244	2.2020	0.9855	0.0741	0.0065	0.0001	0.0000	0.0000
	50			4.7987	2.7829	0.8676	0.1505	0.0103	0.0000	0.0000
	100					2.2853	0.6612	0.0695	0.0001	0.0000
	200					3.7797	1.6352	0.1849	0.0003	0.0000
	350						2.4275	0.2831	0.0005	0.0000

Figure A1.2 Livestock densities corresponding to areas with H2 soil type



Aquaculture treatments

The veterinary medicines being assessed as aquaculture treatments are employed in aquaculture systems for two purposes:

- treatment of eggs in hatcheries (bronopol);
- treatment of free-living stock within pond or tank-based systems (amoxicillin, oxytetracycline).

Two modelling scenarios were therefore used:

- a trout hatchery (for the egg treatment);
- a land-based trout farm (for fish treatments).

Hatchery scenario

The hatchery scenario assumed a farm with a continuous flow egg hatchery system, with treatment applied into the water supply to ensure a fixed concentration of the treatment chemical for a specified time period (30 minutes). It was assumed that the farm had a settlement pond, which ultimately discharged into a river.

The model used for the simulations was based on plug flow of the medicine through the farm system over a 24-hour period, and was implemented as a Microsoft Excel spreadsheet. Details of farm system and the simulation parameters used are given in Table A1.6.

Table A1.6 Details of the hatchery scenario used in the model simulations of disease treatment emissions from land-based aquaculture facilities

Species	rainbow trout
Egg incubator volume (m^3)	0.2
Treatment volume (m^3)	0.2
Settlement pond volume (m^3)	600
Farm discharge flow (l min^{-1})	6,000
Receiving water flow (l min^{-1})	20,000

Stocked fish scenario

The stocked fish scenario assumed a farm consisting of 10 raceways (concrete tanks) operating at a high stocking density and discharging into a river via a settlement pond. Although the stocking density used was high, the scenario was considered representative of a large commercial land-based aquaculture facility in England and Wales.

The model used for the simulations was based on plug flow of the medicine through the farm system over a 24-hour period, and was implemented as a Microsoft Excel spreadsheet. Details of farm system and the simulation parameters used are given in Table A1.7.

Table A1.7 Details of the farm scenario used in the model simulations of disease treatment emissions from land-based aquaculture facilities

Species	rainbow trout
Stocking density (kg m^{-3})	400
Number of raceways	10
Raceway dimensions (length x width x depth) (m)	12 x 3 x 1
Settlement pond volume (m^3)	600
Farm discharge flow (l min^{-1})	6,000
Receiving water flow (l min^{-1})	20,000

All scenarios were modelled using the recommended dose of each medicine (NOAH 2002). In all cases, the simulations of medicine treatments indicated a similar pattern of emission which was a pulse, peaking <1 hour after treatment, and dissipating completely after 24 hours. This was considered worst case, as in practice, some adsorption/loss of the compound would be expected as it passed through the farm system.

The settlement pond acted as a buffer to compound release and thus, in the case of compounds with a high Koc (e.g. oxytetracycline), the possibility existed that compound could accumulate in the settlement pond, being released during storm events or removed when the settlement pond was periodically cleaned out. In either case, the release of compound into the receiving waters was not likely to exceed an immediate treatment pulse, so the simpler scenario used here was again considered to be worst case.

Appendix 2 Treatment scenarios used to assess the study compounds

Compound	Treatment group	Category	Method of administration	Dose (mg kg^{-1})	Duration of treatment (d)	Number of treatments per year	Proportion of animals treated (%)	Metabolism (%)
amoxicillin	cattle	I,P	injection	7	3	1	100	0
	sheep	P	injection	7	3	1	100	0
	pigs	I,P	injection	7	3	1	100	0
	cattle	I,P	bolus	400 mg/animal	1	1	100	0
	pigs	I,P	suspension	10	3	1	100	0
	poultry	I	powder	20	3	1	100	0
	pigs	I,P	feed additive	15	15	1	100	0
amprolium	poultry	I	premix	5.7/animal/d	112	1	100	0
apramycin	pigs	I,P	injection	20	5	1	100	0
	pigs	I,P	oral	20	5	1	100	0
	lambs	P	oral	20	5	1	100	0
	pigs	I,P	premix	8	18	1	100	0
	pigs	I,P	powder	12.5	12	1	100	0
	cattle	I,P	powder	40	5	1	100	0
	poultry	I	powder	12.5	5	1	100	0
chlorhexidine	cattle	I,P	teat dip	4.5 mg/animal/d	1	365	100	0
clavulanic acid	cattle	I,P	injection	1.75	5	1	100	0
	pigs	I,P	injection	1.75	5	1	100	0
	sheep	P	injection	1.75	5	1	100	0
	cattle	I,P	bolus	100	5	1	100	0
cyromazine	sheep	P	pour-on	900 mg/animal	1	1	100	0
decoquinate	cattle	I,P	premix	1	28	1	100	0
diclazuril	poultry	I	premix	0.04/animal/d	112	1	100	0
	sheep	P	oral suspension	1	1	2	100	0
	sheep	P	pour on	100	1	1	100	0
doramectin	cattle	I,P	injection	0.2	1	3	100	0

Compound	Treatment group	Category	Method of administration	Dose (mg kg^{-1})	Duration of treatment (d)	Number of treatments per year	Proportion of animals treated (%)	Metabolism (%)
	sheep	P	injection	0.3	1	1	100	0
	pigs	I,P	injection	0.3	1	1	100	0
doramectin	cattle	I,P	pour-on	0.5	1	2	100	0
enrofloxacin	cattle	I,P	injection	5	5	1	100	0
	pigs	I,P	injection	5	5	1	100	0
	cattle	I,P	oral	2.5	5	1	100	0
	pigs	I,P	piglet doser	5	1	1	100	0
	poultry	I	soluble	10	10	1	100	0
eprinomectin	cattle	I,P	pour-on	0.5	1	2	100	0
fenbendazole	horse	P	liquid oral	7.5	1	3	100	0
	cattle	I,P	liquid oral	7.5	1	3	100	0
	sheep	P	liquid oral	5	1	2	100	0
	pigs	I,P	liquid oral	7.5	1	3	100	0
	cattle	I,P	feed pellets	7.5	1	3	100	0
	pigs	I,P	feed pellets	5	1	3	100	0
	cattle	I,P	powder	7.5	1	3	100	0
	pigs	I,P	powder	5	1	3	100	0
	cattle	I	bolus	86 mg/animal/d	140	1	100	0
	cattle	P	bolus	86 mg/animal/d	140	1	100	0
florfenicol	cattle	I,P	injection	20	2	1	25	0
ivermectin	cattle	I,P	injection	0.2	1	3	100	0
	sheep	P	injection	0.2	1	4	100	0
	pigs	I,P	injection	0.3	1	4	100	0
	sheep	P	liquid oral	0.2	1	2	100	0
	cattle	I,P	pour-on	0.5	1	3	100	0
	horse	P	paste	0.2	1	4	100	0
	cattle	I,P	bolus	12.7 mg/animal	135	1	100	0
lasalocid	poultry	I	feed	99 mg/kg feed	112	1	100	0
levamisole	cattle	I,P	injection	7.5	1	2	100	0
	sheep	P	injection	7.5	1	2	100	0
	cattle	I,P	liquid oral	7.5	1	2	100	0
	sheep	P	liquid oral	7.5	1	2	100	0

Compound	Treatment group	Category	Method of administration	Dose (mg kg^{-1})	Duration of treatment (d)	Number of treatments per year	Proportion of animals treated (%)	Metabolism (%)
levamisole	cattle	I,P	pour on	10	1	2	100	0
lincomycin	pigs	I,P	premix	22	21	1	100	0
	pigs	I,P	soluble	4.4	10	1	100	0
monensin	poultry	I	premix	5/animal/d	112	1	100	0
	cattle	I	premix	350/animal/d	182	1	100	0
morantel	sheep	P	liquid oral	5.94	1	6	100	0
	cattle	I,P	bolus	131 mg/animal	90	1	100	0
moxidectin	cattle	I,P	injection	0.002	1	2	100	0
	sheep	P	injection	0.002	1	2	100	0
	sheep	P	oral liquid	0.002	1	2	100	0
	cattle	I,P	pour-on	0.005	1	2	100	0
nicarbazin	poultry	I	feed additive	1.8/animal/d	112	1	100	0
nitroxynil	cattle	I,P	injection	10	1	2	100	0
	sheep	P	injection	10	1	2	100	0
oxytetracycline	horse	P	injection	5	5	1	25	0
	cattle	I	injection	3	5	1	25	0
	cattle	P	injection	10	2	1	25	0
	sheep	P	injection	20	1	1	100	0
	pigs	I	injection	5	5	1	25	0
	pigs	P	injection	10	2	1	25	0
	cattle	I,P	bolus	20	1	1	25	0
	pigs	I,P	feed additive	20	15	1	100	0
	cattle	I,P	soluble	18	1	1	25	0
	pigs	I,P	soluble	30	1	1	25	0
	poultry	I	soluble	15	1	1	25	0
	sheep	I	injection	8	5	1	100	0
	sheep	P	injection	20	2	1	100	0
	sheep	I	aerosol	29	1	1	1	0
	horse	P	topical	29	1	1	80	0
	cattle	I,P	topical	29	1	1	80	0
	pigs	I,P	topical	29	1	1	80	0
poloxalene	cattle	I,P	drench	22	1	1	5	0

