8-1-2003

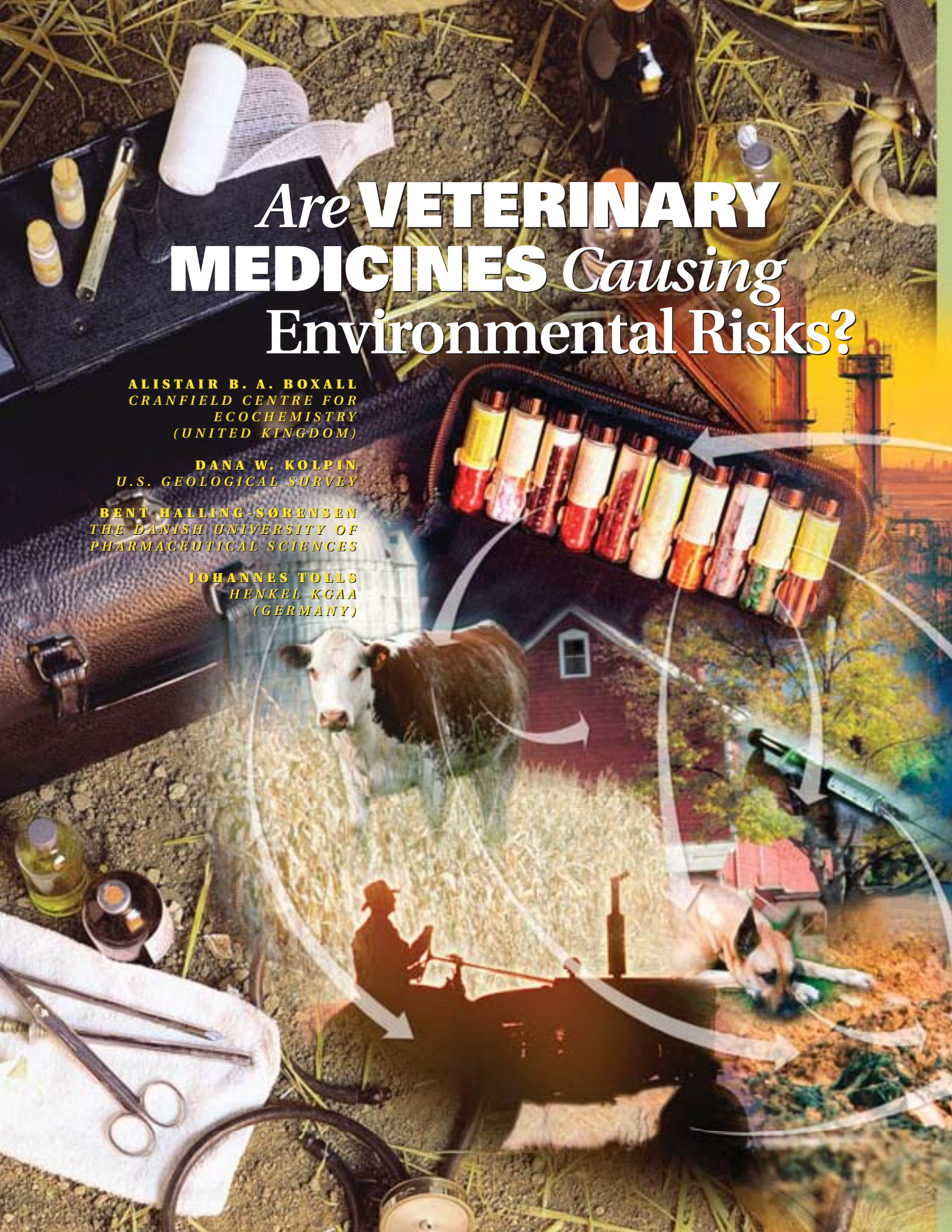
Are Veterinary Medicines Causing Environmental Risks?

Alistair Boxall
Cranfield Centre for Ecochemistry, United Kingdom

Dana Kolpin
USGS

Bent Holling-Sorensen
The Danish University of Pharmaceutical Sciences

Johannes Tolls
Henkel KCAA, Germany



Are VETERINARY MEDICINES *Causing* Environmental Risks?

ALISTAIR B. A. BOXALL
CRANFIELD CENTRE FOR ECOCHEMISTRY (UNITED KINGDOM)

DANA W. KOLPIN
U.S. GEOLOGICAL SURVEY

BENT HALLING-SØRENSEN
THE DANISH UNIVERSITY OF PHARMACEUTICAL SCIENCES

JOHANNES TOLLS
HENKEL KGAA (GERMANY)

Too little is known about the effects of these compounds, their metabolites, and degradation products.

Recently, low levels of veterinary medicines have been detected worldwide in soils, surface waters, and groundwaters (*1, 2*). Although the impacts of selected compounds—most notably anthelmintics and selected antibacterial compounds—have been extensively investigated (*3, 4*), many other substances found in the environment are less publicly well understood. As a result, researchers have raised questions about the impact of veterinary medicines on organisms in the environment and on human health. Several key questions will be addressed in this article. What other veterinary medicines might be in the environment, and should we be concerned about these? How do these substances behave in the environment, and do they differ from other chemical classes (e.g., pesticides)? What are the effects of long-term, low-level exposure to these medicines? Do their degradation products present environmental risks? What subtle human and environmental effects may be elicited by these drugs? Do medicines in the environment play a role in antibacterial resistance? How do these substances interact in the environment with other veterinary medicines and other contaminants?

Environmental assessments of veterinary medicines have been required by the U.S. Food and Drug Administration (FDA) since 1980 and in the European Union since 1997. During these assessments, data are generated on the effects of the veterinary medicine on fish, daphnids, algae, microbes, earthworms, plants, and dung invertebrates (*5, 6*). As the results of the studies performed during these assessments are becoming increasingly accessible—for example, many of the environmental assessments are now posted on the U.S. FDA's website (*7*)—and as numerous publications in this general area emerge, a wealth of information has become accessible on the environmental fate and effects of veterinary medicines.

In this article, we use the newly available data to begin to address the major questions and concerns about veterinary medicines in the environment. We also identify major gaps in the current knowledge and future research needs, hoping that this feature will encourage readers to become involved in this topical and expanding area. We will not address how human pharmaceuticals impact the environment; several recent reviews provide detailed information on human medicines (*8, 9*).

What substances are likely to enter the environment and how?

Veterinary medicines are widely used to treat disease and protect the health of animals. Some drugs are considered feed additives, often improving and thereby allowing animals to be brought to market faster and at lower cost. Livestock farmers supplement their animal feed with a wide range of compounds from a number of therapeutic classes, including antimicrobials, antiprotozoals, ecto- and endo-parasiticides, and hormones (see Table 1). Many of the substances, such as cypermethrin, diazinon, and oxytetracycline, are used as pesticides or human medicines.

Obtaining information on the usage of individual veterinary medicines is difficult, which makes the design of monitoring and experimental studies problematic. However, limited data on the sale and usage of the different chemical classes in countries such as the United Kingdom, Denmark, Germany, and The Netherlands are available in the public domain (*4, 10–12*). Detailed data from the United Kingdom, The Netherlands, and Denmark indicate that antimicro-

TABLE 1

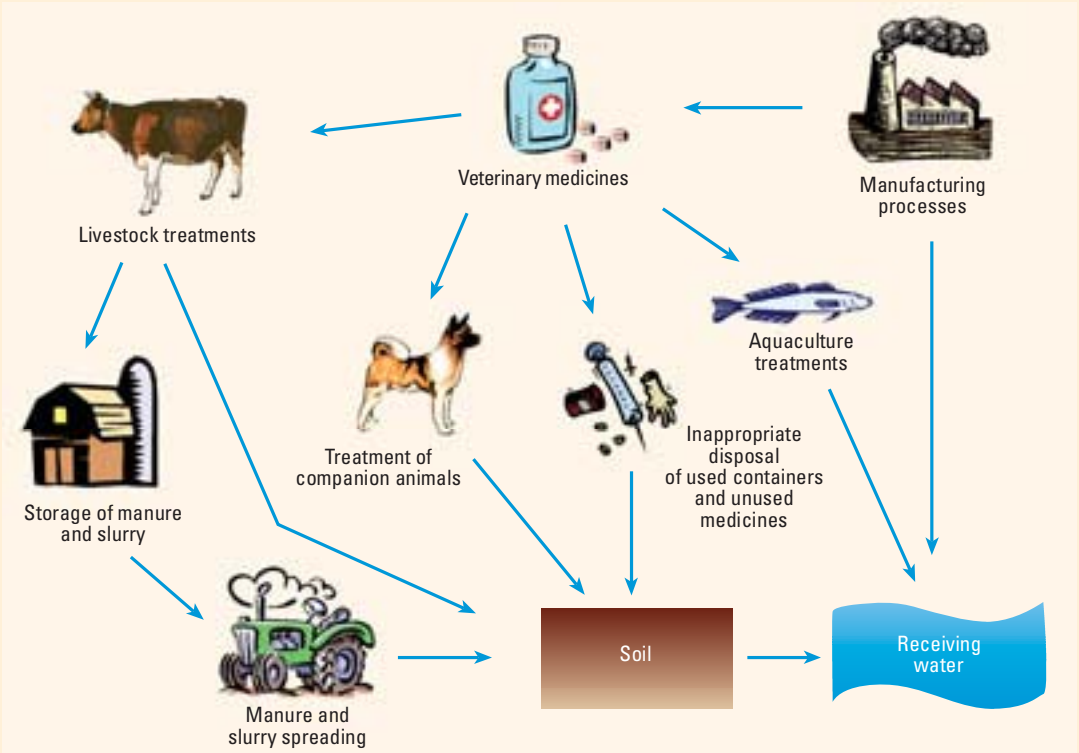
Major usage veterinary medicines based on data obtained for the United Kingdom and The Netherlands