Compound	Treatment group	Category	Method of administration	Dose (mg kg^{-1})	Duration of treatment (d)	Number of treatments per year	Proportion of animals treated (%)	Metabolism (%)
poloxalene	cattle	I,P	premix	22	1	1	5	0
procaine	cattle	I,P	Injection, feed	8-10	3-5	1	100	0
penicillin	sheep	I,P	Injection, feed	8-10	3-5	1	100	0
	pigs	I,P	Injection, feed	8-10	3-5	1	100	0
salinomycin	poultry	I	feed additive	2.5/animal/d	112	1	100	0
	pigs	I	feed additive	54/animal/d	182	1	100	0
sulfadiazine	horse	P	injection	12	3	1	100	0
	cattle	I,P	injection	12	3	1	100	0
	sheep	P	injection	12	3	1	100	0
	pigs	I,P	injection	12	3	1	100	0
	cattle	I,P	bolus	1 g/d	5	1	25	0
	pigs	I,P	suspension	25	3	1	100	0
	horse	P	granules	25	3	1	100	0
	pigs	I	powder	25	5	1	100	0
	horse	P	paste	25	3	1	100	0
	horse	P	powder	25	5	1	10	0
	poultry	I	soluble	33	3	1	100	0
	poultry	I	powder	22	10	1	1	
tiamulin	pigs	I	injection	10	10	1	100	0
	pigs	I	premix	5	10	1	100	0
	pigs	P	injection	10	10	1	100	0
	pigs	P	premix	5	10	1	100	0
	poultry	I	soluble	25	3	1	100	0
tilmicosin	cattle	I	injection	10	1	1	50	0
	cattle	P	injection	10	1	1	10	0
	sheep	P	injection	10	1	1	10	0
	pigs	I	premix	16	15	1	100	0
	pigs	P	premix	16	15	1	100	0
	poultry	I	soluble	25	3	1	100	0
triclabendazole	cattle	I	oral liquid	12	1	1	100	100
	sheep	P	oral liquid	10	1	3	100	100
	cattle	P	oral liquid	12	1	3	100	100

Compound	Treatment group	Category	Method of administration	Dose (mg kg^{-1})	Duration of treatment (d)	Number of treatments per year	Proportion of animals treated (%)	Metabolism (%)
trimethoprim	horse	P	injection	3	2	1	25	20
trimethoprim	cattle	I,P	injection	3	3	1	25	20
	sheep	P	injection	3	3	1	100	20
	pigs	I	injection	3	2	1	25	20
	pigs	P	injection	3	2	1	25	20
	cattle	I,P	bolus	200 mg/animal	5	1	25	20
	pigs	I,P	suspension	5	3	1	100	20
	horse	P	granules	5	3	1	100	20
	pigs	I	powder	8	5	1	100	20
	pigs	P	powder	8	5	1	100	20
	poultry	I	powder	8	5	1	100	20
	horse	P	paste	5	5	1	10	20
	pigs	I	soluble	5	5	1	100	20
	poultry	I	soluble	6	21	1	100	20
	poultry	I	powder	4	10	1	1	20
tylosin	cattle	I	injection	10	3	1	100	0
	cattle	P	injection	10	1	1	10	0
	pigs	I	injection	20	2	1	100	0
	pigs	P	injection	10	1	1	10	0
	sheep	P	injection	10	3	1	100	0
	pigs	I,P	feed additive	6	21	1	100	0
	cattle	I	soluble	2 g/animal	14	1	50	0
	cattle	P	soluble	2 g/animal	14	1	50	0
	poultry	I	soluble	3.5 mg/animal	1	1	100	0
	pigs	I	soluble	25	1	1	100	0
	pigs	P	soluble	25	1	1	100	0

I = intensive; P = pasture

Appendix 3 Sorption data for the study compounds

Compound	Soil type	Kd	Koc	Source
diclazuril	silty clay loam	204	–	Boxall *et al.* 2002
	sandy loam	1824	–	
	silt loam	1009	–	
	silty clay loam	720	–	
doramectin	clay loam	71	7,520	Pfizer 1996
	clay loam	234	13,300	
	silty clay loam	562	86,900	
	steer faeces	15600	34,100	
enrofloxacin	chicken faeces	139	395	Bayer 1996
	turkey faeces	65	198	
fenbendazole	New Jersey soil	1000	–	Hoechst Roussel 1995
	Texas soil	1000	–	
	Louisiana soil	631	–	
	New Jersey sediment	1000	–	
florfenicol	loam	0.95	46	Schering Plough 1996
	silt loam	0.16	24	
	silt loam	0.88	52	
ivermectin	clay loam	333	12,600	Boxall *et al.* 2002
	silty clay loam	227	15,700	
levamisole	–	–	–	
monensin	soil	9.3		
moxidectin	soil	580	18,000–41,000	Fort Dodge 1997
oxytetracycline	sandy loam soil	680	42,506	Boxall *et al.* 2002
	sandy soil	670	47,881	
	sandy loam soil	1026	93,317	
	loamy sand	417	27,792	
tiamulin	silt loam pH 8	88	–	Fermenta 1994
tiamulin	clay	75	–	
tiamulin	silt loam	74	–	
tiamulin	loamy sand	8	–	
tilmicosin	clay loam	318		
tilmicosin	loam	181		
tilmicosin	loam (pH 8.9)	86		
tilmicosin	sandy loam	129		
tylosin	sandy loam soil	128	7,988	Boxall *et al.* 2002
tylosin	sandy soil	10.8	771	
tylosin	sandy loam soil	62.3	5,664	
tylosin	loamy sand soil	8.3	553	

Appendix 4 Persistence of the study compounds in manure and soil

Compound	Test substrate	DT50 (d)	Source
amoxicillin	calcareous soil	0.16	Boxall *et al.* 2002
	acidic soil	0.29	
	manure	< 4	
ciprofloxacin	3 soils	minimal after 65 d	Bayer 1996
decoquinate	soil	18 months	Boxall *et al.* 2002
diclazuril	sandy loam	303	Boxall *et al.* 2002
	loam	183	
	silty loam	130	
doramectin	clay loam	79	Pfizer 1996
	silt loam	62	
	loam	61	
enrofloxacin	3 soil types	359 – 696	Bayer 1996
eprinomectin	3 soils	approx. 64 d	Merck and Co. 1996
	cow pats	minimal over 126 d	
florfenicol	silty clay	9	Schering Plough 1996
	sandy loam	4	
	loam	27	
ivermectin	soil/faeces mix (summer)	7–14	Boxall *et al.* 2002
	soil/faeces mix (winter)	91–217	
	sandy loam soil	14–28	
	clay soil	28–56	
	sandy soil	56	
	dung	limited degradation after 45d	
monensin	soil, greenhouse conditions		Elanco 1989
	soil + steer manure, greenhouse conditions	5.8	
	field dissipation (+ manure)	7.5	
	field dissipation (– manure)	7.4	
moxidectin	soil (average of 3 types)	62	Fort Dodge 1997
oxytetracycline	sandy loam	16	Blackwell P, personal communication
oxytetracycline	clay loam	18	
salinomycin	sandy loam	<64	
salinomycin	sandy loam	<64	
	sandy loam	0% after 64 d	
tiamulin	sand	48	Fermenta 1994
	sandy loam	52	
	silty clay loam	61	
	silt loam	97	
	sand	43	
	silt loam	100	
	clay	150	
	pH 8 soils	301	
tilmicosin	clay loam	>64	Boxall *et al.* 2002
	loam	>64	
	sandy loam	>64	
	slurry/manure	limited degradation	