Groups	What are they?	Treatment details	Examples
Antimicrobials	Substances that kill microorganisms or suppress their multiplication or growth	Treatment and prevention of bacterial diseases	amoxicillin, dihydrostreptomycin, enrofloxacin, lincomycin, oxytetracylcine, sulfadiazine, tylosin
Endectocides	Antiparasitic agents used to control internal and external parasites	Control of gastrointestinal worms, liver flukes, and lung worms	ivermectin, pyrantel, triclabendazole
Coccidiostats and antiprotozoals	Chemical agents effective against the control of infections of the intestinal tract caused by single-cell parasites; used in all areas of farming, especially poultry	Prevention of coccidiosis and swine dysentery	amprolium, clopidol, dimetridazole, narasin, nicarbazin
Antifungals	Agents that kill or control fungi	Treatment of fungal and yeast infections	chlorhexidine, griseofulvin, miconazole
Aquaculture treatments	Used in the propagation and rearing of aquatic species in controlled or selected environments	Treatment of sea lice infestations and funrunculosis	amoxicillin, azamethiphos, cypermethrin, emamectin, florfenicol, hydrogen peroxide, oxolinic acid, oxytetracycline
Hormones	Active regulatory chemicals that signal the coordination of cellular functions	Induction of ovulatory oestrus, suppression of oestrus, systemic progesterone therapy	altrenogest, estradiol benzoate, ethinyl estradiol, methyltestosterone, melatonin, progesterone
Growth promoters	Used to promote the growth of food-producing animals	Increase food digestion	flavophospholipol, monensin, salinomycin
Anaesthetics	Used to anaesthetize animals		halothane, isoflurane, lidocaine/lignocaine, procaine
Euthanasia products	Used to kill sick animals		pentobarbitone sodium
Tranquilizers	Used to sedate animals		phenobarbitone
NSAIDS	Nonsteroidal anti-inflammatory agents that work by inhibiting the production of prostaglandins		phenyl butazone
Enteric bloat preparations	Used to treat bloat, mainly in cattle		dimethicones, ploxalene

FIGURE 1

Pathways into the environment for veterinary medicines

Veterinary medicines can take several routes to enter water and soil.



bial substances are sold in the highest amounts followed by coccidiostats, sheep dip chemicals, growth promoters, endoparasitic wormers, antifungals, anti-inflammatory preparations, and enteric preparations (Table 1). Several other groups of chemicals may also be potentially important because of their heavy usage, including antiseptics, steroids and other hormones, diuretics, cardiovascular and respiratory treatments, and immunological products.

In the United States, sales of animal health products totaled $3.3 billion in 1996. Of these, dosage-form medicines and other pharmaceutical preparations used in disease prevention and treatment programs for both pets and farm animals made up $2.3 billion; feed additives to control or prevent disease, enhance growth, or improve feed efficiency accounted for $540 million; and biologicals (vaccines, bacterins, and antitoxins used to immunize livestock and pets) grossed $466 million (*13*). Estimates of antibacterial use in U.S. aquaculture alone ranges from 92,500 to 196,400 kg annually (*14*). Values for the total general use of these medicines is more uncertain. One study estimates that 8.5 million kg of antibacterials are used annually in the United States for agricultural purposes (*15*), whereas another estimates that nontherapeutic uses of antibacterials for livestock production alone account for 11.2 million kg annually (*16*).

Figure 1 shows that veterinary medicines can enter the environment via different pathways, including emissions during the manufacture, formulation, and treatment processes, and as a result of the disposal of unused medicines and their containers. How the drug is emitted during the treatment process will depend on whether the animal received the treatment topically, in feed, or as an injection or bolus, and on the methods of animal husbandry. The most important routes of entry into the environment are likely the direct discharge of aquaculture products, the excretion of substances in urine and feces of livestock animals, and the washoff of topical treatments from livestock animals. Contributions from the manufacturing process are likely low in the United States and European Union, where manufacture and formulation are subject to tight regulatory controls.