Appendix 5 Public domain aquatic toxicity data for the priority compounds

Compound	Aquatic toxicity endpoint	Units	Value	Source
amoxicillin	*M. aeruginosa* EC50	mg l^{-1}	0.0037	Boxall *et al.* 2002
	S. capricornutum NOEC	mg l^{-1}	250	
	Rhodomonas salina EC50	mg l^{-1}	3108	
apramycin	Rainbow trout 96 h LC50	mg l^{-1}	>300	Boxall *et al.*, 2002
	Bluegill sunfish 96 h LC50	mg l^{-1}	>300	
	D. magna 48 h EC50	mg l^{-1}	101.6	
cyromazine	*D. magna* 48 h EC50	mg l^{-1}	97.8	Boxall *et al.* 2002
	Deleatidium spp. 48 h LC50	mg l^{-1}	>300	
	Gambusia affinis 72 h LC50	mg l^{-1}	0.037	
	I. Punctatus 96 h LC50	mg l^{-1}	91.6	
	L. macrochirus 96 h LC50	mg l^{-1}	89.7	
	O. mykiss 96 h LC50	mg l^{-1}	87.9	
	Dugesia dorotocephala 72 h LC50	mg l^{-1}	>10	
	Dugesia tigrina 72 h LC50	mg l^{-1}	>10	
	Dugesia tigrina 72 h EC50 (reproduction)	mg l^{-1}	>10	
	Dugesia tigrina 72 h EC50 (reproduction)	mg l^{-1}	>10	
diclazuril	*L. macrochirus* 96 h LC50	mg l^{-1}	0.58	
	D. magna 21 d reproduction NOEL	mg l^{-1}	0.16	
	S. capricornutum 72 h EC50	mg l^{-1}	>1.1	
	Anabaena cylindrica MIC	mg l^{-1}	>100	
	Nostoc muscorum MIC	mg l^{-1}	>1000	
	Chironomus tentans 14 d NOEL	mg kg^{-1}	7.3	
doramectin	*Selenastrum*		not acutely toxic	Boxall *et al.* 2002, Pfizer 1996
	D. magna 48 h EC50	mg l^{-1}	0.0001	
	D. magna 48 h NOEC	mg l^{-1}	0.000025	
	L. macrochirus 96 h LC50	mg l^{-1}	0.011	
	L. macrochirus 96 h NOEC	mg l^{-1}	0.0023	

Compound	Aquatic toxicity endpoint	Units	Value	Source
	O. mykiss 96 h LC50	mg l^{-1}	0.0051	
	O. mykiss 96 h NOEC	mg l^{-1}	0.0025	
enrofloxacin	*L. macrochirus* 96 h LC50	mg l^{-1}	79.5	Bayer 1996
	L. macrochirus 96 h NOEC	mg l^{-1}	18.6	
	O. mykiss 96 h LC50	mg l^{-1}	>196	
	O. mykiss 96 h NOEC	mg l^{-1}	33.5	
	D. magna 48 h EC50	mg l^{-1}	79.9	
	D. magna chronic NOEC	mg l^{-1}	9.8	
	D. magna 48 h NOEC	mg l^{-1}	23	
	Hyallela LC50	mg l^{-1}	>206	
	Selenastrum and *Microcystis*		Effects observed on growth	
	Hyallela NOEC	mg l^{-1}	<12.7	
eprinomectin	*D. magna* 24 h EC50	mg l^{-1}	0.0016	Merck and Co. 1996
	D.magna 48 h EC50	mg l^{-1}	0.00045	
	O. mykiss 96 h LC50	mg l^{-1}	1.2	
	O. mykiss 96 h NOEC	mg l^{-1}	0.37	
	L. macrochirus 96 h LC50	mg l^{-1}	0.37	
	L. macrochirus 96 h NOEC	mg l^{-1}	0.14	
	S. capricornutum 14 d MIC	mg l^{-1}	29	
	S. capricornutum 14 d NOEC	mg l^{-1}	7	
fenbendazole	*D. magna* 48 h EC50	mg l^{-1}	0.012	Boxall *et al.* 2002, Hoechst Roussel 1995
	S. gardneri 96 h LC50	mg l^{-1}	7.5	
	L. macrochirus 96 h LC50	mg l^{-1}	>0.061	
	L. macrochirus 7 d LC50	mg l^{-1}	>0.061	
	L. macrochirus 14 d LC50	mg l^{-1}	0.035	
	L. macrochirus 21 d LC50	mg l^{-1}	0.019	
	L. macrochirus 96 h LC50	mg l^{-1}	0.08	
	L. macrochirus 7 d LC50	mg l^{-1}	0.08	
	L. macrochirus 14 d LC50	mg l^{-1}	0.033	
	L. macrochirus 21 d LC50	mg l^{-1}	0.028	
	Zebra fish 48 h LC50	mg l^{-1}	>500	
	Zebra fish 96 h LC50	mg l^{-1}	>500	
florfenicol	*S. capricornutum* (growth) LC50	mg l^{-1}	>2.9	
	S. capricornutum (growth) NOEC	mg l^{-1}	2.9	
	D. magna 48 h EC50	mg l^{-1}	>330	

Compound	Aquatic toxicity endpoint	Units	Value	Source
	D. magna 48 h NOEC	mg l^{-1}	<100	
	L. macrochirus 96 h LC50	mg l^{-1}	>830	
	L. macrochirus 96 h NOEC	mg l^{-1}	830	
	O. mykiss 96 h LC50	mg l^{-1}	>780	
	O.mykiss 96 h NOEC	mg l^{-1}	780	
ivermectin	*Asterias rubens* 10 d LC50	mg kg^{-1}	23.6	Boxall *et al.* 2002
	C. volutator 10 d LC50	mg kg^{-1}	0.18	
	A. marina 10 d LC50	mg kg^{-1}	0.018	
	A. marina effects on feeding	mg kg^{-1}	<0.005	
	A. marina effect on burrowing	mg kg^{-1}	>0.008	
	S. gardneiri 96 h LC50	mg l^{-1}	0.003	
	L. macrochirus 96 h LC50	mg l^{-1}	0.0048	
	Crangon septemspinosa 96 h LC50	mg l^{-1}	>.021	
	Neomysis integer 96 h LC50	mg l^{-1}	0.07	
	Neomysis integer 48 h LC50	mg l^{-1}	0.000026	
	Gammarus sp. 96 h LC50	mg l^{-1}	0.000033	
	Palaemonectes varians 96 h LC50	mg l^{-1}	0.054	
	A. salina 24 h LC50	mg l^{-1}	>0.3	
	Sphaeroma rugicauda 96 h LC50	mg l^{-1}	0.348	
	Carcinas maenas 96 h LC50	mg l^{-1}	0.957	
	Crassotrea gigas (larvae) 96 h LC50	mg l^{-1}	80–100	
	Crassotrea gigas (spat) 96 h LC50	mg l^{-1}	460	
	Mytilus edulis 96 h LC50	mg l^{-1}	400	
	Tapes semidecassata (larvae) 96 h LC50	mg l^{-1}	0.38	
	Tapes semidecassata (spat) 96 h LC50	mg l^{-1}	0.6	
	Pecten maximus	mg l^{-1}	0.3	
	Monodonta lineata	mg l^{-1}	0.78	
	Nucella lapillus 96 h LC50	mg l^{-1}	0.39	
	Littorina littorea 96 h LC50	mg l^{-1}	0.58	
	Hydrobia ulvae 96 h LC50	mg l^{-1}	>10	
	Potamopyrgus jenkinsii 96 h LC50	mg l^{-1}	<9	
	Nereis diversicolor 96 h LC50	mg l^{-1}	0.0075	
	A. marina 10 d LC50	mg kg^{-1}	0.023	
	Biomphalaria glabrata 24 h LC50	mg l^{-1}	0.03	
	D. magna 48 h EC50	mg l^{-1}	0.000025	
	Chlorella pyrenoidosa 14 d NOEC	mg l^{-1}	<0.001	
levamisole	*A. anguilla*	mg l^{-1}	88% physiology effect over 25 h	Boxall *et al.* 2002

Compound	Aquatic toxicity endpoint	Units	Value	Source
lincomycin	*D. magna* 48 h EC50	mg l^{-1}	379.4	
	D. magna phototactic behaviour decreased	mg l^{-1}	5	
	Artemia spp. 72 h EC50	mg l^{-1}	283	
monensin	*L. macrochirus* 96 h LC50	mg l^{-1}	16.6	Boxall *et al.* 2002, Elanco 1989
	L. macrochirus 96 h effects on behaviour	mg l^{-1}	>4.4	
	O. mykiss 96 h LC50	mg l^{-1}	9	
	O. mykiss 96 h effects on behaviour	mg l^{-1}	>1.12	
	D. magna 48 h EC50	mg l^{-1}	10.7	
	D. magna 48 h abnormal behaviour	mg l^{-1}	>5.6	Schering Plough 1996
moxidectin	*L. macrochirus* 96 h LC50	mg l^{-1}	0.00062	Fort Dodge 1997
	L. macrochirus 96 h NOEC	mg l^{-1}	<0.00052	
	D. magna 48 h EC50	mg l^{-1}	0.00003	
	D. magna 48 h NOEC	mg l^{-1}	0.000011	
	O. mykiss 96 h LC50	mg l^{-1}	0.00016	
	green algae 72 h EC50	mg l^{-1}	0.087	
	O. mykiss 96 h NOEC	mg l^{-1}	<0.00015	
oxytetracycline	*M. aeruginosa* EC50	mg l^{-1}	0.207	Boxall *et al.* 2002
	S. capricornutum	mg l^{-1}	4.5	
	R. salina	mg l^{-1}	1.6	
	D. magna 48 h LOEC	mg l^{-1}	100	
	D. magna 48 h EC50	mg l^{-1}	>102	
	L. macrochirus 96 h LC50	mg l^{-1}	>100	
	M. saxatilis (larvae) 24 h LC50	mg l^{-1}	62.5	
	M. saxatilis (larvae) 48 h LC50	mg l^{-1}	62.5	
	M. saxatilis (larvae) 72 h LC50	mg l^{-1}	62.5	
	M. saxatilis (larvae) 96 h LC50	mg l^{-1}	62.5	
	M. saxatilis (fingerling) 24 h LC50	mg l^{-1}	150	
	M. saxatilis (fingerling) 48 h LC50	mg l^{-1}	125	
	M. saxatilis (fingerling) 72 h LC50	mg l^{-1}	100	
	M. saxatilis (fingerling) 96 h LC50	mg l^{-1}	75	
	O. mykiss 96 h LC50	mg l^{-1}	>116	
	P. vannamei 24 h EC50 intoxication	mg l^{-1}	0.16	
	P. vannamei 48 h EC50 intoxication	mg l^{-1}	0.061–0.21	
	P. vannamei 24 h LC50	mg l^{-1}	0.16	

Compound	Aquatic toxicity endpoint	Units	Value	Source
	P. vannamei 48 h LC50	mg l^{-1}	0.16-0.24	
	P. vannamei 24 h LOEC intoxication	mg l^{-1}	0.16	
	P. vannamei 24 h NOEC intoxication	mg l^{-1}	0.16	
	P. vannamei 48 h NOEC intoxication	mg l^{-1}	0.055–0.16	
	S. namaycush 24 h LC50	mg l^{-1}	<200	
salinomycin	*Oryzias latipes* TLM	mg l^{-1}	63.5	
sulfadiazine	*M. aeruginosa* EC50 population	mg l^{-1}	0.135	Boxall *et al.* 2002
	S. capricornutum EC50	mg l^{-1}	7.8	
	R. salina EC50	mg l^{-1}	403	
	D. magna 48 h EC50	mg l^{-1}	221	
	D. magna 24 h EC50 physiology	mg l^{-1}	112	
	D. magna 72 h EC50 physiology	mg l^{-1}	57	
	Cirrhinus mrigala effect on growth	mg/100g	20	
tiamulin	*D. magna* 48 h EC50	mg l^{-1}	40–67	Fermenta 1994
	Unspecified fish 96 h LC50	mg l^{-1}	5.2	
	unspecified algae 96 h EC50	mg l^{-1}	>0.62	
	M. aeruginosa 7 d EC50	mg l^{-1}	0.003	
	S. capricornutum	mg l^{-1}	0.165	
tilmicosin	*L. macrochirus* 96 h LC50	mg l^{-1}	716	
	S. gairdneri 96 h LC50	mg l^{-1}	851	
	D. magna 48 h EC50	mg l^{-1}	57.3	
triclabendazole	unspecified algae 72 h EC50	mg l^{-1}	45	Boxall *et al.* 2002
	D. magna 48 h EC50	mg l^{-1}	133	
	unspecified fish	mg l^{-1}	117	
trimethoprim	*M. aeruginosa* EC50	mg l^{-1}	112	Boxall *et al.* 2002
	R. salina	mg l^{-1}	130	
	S. capricornutum	mg l^{-1}	16	
tylosin	*D. magna* 48 h EC50	mg l^{-1}	680	Boxall *et al.* 2002
	M. aeruginosa 7 d EC50	mg l^{-1}	0.034	
	S. capricornutum 72 h EC50	mg l^{-1}	1.38	
	Rainbow trout 96 h LC50	mg l^{-1}	851	
	Bluegill sunfish 96 h LC50	mg l^{-1}	716	
	D. magna 48 h EC50	mg l^{-1}	57.3	
	S. capricornutum	mg l^{-1}	0.354	

TLM = median tolerance limit

Appendix 6 Terrestrial toxicity data for the priority compounds

Compound	Terrestrial toxicity (endpoint)	Terrestrial toxicity (units)	Terrestrial toxicity (value)	Source
apramycin	bobwhite quail 14 d LD50 oral	mg kg^{-1}	1669	Boxall *et al.* 2002
	bobwhite quail 5 d LD50 (dietary)	mg kg^{-1}	>5000	
	mallard duck 5 d LD50 (dietary)	mg kg^{-1}	>5000	
	earthworm 14 d LD50	mg kg^{-1}	>100	
	A. chroococcum inhibition	mg kg^{-1}	0.1	
	A. floss aqua	mg kg^{-1}	0.1	
	R. leguminosarum	mg kg^{-1}	0.1	
	R. japonicum	mg kg^{-1}	1–10	
	corn seedling growth NOEC	mg kg^{-1}	1600	
	cucumber seedling growth NOEC	mg kg^{-1}	1600	
	ryegrass seedling growth NOEC	mg kg^{-1}	1600	
	soybean seedling growth NOEC	mg kg^{-1}	1600	
	tomato seedling growth NOEC	mg kg^{-1}	36	
	wheat seedling growth NOEC	mg kg^{-1}	1600	
	tomato seedling growth LOEC	mg kg^{-1}	64	
	corn root elongation NOEC	mg kg^{-1}	970	
	cucumber root elongation NOEC	mg kg^{-1}	970	
	ryegrass root elongation NOEC	mg kg^{-1}	970	
	soybean root elongation NOEC	mg kg^{-1}	1000	
	tomato root elongation NOEC	mg kg^{-1}	1000	
	wheat root elongation NOEC	mg kg^{-1}	1000	
	Onthophagus gazella 7 d LC50	mg kg^{-1}	>0.77	
	Onthophagus gazella 7 d NOEC	mg kg^{-1}	0.77	
cyromazine	Mallard duck 14 d LD50	mg kg^{-1}	>2510	Boxall *et al.* 2002
	Mallard duck 8d LD50	mg kg^{-1}	>5620	
	Honey bee 48 h LD50	mg/bee	>0.025	
	Northern bobwhite 14d LD50	mg kg^{-1}	1785	

Compound	Terrestrial toxicity (endpoint)	Terrestrial toxicity (units)	Terrestrial toxicity (value)	Source
	Northern bobwhite 8d LC50	mg kg^{-1}	>5620	
	earthworm 14 d LC50	mg kg^{-1}	1000	
diclazuril	corn, cucumber and ryegrass no effect on germination	mg kg^{-1}	830	
	corn, cucumber and ryegrass no effect on radicle length	mg kg^{-1}	830	
	pinto beans, soybean, wheat no effect on germination	mg kg^{-1}	700	
	pinto beans, soybean, wheat no effect on radicle length	mg kg^{-1}	700	
	all six species no effect on shoot length, weight and root weight	mg kg^{-1}	720	
	radish, wheat no effect on emergence	mg kg^{-1}	100	
	lettuce 15% reduction in emergence	mg kg^{-1}	100	
	corn, wheat, ryegrass, tomato, cucumber 21 d NOEC (morphology)	mg kg^{-1}	914	
	L. terrestris 28 d NOEL (mortality)	mg kg^{-1}	1100	
	E. foetida 14 d NOEC	mg kg^{-1}	900-1100	
	Mallard duck 14 d LD50 and NOEL	mg kg^{-1}	>2150	
	Mallard duck 28 d NOEL (reproduction)	mg kg^{-1}	1000	
	Japanese quail 42 d dietary no effect on egg production, fertility etc	mg kg^{-1}	50	
	11 pathogenic + saprogenic fungi + 11 pathogenic bacteria, no effects except:			
	Trichophyton mentagrophytes development inhibited	mg l^{-1}	100	
	Candida albicans no growth	mg l^{-1}	100	
	Soil respiration		no effect	
doramectin	corn % germination NOEC	mg kg^{-1}	840	Boxall *et al.* 2002, Pfizer 1996
	cucumber % germination NOEC	mg kg^{-1}	840	
	ryegrass % germination NOEC	mg kg^{-1}	6.6	
	soy bean % germination NOEC	mg kg^{-1}	990	
	tomato % germination NOEC	mg kg^{-1}	840	
	wheat % germination NOEC	mg kg^{-1}	57	
	corn % root elongation NOEC	mg kg^{-1}	840	
	cucumber root elongation NOEC	mg kg^{-1}	840	
	ryegrass % root elongation NOEC	mg kg^{-1}	1.6	