Although recent studies suggest that veterinary medicines may enter the environment as aerosols and dusts, the significance of these releases into the atmosphere is unknown (*17*). Similarly, the impacts of emissions from treating pets and disposing of unused or expired products and waste containers cannot be established. However, researchers consider emissions via these routes less relevant than emissions to soils and surface waters from aquaculture and intensive livestock treatments (*18*).

Moreover, substances absorbed by an animal can be metabolized. The degree of metabolism will depend on the type of substance, the species treated, and the age and condition of the treated animal. This type of information can be obtained from the phar-

macokinetics literature for veterinary medicines. If the compound is not metabolized, it will be excreted unchanged. Because of the hydrolysis of certain compounds such as sulfonamides (*19*) or the photolysis of the parent compound, such as what occurs with tetracyclines (*20*), abiotic degradation products can end up in the urine. Consequently, urine and feces from a treated animal may contain a mixture of the parent compound and transformation products (*18*).

Veterinary medicines that have a high potential of entering the environment

Stars indictate compounds that have been monitored and detected (*18*).

amitraz	enrofloxacin	oxolinic acid*
amoxicillin	fenbendazole	oxytetracycline*
amprolium	flavomycin	phosmet
antiseptics	flavophospholipol	piperonyl butoxide
baquiloprim	florfenicol	poloxalene
cephalexin	flumethrin	procaine benzylpenicillin
chlortetracycline*	immunological products	procaine penicillin
clavulanic acid	ivermectin*	robenidine hydrochloride
clindamycin	lasalocid sodium	salinomycin sodium
clopidol	levamisole	sarafloxacin*
cypermethrin*	lido/ligocaine HCL	sulphadiazine
cyromazine	lincomycin*	tetracycline*
decoquinate	maduramicin	tiamulin
deltamethrin	monensin	tilmicosin
diazinon*	morantel	toltrazuril
diclazuril	neomycin	triclabendazole
dihydrostreptomycin	nicarbazin	trimethoprim*
dimethicone	nitroxynil	tylosin*
emamectin benzoate*		

Source: Data from Ref. 10.

In a recent prioritization exercise, information on amounts, pathways to the environment, and metabolism of veterinary medicines used in the United Kingdom helped identify veterinary medicines that are likely to occur in the environment (*10*). On the basis of this information, 56 substances or groups of substances that may be released to the environment in significant amounts were identified (see the box above). Studies show that the monitored compounds on the list do indeed occur in surface waters or soils (*2, 3, 21*). However, no one has yet looked for many of the other substances (*18*).

How do they behave?

Once released into the environment, veterinary medicines and their corresponding degradation products will be transported and distributed to air, water, soil, or sediment on the basis of factors and processes including physicochemical properties of the substance; extent of degradation in manure, slurry, soil, or water; propensity to partition to soil and sediment; and the characteristics of the receiving environment.

For animals at pasture or in aquaculture, the medicines may be excreted directly to soil or water, respectively. However, on livestock farms that house many animals, large quantities of manure or slurry are produced. Typically, this manure is stored for varying lengths of time before it is applied to land as fertilizer. During this storage period, veterinary medicines and their degradation products could potentially degrade further. Veterinary medicines can persist in manure for days (e.g., tylosin in pig slurry, penicillin in poultry manure, nicarbazin in poultry manure) to months (e.g., ivermectin, chlortetracycline, amprolium) (*22–24*). Degradation rates can also vary across manure types; for example, sulfachloropyridazine has been shown to rapidly degrade in broiler feces but persist in laying hen feces (*25*). In addition, metabolites may revert to the active parent compound in the manure (*26*).

Once a compound is released to the environment, key chemical properties—such as water solubility, pH of the matrix, volatility, and sorption potential—will influence its behavior. Sorption coefficients (K_d) for veterinary medicines to soils and sediments range from 0.2 (chloramphenicol in marine sediment) to 5610 (enrofloxacin in soil) L/kg. K_d values vary considerably for a given compound in different soils (*25*). Unlike many pesticides and industrial chemicals, these variations cannot be explained by differences in soil organic carbon content (*26*). Moreover, unlike many other groups of organic compounds, prediction of organic-carbon normalized sorption coefficients (K_{oc}s) from the octanol–water partition coefficient (K_{ow}) leads to significant underestimation of K_{oc} values (*27*). Mechanisms other than hydrophobic partitioning, such as cation exchange, cation bridging at clay surfaces, surface complexation, and hydrogen bonding, may play a role in the sorption of veterinary medicines to soils and sediments (*28*). Therefore, the observed sorption of selected veterinary medicines may depend heavily on pH and ionic strength (*29*).