Compound	Terrestrial toxicity (endpoint)	Terrestrial toxicity (units)	Terrestrial toxicity (value)	Source
	soy bean % root elongation NOEC	mg kg^{-1}	990	
	tomato % root elongation NOEC	mg kg^{-1}	840	
	wheat % root elongation NOEC	mg kg^{-1}	57	
	corn % seedling growth NOEC	mg kg^{-1}	980	
	cucumber seedling growth NOEC	mg kg^{-1}	53–130	
	ryegrass % seedling growth NOEC	mg kg^{-1}	<33	
	soy bean % seedling growth NOEC	mg kg^{-1}	47	
	tomato % seedling growth NOEC	mg kg^{-1}	47	
	wheat % seedling growth NOEC	mg kg^{-1}	47	
	Clostidium perfringens MIC	mg l^{-1}	40	
	Nostoc MIC	mg l^{-1}	60	
	Aspergillus flavus MIC	mg l^{-1}	600	
	Pseudomonas aeruginosa MIC	mg l^{-1}	800	
	Chaetomium globosum MIC	mg l^{-1}	800	
	E. foetida 28 d LC50	mg kg^{-1}	>1000	
	E. foetida 28 d NOEC (growth)	mg kg^{-1}	2	
	E. foetida 28 d LOEC (growth)	mg kg^{-1}	4	
	Haemotobia irritans LC90	mg kg^{-1} dung	3	
	O. gazella LC50	mg kg^{-1} dung	12.5	
	O. gazella LC90	mg kg^{-1} dung	38.2	
enrofloxacin	soybean, lettuce, ryegrass, wheat, tomato, cucumber NOEC germination	mg kg^{-1}	>882	Bayer 1996
	cucumber effect on root growth	mg kg^{-1}	0.27	
	cucumber effect on germination (soil)	mg kg^{-1}	9.1	
	cucumber effect on root growth (soil)	mg kg^{-1}	9.1	
	wheat effect on seedling growth NOEC	mg kg^{-1}	<0.13	
	wheat effect on seedling growth NOEC (soil)	mg kg^{-1}	4.7	
	Pseudomonas MIC	mg kg^{-1}	12.5	
	Arthrobacter MIC	mg kg^{-1}	12.5	
	Azobacter MIC	mg kg^{-1}	1.3	
	Anabaena MIC	mg kg^{-1}	12.5	
	Aspergillus MIC	mg kg^{-1}	>250	
	Penicillium MIC	mg kg^{-1}	>250	
	Trichoderma MIC	mg kg^{-1}	>250	
	Test on soil with *Arthrobacter* and *Azobacter* no inhibitory effect	mg kg^{-1}	500	

Compound	Terrestrial toxicity (endpoint)	Terrestrial toxicity (units)	Terrestrial toxicity (value)	Source
eprinomectin	bobwhite quail 14 d LD50	mg kg^{-1}	272	Boxall *et al.* 2002, Merck and Co. 1996
	bobwhite quail 14 d NOEC	mg kg^{-1}	<62.5	
	mallard 14 d LD50	mg kg^{-1}	24	
	mallard 14 d NOEC	mg kg^{-1}	<7.8	
	bobwhite (dietary) 8 d LC50	ppm	1813	
	bobwhite (dietary) 8 d NOEC	mg kg^{-1}	1000	
	mallard (dietary) 8 d LC50	ppm	447	
	mallard (dietary) 8d NOEC	mg kg^{-1}	<100	
	26 microbial species NOEC antimicrobial activity	mg kg^{-1}	1000	
	L. terrestris 28 d LC50	mg kg^{-1}	>951	
	L. terrestris 28 d NOEC (mortality)	mg kg^{-1}	295	
	L. terrestris 28 d NOEC (weight)	mg kg^{-1}	90.8	
	cucumber, lettuce, soybean, ryegrass, tomato, wheat NOEC germination	mg kg^{-1}	1300	
	cucumber, soybean NOEC root elongation	mg kg^{-1}	9.5	
	lettuce, ryegrass, tomato, wheat NOEC root elongation	mg kg^{-1}	8.5	
	cucumber, ryegrass, tomato, wheat NOEC shoot length and root weight	mg kg^{-1}	0.47	
	lettuce, soybean NOEC shoot length and root weight	mg kg^{-1}	6.5	
fenbendazole	Bacteria no effect concentration	mg kg^{-1}	100	Boxall *et al.* 2002, Hoechst Roussel 1995
	Protozoa no effect concentration	mg l^{-1}	100	
	Fungi no effect concentration	mg l^{-1}	100	
	E. Foetida 14 d LC50	mg kg^{-1}	1068	
	E. Foetida 14 d 35% reduction in weight	mg kg^{-1}	100	
	E. Foetida 14 d reduction in cocoon production	mg kg^{-1}	100	
	L. terrestris 28 d LC50	mg kg^{-1}	180	
	L. terrestris 28 d LOEC	mg kg^{-1}	120	
	L. terrestris 28 d NOEC	mg kg^{-1}	56	
	corn germination NOEC	mg kg^{-1}	970	
	cucumber germination NOEC	mg kg^{-1}	970	
	ryegrass germination NOEC	mg kg^{-1}	970	
	soybean germination NOEC	mg kg^{-1}	1000	
	tomato germination NOEC	mg kg^{-1}	1000	
	wheat germination NOEC	mg kg^{-1}	1000	

Compound	Terrestrial toxicity (endpoint)	Terrestrial toxicity (units)	Terrestrial toxicity (value)	Source
	corn seedling growth NOEC	mg kg^{-1}	1600	
	cucumber seedling growth NOEC	mg kg^{-1}	1600	
	ryegrass seedling growth NOEC	mg kg^{-1}	1600	
	soybean seedling growth NOEC	mg kg^{-1}	1600	
	tomato seedling growth NOEC	mg kg^{-1}	36	
	wheat seedling growth NOEC	mg kg^{-1}	1600	
	tomato seedling growth LOEC	mg kg^{-1}	64	
	corn root elongation NOEC	mg kg^{-1}	970	
	cucumber root elongation NOEC	mg kg^{-1}	970	
	ryegrass root elongation NOEC	mg kg^{-1}	970	
	soybean root elongation NOEC	mg kg^{-1}	1000	
	tomato root elongation NOEC	mg kg^{-1}	1000	
	wheat root elongation NOEC	mg kg^{-1}	1000	
	Onthophagus gazella 7 d LC50	mg kg^{-1}	>0.77	
	Onthophagus gazella 7 d NOEC	mg kg^{-1}	0.77	
florfenicol	*Aspergillus niger* MIC	mg l^{-1}	>1000	Schering Plough 1996
	Trichoderme viride MIC	mg l^{-1}	>1000	
	Clostridium perfringens MIC	mg l^{-1}	1	
	Bacillus subtilus MIC	mg l^{-1}	0.4	
	Nostoc MIC	mg l^{-1}	4	
ivermectin	Earthworms NOEC	mg kg^{-1}	12	Boxall *et al.*, 2002
	Eisenia foetida 28 d LC50	mg kg^{-1}	315	
	plants NOEC	mg kg^{-1}	0.56	
	N. cornicina behaviour	mg kg^{-1}	0.125	
	N. cornicina 47% mortality over 7 d (dung)	mg kg^{-1}	0.125	
	N. cornicina 77% mortality over 7 d (dung)	mg kg^{-1}	0.25	
	N. cornicina 87% mortality over 7 d (dung)	mg kg^{-1}	0.5	
	N. cornicina 100% mortality over 7 d (dung)	mg kg^{-1}	1	
	N. cornicina 7 d LC50	mg kg^{-1}	0.139	
	Scatophagia stercoraria (larvae) 24 h EC50	mg kg^{-1}	0.051	
	Scatophagia stercoraria (larvae) 48 h EC50	mg kg^{-1}	0.036	
	Scatophagia stercoraria (adults) developmental abnormalities	mg kg^{-1}	0.0005	
	Scatophagia stercoraria 50% reduction in emergence	mg kg^{-1}	0.001	
	Scatophagia stercoraria 50% reduction in pupation	mg kg^{-1}	0.015	
lincomycin	earthworms NOEC	mg kg^{-1}	1000	Boxall *et al.* 2002

Compound	Terrestrial toxicity (endpoint)	Terrestrial toxicity (units)	Terrestrial toxicity (value)	Source
	microbes MIC or NOEC	mg kg^{-1}	0.78	
monensin	Earthworm 14 d, 6 out of 15 animals dead	mg kg^{-1}	100	Elanco 1996
	Earthworm normal physical condition + no mortality	mg kg^{-1}	<22.5	
	14 plant species non phytotoxic	mg kg^{-1}	1–2	
	14 plant species – moderate to severe injury of several species	mg kg^{-1}	4–8	
morantel	Microbes MIC or NOEC	mg kg^{-1}	50	Boxall *et al.* 2002
moxidectin	bobwhite quail 21 d LD50	mg kg^{-1}	278	Fort Dodge 1997
	mallard duck 21 d LD50	mg kg^{-1}	365	
	chicken 14 d LD50	mg kg^{-1}	283	
	plant phytotoxicity NOEC	kg/ha	4	
	earthworm 28 d LC50	mg kg^{-1}	37.2	
	dung insects:			
	O. gazella - adult NOEC	mg kg^{-1}	>0.50	
	O. gazella - progeny EC50	mg kg^{-1}	2.5677	
	E. intermedius - adult NOEC	mg kg^{-1}	>0.50	
	E. intermedius - progeny EC50	mg kg^{-1}	0.4693	
	E. intermedius - progeny NOEC	mg kg^{-1}	>0.269	
	H. irritans exigua EC50	mg kg^{-1}	0.134	
	H. irritans exigua NOEC	mg kg^{-1}	0.064	
oxytetracycline	mallard duck 8 d LC50	ppm	>5620	Boxall *et al.* 2002
	northern bobwhite 8 d LC50	ppm	>5620	
	northern bobwhite 14 d LC50	ppm	>2000	
	F. fimetaria LC50	mg kg^{-1}	>5000	
	F. fimetaria EC50 reproduction	mg kg^{-1}	>5000	
	E. crypticus LC50	mg kg^{-1}	>5000	
	E. crypticus EC50 reproduction	mg kg^{-1}	2701	
	A. caliginosa LC50	mg kg^{-1}	>5000	
	A. caliginosa EC50 reproduction	mg kg^{-1}	4420	
	A. caliginosa EC50 growth	mg kg^{-1}	>5000	
	A. caliginosa EC50 hatchability	mg kg^{-1}	>5000	
	Phaseolus vulgaris LC100	mg kg^{-1}	160	
salinomycin	gram -ve bacteria and fungi no effect	mg l^{-1}	100	
sulfadiazine	*Lupinus albus* 1 d 13% reduction in root size	mg kg^{-1}	100	Boxall *et al.* 2002
tiamulin	microbes MIC or NOEC	mg kg^{-1}	500	Fermenta 1994
tilmicosin	corn, cucumber, soybean, wheat no effect on	ppm	100	

Compound	Terrestrial toxicity (endpoint)	Terrestrial toxicity (units)	Terrestrial toxicity (value)	Source
	germination			
	cucumber radicle length reduced by 45%	ppm	100	
	corn, soybean and wheat no effect on radicle length	ppm	100	
	corn, cucumber, ryegrass, soybean, tomato, wheat 21d NOEC seed growth (sand)	mg kg^{-1}	100	
	corn, ryegrass, soybean, tomato and wheat 21 d NOEC seed growth (sandy loam)	mg kg^{-1}	300	
	cucumber seed growth significantly affected (sandy loam)	mg kg^{-1}	100	
	earthworm 28 d NOEC	mg l^{-1}	918	
	bobwhite 5 d dietary LD50	mg kg^{-1}	>4820	
	mallards 5 d dietary LD50	mg kg^{-1}	>4710	
	range of gram +ve and -ve organisms MIC	mg kg^{-1}	0.024-50	
tylosin	bobwhite quail 5 d LD50 (dietary)	mg kg^{-1}	4820	Boxall *et al.* 2002
	mallard duck 5 d LD50 (dietary)	mg kg^{-1}	4710	
	earthworm 28 d LD50	mg kg^{-1}	918	
	C. globosum	mg kg^{-1}	>1000	
	A. flavus	mg kg^{-1}	>1000	
	C. acidvorans	mg kg^{-1}	250	
	A. chroococcum	mg kg^{-1}	5	
	F. fimetaria LC50	mg kg^{-1}	>5000	
	F. fimetaria EC50 reproduction	mg kg^{-1}	2520	
	E. crypticus LC50	mg kg^{-1}	3381	
	E. crypticus EC50 reproduction	mg kg^{-1}	3109	
	A. caliginosa LC50	mg kg^{-1}	>5000	
	A. caliginosa EC50 reproduction	mg kg^{-1}	4530	
	A. caliginosa EC50 growth	mg kg^{-1}	>5000	
	A. caliginosa EC50 hatchability	mg kg^{-1}	4823	

Appendix 7 Terrestrial ranking for the pasture treatments

Compound	Animal type	Treatment type
RCR = 0		
fenbendazole	sheep	liquid oral
moxidectin	sheep	injection
moxidectin	sheep	liquid oral
moxidectin	cattle	injection
moxidectin	cattle	pour on
oxytetracycline	pigs	injection
trimethoprim	cattle	bolus
trimethoprim	pigs	injection
RCR = 0.01		
cyromazine	sheep	pour on
doramectin	sheep	injection
doramectin	pigs	injection
doramectin	cattle	injection
eprinomectin	cattle	pour on
fenbendazole	pigs	feed pellets
fenbendazole	pigs	powder
fenbendazole	pigs	liquid oral
fenbendazole	horse	liquid oral
fenbendazole	cattle	bolus
fenbendazole	cattle	powder
fenbendazole	cattle	liquid oral
fenbendazole	cattle	feed pellets
ivermectin	sheep	injection
ivermectin	sheep	liquid oral
ivermectin	horse	paste
oxytetracycline	pigs	soluble
oxytetracycline	sheep	injection
oxytetracycline	cattle	injection
oxytetracycline	cattle	bolus
oxytetracycline	cattle	injection
oxytetracycline	cattle	soluble
oxytetracycline	sheep	injection
oxytetracycline	horse	topical
tiamulin	pigs	premix
tiamulin	pigs	injection
trimethoprim	horse	paste
trimethoprim	sheep	injection
trimethoprim	cattle	injection
trimethoprim	pigs	suspension
trimethoprim	horse	granules
RCR = 0.1		
apramycin	sheep	oral
apramycin	pigs	injection
apramycin	pigs	oral
apramycin	pigs	premix
apramycin	pigs	powder
doramectin	cattle	pour on

Compound	Animal type	Treatment type
ivermectin	pigs	injection
ivermectin	cattle	injection
ivermectin	cattle	pour on
oxytetracycline	cattle	topical
oxytetracycline	pigs	feed
sulfadiazine	cattle	bolus
trimethoprim	pigs	powder
tylosin	cattle	injection
tylosin	sheep	injection
tylosin	pigs	injection
RCR = 1.0		
apramycin	cattle	powder
enrofloxacin	pigs	piglet dose
enrofloxacin	pigs	injection
enrofloxacin	cattle	oral
enrofloxacin	cattle	injection
florfenicol	cattle	injection
lincomycin	pigs	soluble
lincomycin	pigs	premix
sulfadiazine	pigs	injection
sulfadiazine	pigs	suspension
sulfadiazine	sheep	injection
sulfadiazine	horse	injection
sulfadiazine	horse	granules
sulfadiazine	cattle	injection
tilmicosin	sheep	injection
tilmicosin	cattle	injection
tilmicosin	pigs	premix
tylosin	cattle	soluble
tylosin	pigs	soluble
tylosin	pigs	feed
Not ranked		
amoxicillin	cattle	bolus
amoxicillin	sheep	injection
amoxicillin	pigs	injection
amoxicillin	pigs	suspension
amoxicillin	cattle	injection
amoxicillin	pigs	feed
chlorhexidine	cattle	teat dip
levamisole	cattle	injection
levamisole	cattle	liquid oral
levamisole	cattle	pour on
levamisole	sheep	injection
levamisole	sheep	liquid oral
morantel	cattle	bolus
morantel	sheep	liquid oral
nitroxynil	cattle	injection
nitroxynil	sheep	injection
poloxalene	cattle	injection
poloxalene	cattle	premix
procaine penicillin		
triclabendazole	cattle	liquid oral
triclabendazole	sheep	liquid oral