Veterinary medicines may degrade biotically or abiotically in soils and water. Generally, these processes will reduce the potency of the veterinary medicines; however, some degradation products have similar toxicity to their parent compound (*30*). Degradation rates vary significantly across chemicals. In soils, for example, diazinon, emamectin, olaquindox, and tylosin rapidly degrade (*31–33*); ivermectin, ceftiofur, and metronidazole are moderately persistent (*31, 34*); and sarafloxacin is highly persistent (*35*). Degradation may be affected by environmental conditions, such as temperature, soil type, and pH. For example, the degradation half-life for ivermectin under winter conditions is more than 6 times greater than during summer conditions, and the compound degraded faster in a sandy soil than in a sandy loam soil (*34, 36*). The presence of manure or slurry in soils may increase the degradation rates of veterinary medicines, although recent studies have shown that this may not be the case (*31*).

Recent studies have also assessed the major routes of transport for veterinary medicines in the environment (*37*). Nonsorptive medicines, such as sulfonamides, appear to be quickly transported to surface waters, whereas the transport of highly sorptive substances appears to be much slower, with concentrations measured in drainage outfalls many months after application.

What are their effects?

Data are available on the toxicity of many veterinary medicines to a range of organisms. That is because during the risk assessment process, data are typically needed on the toxicity of these substances to fish, daphnids, algae, microbes, earthworms, plants, and sometimes dung invertebrates.

Data on acute aquatic toxicity of commonly used veterinary medicines are publicly available for daphnids but are more limited for fish and algae (*18*). Daphnids and fish appear to be sensitive to the macrocyclic lactones (48-hour 50% immobilization concentrations [48 h EC_{50}] values range from 0.000025 for ivermectin to 0.00045 mg/L for eprinomectin); organophosphorus compounds (48 h EC_{50} for diazinon range from 0.0009 to 0.0018 mg/L); and synthetic pyrethroids (48 h EC_{50} for cypermethrin is 0.00015 mg/L) (*33, 36*). In contrast, blue-green algae (cyanobacteria) appear to be sensitive to many of the antimicrobial groups. For example, reported EC_{50} values for cyanobacteria with amoxicillin, benzyl penicillin, sarafloxacin, spiramycin, tetracycline, and tiamulin are all less than 100 µg/L (*37*).

Limited information is available on the effects of veterinary medicines on soil-dwelling organisms. Earthworms appear to be sensitive to parasiticides, whereas plants appear to be sensitive to many of the antimicrobial groups and the macrocyclic lactones. Not surprisingly, the antimicrobial compounds are most toxic to soil microbes.

Data on the effects of substances on dung invertebrates may also be required. Ecotoxicity studies for dung-dwelling organisms have generally been performed on anthelmintic compounds (macrocyclic lactones, milbemycins, and benzimidazoles) and pyrethroids. Macrocyclic lactones (ivermectin, doramectin, and eprinomectin) have been shown to affect the mortality of dung invertebrate larvae at very low dung concentrations with 50% lethal concentration (LC_{50}) values less than 0.036 mg/kg (*38*). Studies on manure excreted from animals treated with the macrocyclic lactones demonstrate that the dung can be highly toxic to dung invertebrates for prolonged periods. In contrast to the macrocyclic lactones, the pyrethroids are most toxic to the adult invertebrates and demonstrate high mortality for a period of months following topical treatment (*39*). The benzimidazoles appear much less toxic, with no mortality of dung invertebrates observed in manure (*40*); however, chemical structure indicates that these drugs may affect dung fungi.

A comparison of available ecotoxicity data on standard organisms for commonly used medicines with available monitoring data from water, soil, and dung samples indicates that, in general, environmental concentrations are more than an order of magnitude lower, as shown in Figure 2. Thus, for many veterinary medicines, acute environmental effects are unlikely, and the regulatory framework is working. Exceptions include ivermectin and doramectin in dung and monensin in soil, for which concentrations have been found in the environment that are higher than effects concentrations for selected species. Therefore, it appears that under certain circumstances, veterinary medicines could affect terrestrial and aquatic systems.

What are the impacts of degradation products?