Appendix 8 Aquatic ranking for pasture treatment scenarios

Compound	Animal type	Treatment type
RCR = 0		
amoxicillin	cattle	bolus
amoxicillin	sheep	injection
amoxicillin	pigs	injection
amoxicillin	pigs	suspension
cyromazine	sheep	pour on
enrofloxacin	pigs	piglet dose
enrofloxacin	pigs	injection
enrofloxacin	cattle	oral
enrofloxacin	cattle	injection
lincomycin	pigs	soluble
oxytetracycline	pigs	injection
oxytetracycline	pigs	soluble
tilmicosin	sheep	injection
tilmicosin	cattle	injection
trimethoprim	cattle	bolus
trimethoprim	pigs	injection
trimethoprim	horse	paste
RCR = 0.1		
amoxicillin	cattle	injection
amoxicillin	pigs	feed
florfenicol	cattle	injection
lincomycin	pigs	premix
oxytetracycline	sheep	injection
oxytetracycline	cattle	soluble
oxytetracycline	cattle	injection
oxytetracycline	cattle	bolus
oxytetracycline	cattle	injection
oxytetracycline	sheep	injection
oxytetracycline	horse	topical
oxytetracycline	cattle	topical
sulfadiazine	cattle	bolus
sulfadiazine	sheep	injection
sulfadiazine	pigs	injection
sulfadiazine	horse	injection
trimethoprim	sheep	injection
trimethoprim	cattle	injection
trimethoprim	pigs	suspension
trimethoprim	horse	granules
tylosin	pigs	injection
tylosin	cattle	injection
RCR = 1.0		
apramycin	sheep	oral
apramycin	pigs	injection
apramycin	pigs	oral
apramycin	pigs	premix
apramycin	pigs	powder
apramycin	cattle	powder

Compound	Animal type	Treatment type
doramectin	sheep	injection
doramectin	pigs	injection
doramectin	cattle	injection
doramectin	cattle	pour on
eprinomectin	cattle	pour on
fenbendazole	sheep	liquid oral
fenbendazole	pigs	feed pellets
fenbendazole	pigs	powder
fenbendazole	pigs	liquid oral
fenbendazole	horse	liquid oral
fenbendazole	cattle	powder
fenbendazole	cattle	liquid oral
fenbendazole	cattle	feed pellets
fenbendazole	cattle	bolus
ivermectin	sheep	injection
ivermectin	sheep	liquid oral
ivermectin	horse	paste
ivermectin	pigs	injection
ivermectin	cattle	injection
ivermectin	cattle	pour on
moxidectin	sheep	injection
moxidectin	sheep	liquid oral
moxidectin	cattle	injection
moxidectin	cattle	pour on
oxytetracycline	pigs	feed
sulfadiazine	pigs	suspension
sulfadiazine	horse	granules
sulfadiazine	cattle	injection
tiamulin	pigs	premix
tiamulin	pigs	injection
tilmicosin	pigs	premix
trimethoprim	pigs	powder
tylosin	sheep	injection
tylosin	pigs	soluble
tylosin	cattle	soluble
tylosin	pigs	feed
Not ranked		
chlorhexidine	cattle	teat dip
levamisole	cattle	injection
levamisole	cattle	liquid oral
levamisole	cattle	pour on
levamisole	sheep	injection
levamisole	sheep	liquid oral
morantel	cattle	bolus
morantel	sheep	liquid oral
nitroxynil	cattle	injection
nitroxynil	sheep	injection
poloxalene	cattle	injection
poloxalene	cattle	premix
procaine penicillin		
triclabendazole	cattle	liquid oral
triclabendazole	sheep	liquid oral

Appendix 9 Groundwater ranking for pasture scenarios

Compound	Animal type	Treatment type
PEC = 0 μg l^{-1}		
amoxicillin	cattle	bolus
amoxicillin	sheep	injection
amoxicillin	pigs	injection
amoxicillin	pigs	suspension
amoxicillin	cattle	injection
amoxicillin	pigs	feed
apramycin	sheep	oral
apramycin	pigs	injection
apramycin	pigs	oral
cyromazine	sheep	pour on
doramectin	sheep	injection
doramectin	pigs	injection
doramectin	cattle	injection
doramectin	cattle	pour on
enrofloxacin	pigs	piglet dose
enrofloxacin	pigs	injection
enrofloxacin	cattle	oral
enrofloxacin	cattle	injection
eprinomectin	cattle	pour on
fenbendazole	sheep	liquid oral
fenbendazole	pigs	feed pellets
fenbendazole	pigs	powder
fenbendazole	pigs	liquid oral
fenbendazole	cattle	bolus
fenbendazole	horse	liquid oral
fenbendazole	cattle	powder
fenbendazole	cattle	liquid oral
fenbendazole	cattle	feed pellets
ivermectin	sheep	injection
ivermectin	sheep	liquid oral
ivermectin	horse	paste
ivermectin	pigs	injection
ivermectin	cattle	injection
ivermectin	cattle	pour on
levamisole	sheep	injection
levamisole	sheep	liquid oral
levamisole	cattle	injection
levamisole	cattle	liquid oral
levamisole	cattle	pour on
moxidectin	sheep	injection
moxidectin	sheep	liquid oral
moxidectin	cattle	injection
moxidectin	cattle	pour on
oxytetracycline	pigs	injection
oxytetracycline	pigs	soluble
oxytetracycline	sheep	injection
oxytetracycline	cattle	soluble

Compound	Animal type	Treatment type
oxytetracycline	cattle	injection
oxytetracycline	cattle	bolus
oxytetracycline	cattle	injection
oxytetracycline	sheep	injection
oxytetracycline	horse	topical
oxytetracycline	cattle	topical
oxytetracycline	pigs	feed
streptomycin	sheep	injection
sulfadiazine	cattle	bolus
sulfadiazine	sheep	injection
sulfadiazine	pigs	injection
sulfadiazine	horse	injection
sulfadiazine	pigs	suspension
sulfadiazine	horse	granules
sulfadiazine	cattle	injection
tilmicosin	sheep	injection
tilmicosin	cattle	injection
triclabendazole	cattle	liquid oral
triclabendazole	sheep	liquid oral
trimethoprim	cattle	bolus
trimethoprim	pigs	injection
trimethoprim	horse	paste
trimethoprim	sheep	injection
trimethoprim	cattle	injection
trimethoprim	pigs	suspension
trimethoprim	horse	granules
trimethoprim	pigs	powder
tylosin	pigs	injection
tylosin	cattle	injection
tylosin	sheep	injection
tylosin	pigs	soluble
Groundwater PEC = 0.1 μg/l		
apramycin	pigs	premix
apramycin	pigs	powder
apramycin	cattle	powder
florfenicol	cattle	injection
lincomycin	pigs	soluble
lincomycin	pigs	premix
streptomycin	horse	injection
streptomycin	cattle	injection
tilmicosin	pigs	premix
tylosin	cattle	soluble
tylosin	pigs	feed
Not ranked		
chlorhexidine	cattle	teat dip
morantel	cattle	bolus
morantel	sheep	liquid oral
nitroxynil	cattle	injection
nitroxynil	sheep	injection
poloxalene	cattle	injection
poloxalene	cattle	premix
procaine penicillin		
tiamulin	pigs	premix
tiamulin	pigs	injection

Appendix 10 Terrestrial ranking for intensive treatment scenarios

Compound	Animal type	Treatment type
RCR = 0		
moxidectin	cattle	injection
moxidectin	cattle	pour on
triclabendazole	cattle	liquid oral
tylosin	poultry	soluble
tylosin	cattle	injection
tylosin	pigs	soluble
tylosin	cattle	soluble
tylosin	pigs	injection
tylosin	pigs	feed additive
RCR = 0.01		
diclazuril	poultry	premix
eprinomectin	cattle	pour on
ivermectin	cattle	injection
RCR = 0.1		
doramectin	cattle	injection
doramectin	cattle	pour on
doramectin	pigs	injection
fenbendazole	cattle	liquid oral
fenbendazole	cattle	feed pellets
fenbendazole	cattle	powder
fenbendazole	pigs	feed pellets
fenbendazole	pigs	powder
fenbendazole	cattle	bolus
fenbendazole	pigs	liquid oral
ivermectin	cattle	pour on
ivermectin	pigs	injection
ivermectin	pigs	premix
lincomycin	pigs	soluble
oxytetracycline	cattle	injection
oxytetracycline	cattle	soluble
oxytetracycline	cattle	bolus
oxytetracycline	poultry	soluble
tiamulin	pigs	premix
tiamulin	poultry	soluble
tiamulin	pigs	injection
trimethoprim	cattle	injection
trimethoprim	pigs	injection
trimethoprim	pigs	suspension
RCR = 1.0		
enrofloxacin	pigs	piglet doser
enrofloxacin	cattle	oral
enrofloxacin	cattle	injection
enrofloxacin	pigs	injection
enrofloxacin	poultry	soluble
florfenicol	cattle	injection
lincomycin	pigs	premix
monensin	cattle	premix

monensin	poultry	premix
oxytetracycline	cattle	topical
oxytetracycline	pigs	injection
oxytetracycline	pigs	topical
oxytetracycline	pigs	soluble
oxytetracycline	pigs	feed additive
sulfadiazine	cattle	bolus
sulfadiazine	cattle	injection
sulfadiazine	pigs	injection
sulfadiazine	pigs	suspension
sulfadiazine	poultry	soluble
sulfadiazine	pigs	powder
sulfadiazine	poultry	powder
tilmicosin	cattle	injection
tilmicosin	poultry	soluble
tilmicosin	pigs	premix
trimethoprim	poultry	powder
trimethoprim	pigs	powder
trimethoprim	poultry	soluble
trimethoprim	cattle	bolus
Not ranked		
amoxicillin	cattle	injection
amoxicillin	pigs	injection
amoxicillin	pigs	suspension
amoxicillin	poultry	powder
amoxicillin	pigs	feed additive
amoxicillin	cattle	bolus
amoxicillin	cattle	powder
amprolium	poultry	premix
chlorhexidine	cattle	teat dip
clavulanic acid	cattle	injection
clavulanic acid	cattle	injection
clavulanic acid	pigs	injection
decoquinate	cattle	premix
levamisole	cattle	injection
levamisole	cattle	liquid oral
levamisole	cattle	pour on
morantel	cattle	bolus
morantel	cattle	liquid oral
nicarbazin	poultry	feed additive
nitroxynil	cattle	injection
poloxalene	cattle	drench
poloxalene	cattle	premix
procaine penicillin		
salinomycin	poultry	feed additive

Appendix 11 Aquatic ranking for intensive treatment scenarios

Compound	Animal type	Treatment type
RCR = 0		
amoxicillin	cattle	injection
amoxicillin	pigs	injection
amoxicillin	pigs	suspension
amoxicillin	poultry	powder
amoxicillin	pigs	feed additive
amoxicillin	cattle	bolus
diclazuril	poultry	premix
enrofloxacin	pigs	piglet doser
enrofloxacin	cattle	oral
enrofloxacin	cattle	injection
enrofloxacin	pigs	injection
enrofloxacin	poultry	soluble
monensin	cattle	premix
monensin	poultry	premix
moxidectin	cattle	injection
moxidectin	cattle	pour on
oxytetracycline	cattle	injection
oxytetracycline	cattle	soluble
oxytetracycline	cattle	bolus
oxytetracycline	poultry	soluble
oxytetracycline	cattle	topical
oxytetracycline	pigs	topical
oxytetracycline	pigs	injection
oxytetracycline	pigs	soluble
oxytetracycline	pigs	feed additive
tilmicosin	cattle	injection
tilmicosin	poultry	soluble
tilmicosin	pigs	premix
triclabendazole	cattle	liquid oral
trimethoprim	cattle	injection
trimethoprim	pigs	injection
trimethoprim	pigs	suspension
tylosin	poultry	soluble
tylosin	cattle	injection
tylosin	pigs	soluble
tylosin	cattle	soluble
tylosin	pigs	injection
tylosin	pigs	feed additive
RCR = 0.01		
doramectin	cattle	injection
lincomycin	pigs	soluble
trimethoprim	poultry	powder
trimethoprim	pigs	powder
trimethoprim	poultry	soluble
RCR = 0.1		
doramectin	cattle	pour on
doramectin	pigs	injection

eprinomectin	cattle	pour on
fenbendazole	cattle	liquid oral
fenbendazole	cattle	feed pellets
fenbendazole	cattle	powder
fenbendazole	pigs	feed pellets
fenbendazole	pigs	powder
fenbendazole	cattle	bolus
fenbendazole	pigs	liquid oral
ivermectin	cattle	injection
sulfadiazine	cattle	bolus
trimethoprim	cattle	bolus
RCR = 1.0		
florfenicol	cattle	injection
ivermectin	cattle	pour on
ivermectin	pigs	injection
ivermectin	pigs	premix
ivermectin	cattle	bolus
lincomycin	pigs	premix
sulfadiazine	cattle	injection
sulfadiazine	pigs	injection
sulfadiazine	pigs	suspension
sulfadiazine	poultry	soluble
sulfadiazine	pigs	powder
sulfadiazine	poultry	powder
tiamulin	pigs	premix
tiamulin	poultry	soluble
tiamulin	pigs	injection
Not ranked		
amoxicillin	cattle	powder
amprolium	poultry	premix
chlorhexidine	cattle	teat dip
clavulanic acid	cattle	injection
clavulanic acid	cattle	injection
clavulanic acid	pigs	injection
decoquinate	cattle	premix
levamisole	cattle	injection
levamisole	cattle	liquid oral
levamisole	cattle	pour on
morantel	cattle	bolus
morantel	cattle	liquid oral
nicarbazin	poultry	feed additive
nitroxynil	cattle	injection
poloxalene	cattle	drench
poloxalene	cattle	premix
procaine penicillin		
salinomycin	poultry	feed additive

Appendix 12 Groundwater ranking for intensive treatment scenarios

Compound	Animal type	Treatment type
PEC = 0 μg l^{-1}		
amoxicillin	cattle	injection
amoxicillin	pigs	injection
amoxicillin	pigs	suspension
amoxicillin	poultry	powder
amoxicillin	pigs	feed additive
amoxicillin	cattle	bolus
chlorhexidine	cattle	teat dip
diclazuril	poultry	premix
doramectin	cattle	injection
doramectin	cattle	pour on
doramectin	pigs	injection
enrofloxacin	pigs	piglet doser
enrofloxacin	cattle	oral
enrofloxacin	cattle	injection
enrofloxacin	pigs	injection
enrofloxacin	poultry	soluble
eprinomectin	cattle	pour on
fenbendazole	cattle	liquid oral
fenbendazole	cattle	feed pellets
fenbendazole	cattle	powder
fenbendazole	pigs	feed pellets
fenbendazole	pigs	powder
fenbendazole	cattle	bolus
fenbendazole	pigs	liquid oral
ivermectin	cattle	injection
ivermectin	cattle	pour on
ivermectin	pigs	injection
ivermectin	pigs	premix
ivermectin	cattle	bolus
levamisole	cattle	injection
levamisole	cattle	liquid oral
levamisole	cattle	pour on
monensin	cattle	premix
monensin	poultry	premix
morantel	cattle	bolus
morantel	cattle	liquid oral
moxidectin	cattle	injection
moxidectin	cattle	pour on
oxytetracycline	cattle	injection
oxytetracycline	cattle	soluble
oxytetracycline	cattle	bolus
oxytetracycline	poultry	soluble
oxytetracycline	cattle	topical
oxytetracycline	pigs	topical
oxytetracycline	pigs	injection
oxytetracycline	pigs	soluble
oxytetracycline	pigs	feed additive

Compound	Animal type	Treatment type
tilmicosin	cattle	injection
tilmicosin	poultry	soluble
tilmicosin	pigs	premix
triclabendazole	cattle	liquid oral
trimethoprim	cattle	injection
trimethoprim	pigs	injection
trimethoprim	pigs	suspension
trimethoprim	poultry	powder
trimethoprim	pigs	powder
trimethoprim	poultry	soluble
trimethoprim	cattle	bolus
tylosin	poultry	soluble
tylosin	cattle	injection
tylosin	pigs	soluble
tylosin	cattle	soluble
tylosin	pigs	injection
tylosin	pigs	feed additive
Groundwater concentration = 0.1 μg/l		
florfenicol	cattle	injection
lincomycin	pigs	soluble
lincomycin	pigs	premix
sulfadiazine	cattle	bolus
sulfadiazine	cattle	injection
sulfadiazine	pigs	injection
sulfadiazine	pigs	suspension
sulfadiazine	poultry	soluble
sulfadiazine	pigs	powder
sulfadiazine	poultry	powder
Not ranked		
amoxicillin	cattle	powder
amprolium	poultry	premix
clavulanic acid	cattle	injection
clavulanic acid	cattle	bolus
clavulanic acid	pigs	injection
decoquinate	cattle	premix
nicarbazin	poultry	feed additive
nitroxynil	cattle	injection
poloxalene	cattle	drench
poloxalene	cattle	premix
procaine penicillin		
salinomycin	poultry	feed additive
tiamulin	pigs	premix
tiamulin	poultry	soluble
tiamulin	pigs	injection

Appendix 13 Soil characteristics

	Indoor pigs	Outdoor pigs	Poultry
Dry matter content (%)	97.3	99.2	98.5
Water content (%)	2.8	0.8	1.5
600 μm to 2 mm	2.97	2.67	8.64
212–600 μm	18.22	67.91	21.51
106–212 μm	8.05	11.32	20.31
63–106 μm	2.80	3.53	11.47
2–63 μm	21.20	8.01	18.65
<2 μm	46.77	6.56	19.42
pH in water (2 h)	6.8	7.3	7.3
pH in water (24 h)	6.8	7.2	7.3
pH in KCl (2 h)	5.8	6.6	6.7
pH in KCl (24 h)	5.9	6.6	6.7
CEC	16.8	8.0	15.3
Organic carbon (%)	2.6	1.5	2.0

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