With the exception of a few studies, the potential environmental impacts of metabolites have not been extensively studied. Generally, metabolites are less potent than the parent compounds. Yet, these less potent compounds may still have significant activity. Studies performed by pharmaceutical company Pfizer demonstrated that two of the major metabolites of doramectin, 3″-*o*-desmethyldoramectin and 8-α-hydroxydoramectin, were less toxic to daphnids than the parent compound (*38*). However, the ecotoxicity data indicated that both metabolites were still highly toxic to daphnids, with 48 h EC_{50} values of <0.0011 mg/L. Recent studies on tetracyclines have shown that selected degradation products have similar potencies on bacteria as their parent compounds (*30*). For example, anhydrotetracycline (ATC), a metabolite of tetracycline that has one less hydroxyl group than the parent, had an EC_{50} value for sludge bacteria approximately 3 times lower than the EC_{50} value for the parent compound. Similar findings were reported for the photodegradation products of enrofloxacin (*41*).

Consequently, any risk assessment based on the parent compound may underestimate real effects in the environment. Moreover, because the metabolite's behavior could differ from the parent compound, selected environmental compartments may be more susceptible to adverse exposure from metabolites than what would be predicted if only the parent is considered. For example, ATC has a lower sorption coefficient than tetracycline and is therefore likely to be transported more readily to surface water and groundwater. Similar conclusions may be drawn for the tylosin (tylosin A) degradation products: tylosin B, C, and D. K_{ow}s for tylosin B, C, and D are all lower than tylosin A and therefore are expected to be more mobile than tylosin A.

What are the subtle effects?

Despite concentration and effects data that indicate that acute environmental impacts are unlikely for many of the major substances under the current regulatory schemes, some researchers have raised concerns over impacts on other species and the potential longer-term and subtle effects of these medicines. However, little is currently known about the potential chronic effects from long-term, low-level exposures to veterinary medicines. Studies that have looked at these effects have tended to focus on the parasiticides and the antimicrobials.

Several studies investigated the effects of antimicrobial substances on microbes in soils and sediment (*42*). Selected substances have been shown to inhibit soil bacteria growth, as well as reduce the hyphe length in active molds. Effects on the microbial composition of soils have also been demonstrated (*42*). With the exception of a few studies (*43*), effects on soil and sediment functioning have not been considered. Those studies demonstrate that veterinary antibacterials may affect sulfate reduction in soil and inhibit the decomposition of dung organic matter in soil (*43*). The antibacterials work focused on effects on microbes

FIGURE 2

Concentrations of select veterinary medicines in water, soil, and dung samples

Green bars give the concentrations measured in the environment, and blue bars show the effective concentration (EC_{50}) or maximum inhibitory concentration of each medicine with standard test organisms in (a) water, (b) soil, and (c) dung samples. Starred compounds were not detected, and EC_{50} for oxytetracycline and tylosin are off scale. The comparison indicates that veterinary medicines may not pose much of a risk to the environment, except in dung.

and microbial processes, but recent studies indicate that selected antibacterials also limit the growth of aquatic macrophytes at very low concentrations (*43*).

Once in the dung, veterinary medicines may persist, potentially affecting organisms directly exposed to these compounds. Such exposures may lead to sublethal toxic effects. For example, in addition to the acute effects described above, the macrocyclic lac-

tones have been shown to elicit a number of sublethal responses in dung-inhabiting invertebrates, including reduced feeding, disruption of water balance, reduction in growth rate, interference with moulting, inhibition of pupation, prevention of emergence of adults, and the disruption of mating (*45, 46*). Livestock dung usually contains a diverse invertebrate fauna and provides a fruitful foraging habitat for other organisms; therefore, using macrocyclic lactones may indirectly affect certain species by depleting the quality and quantity of an important food resource (*47*). Large data gaps in our current knowledge of the subtle and longer-term effects of veterinary medicines may be filled by using information on a substance's mode of action to identify species potentially sensitive to the medicine and understand the types of effects that might be elicited.

Do medicines cause resistance in the environment?

Antimicrobial resistance is a growing public health concern and has been a subject of debate for decades. Antibacterials given to livestock at subtherapeutic doses prevent infectious diseases, increase feed efficiency, and increase the rate of weight gain (*48*). Numerous studies suggest a link between antibacterial use in agriculture and antibacterial-resistant infections (*49*), and there is evidence that antibacterial resistance from agriculture can be transferred to humans (*50*).

These observations may be due in part to exposure via the environment. For example, numbers of antibacterial-resistant microflora in samples taken from the outlet of fish farms have increased (*51*), and the presence of antibacterial-resistant bacteria in soils treated with pig manure has been documented (*52*). Sengeløv and co-workers showed that resistance to tetracycline, macrolides, and streptomycin measured for a period of eight months in soil bacteria from farmland treated with pig manure slurry was elevated after spreading the slurry but declined throughout the sampling period to a level corresponding to the control soil. Higher loads of pig manure slurry yielded higher occurrences of tetracycline resistance after spreading. Several authors have studied the transfer of genes between bacteria in sediment, soil, water, and wastewater (*53–55*). Finally, studies document transport of tetracycline-resistant genes in groundwater under swine production facilities (*56*).

How do substances interact?

Several veterinary medicines may be used to treat a herd, and it is likely that other chemicals (such as pesticides) will be applied in the same area. Terrestrial and aquatic organisms may therefore be exposed to mixtures of medicines and other chemicals. For example, during a nationwide reconnaissance for pharmaceuticals in U.S. streams (*2*), lincomycin (an antibacterial used for agricultural purposes) was detected in combination with as many as 27 additional chemicals, including chlorpyrifos, coprostanol, diazinon, dieldrin, trimethoprim, and tylosin (*57*).

Interactive effects—including additivity, antagonism, and synergism—could increase or decrease the potential effects in the environment. For example, antibacterials might be expected to interact with other antibacterial substances, leading to a larger effect on the environment than would be predicted if each compound was considered individually. In addition, veterinary medicines may affect key fate processes of other chemical groups. For example, antibacterials are toxic to soil microbes and hence could reduce a soil system's capability to degrade other contaminants, such as pesticides. To date, no data have been generated on the impact of veterinary medicine mixtures on the environment. Preliminary studies are, however, starting to examine the interactions of human pharmaceutical mixtures on pond communities (*58*).

Which is the way forward?

In the previous sections, we have used the information currently available on veterinary medicines to begin identifying the risks that they may pose to the environment. Comparing the results of standard laboratory studies with newly available environmental monitoring data indicate that, for most veterinary medicines, effects concentrations are significantly higher than environmental concentrations, suggesting that veterinary medicines may not acutely impact most aquatic and terrestrial organisms. However, there are instances in which measured concentrations are higher than available effects data. In addition, with many unknowns, the relationship between these standard tests and more subtle longer-term effects have not been established yet.

Therefore, research should focus on a number of key issues, namely, collating better information on the quantity and use of veterinary medicines in different countries, developing sensitive analytical methods to measure parent drugs and their degradation products, and understanding better the potential for releases to the environment for different treatment types—including an assessment of aerial emissions and inputs from pasture treatment and other "novel" routes such as farm runoff. In addition, targeted ecotoxicological studies are needed to investigate the potential subtle and long-term effects of veterinary medicines in the environment, effects of degradation products, interactions of veterinary medicines and their mixtures with other classes of chemicals, and what, if any, role the environment plays in the transfer of antimicrobial resistance to humans and farm animals.

These studies will be challenging and will require input from ecologists, agronomists, ecotoxicologists, exposure modelers, analytical chemists, toxicologists, veterinarians, and medicinal chemists developing new drugs. If studies are executed in an integrated and thoughtful manner, we believe their results will address the question "Are veterinary medicines causing environmental risks?"

Acknowledgments

This work was performed as part of the European Union-funded project ERAVMIS (Project no. EVKT1-CT-1999-00003). Additional support was provided by the U.K. Environment Agency. The authors would like to acknowledge two anonymous referees who provided useful comments on an earlier version of this manuscript.

References

(1) Hamscher, G.; Sczesny, S.; Höper, H.; Nau, H. *Anal. Chem.* **2002,** *74,* 1509–1518.

(2) Kolpin, D. W.; et al. *Environ. Sci. Technol.* **2002,** *36,* 1202–1211.

(3) Wall, R.; Strong, L. *Nature* **1987,** *327,* 418–421.

(4) Halling-Sørensen, B.; Nielsen, S. N.; Jensen, J. *Environmental Assessment of Veterinary Medicines in Denmark*. Danish Environmental Protection Agency: Copenhagen, Denmark, 2002, www.mst.dk/udgiv/Publications/2002/87-7944-971-9/pdf/87-7944-972-7.PDF.

(5) Committee for Veterinary Medicinal Products. Note for Guidance: Environmental Risk Assessment for Veterinary Medicinal Products Other Than GMO-Containing and Immunological Products; EMEA/CVMO/055/96-Final; European Agency for the Evaluation of Medicinal Products: London, 1997. www.emea.eu.int/pdfs/vet/regaffair/005596en.pdf

(6) Eirkson, C.; Harrass, M. C.; Osborne, C. M.; Sayre, P. G.; Zeeman, M. G. Environmental Assessment Technical Handbook; NTIS PB-87-175345/AS; U.S. Food and Drug Administration: Washington, DC, 1987.

(7) U.S. Food and Drug Administration, Center for Veterinary Medicine, www.fda.gov/cvm/efoi/ea/ea.htm.

(8) Ayscough, N. J.; Fawell, J.; Franklin, G.; Young, W. Review of Human Pharmaceuticals in the Environment; Report P390; U.K. Environment Agency: Bristol, United Kingdom, 1999.

(9) Daughton, C. G.; Ternes, T. A. *Environ. Health Perspect.* **1999,** *107* (Suppl. 6), 907–938.

(10) Jongbloed, R. H.; Kan, C. A.; Blankendaal, V. G.; Bernhard, R. *Milieurisico's van diergenesmiddelen en veevoeradditivien in Nederlands oppervlaktewateren;* Rep. 31635; TNO-MEP, Apeldorn, The Netherlands, 2002.

(11) Boxall, A. B. A.; Fogg, L. A.; Pemberton, E. J.; Kay, P.; Blackwell, P. *Toxicol. Lett.* **2003,** *142,* 207–218.

(12) Umweltbundesamt. *UBA Jahresbericht 2001;* Umweltbundesamt (German Government): Berlin, 2001.

(13) Animal Health Institute. *1997 Market Research Report;* U.S. Animal Health Product Industry: Alexandria, VA, p 59.

(14) Benbrook, C. M. *Antibiotic Drug Use in U.S. Aquaculture*. Institute for Agriculture and Trade Policy Report, February 2002, www.iatp.org/library/antibiotics.

(15) Nawaz, M. S.; et al. *Regul. Res. Perspect*. **2001,** *1,* 1–10.

(16) Mellon, M.; Benbrook, C.; Benbrook, K. L. *Hogging It: Estimates of Antimicrobial Abuse in Livestock*. Union of Concerned Scientists: Cambridge, MA, 2001, www.ucsusa.org/publications.

(17) Hamscher, G.; Pawelzick, H. T.; Nau, H.; Hartung, J. Detection of Antibiotics in Dust Originating from Pig Farms. In *Proceedings of the 12th SETAC Europe Meeting,* Vienna, 2002, SETAC Europe: Brussels, Belgium, p 11.

(18) Boxall A. B. A.; Fogg, L. A.; Blackwell, P. A.; Kay, P.; Pemberton, E. J. *Rev. Environ. Contam. Toxicol.* **2003,** *180,* 1–91.

(19) Klimes, J.; Zahradnicek, M. *Fol. Pharm. Univ. Carolinae* **1988,** *11,* 41–55.

(20) Oka, H.; Ikai, J. *J. Agric. Food Chem.* **1989,** *37,* 226–231.

(21) Campagnolo, E. R.; et al. *The Science of the Total Environment* **2002,** *299,* 89–95.

(22) Sommer, C.; et al. *Bull. Entomol. Res.* **1992,** *82,* 257–264.

(23) Gavalchin, J.; Katz, S. E. *J. AOAC Int.* **1994,** *77,* 481–485.

(24) Loke, M. L.; Ingerslev, F.; Halling-Sørensen, B. *Chemosphere* **2000,** *40,* 759–765.

(25) Van Dijk, J.; Keukens, H. J. In *Residues of Veterinary Drugs in Food: Proceedings of the Euroresidue IV Conference;* Van Ginkel, L. A., Ruiter, A., Eds.; Veldhoven, The Netherlands, 2000.

(26) Langhammer, J.-P.; Buening-Pfaue, H. *Wissenschaft und Umwelt* **1989,** *10,* 14–20.

(27) Loke, M. L.; Tjørnelund, J.; Halling-Sørensen, B. *Chemosphere* **2002,** *48,* 351–361.

(28) Tolls, J. *Environ. Sci. Technol.* **2001,** *35*, 3397–3406.

(29) Boxall, A. B. A.; Blackwell, P.; Cavello, R.; Kay, P.; Tolls, J. *Toxicol. Lett.* **2002,** *131,* 19–28.

(30) Halling-Sørensen, B.; Sengeløv, G.; Tjørnelund, J. *Arch. Environ. Contam. Toxicol.* **2002,** *42,* 263–271.

(31) Ingerlev, F.; Halling-Sørensen, B. *Ecotox. Environ. Safe.* **2001,** *48,* 311–320.

(32) Scottish Environmental Protection Agency. *Emamectin Benzoate and Environmental Risk Assessment: Report of the SEPA Fish Farm Advisory Group*; SEPA 66/99; SEPA: East Kilbride, Scotland, 1999.

(33) Lewis, S.; Watson, A.; Hedgecott, S. Proposed Environmental Quality Standard for Sheep Dip Chemicals in Water; R&D Note 216; Scotland and Northern Ireland Forum for Environmental Research and the National Rivers Authority: Briston, England, 1993.

(34) Bull, D. L.; et al. *J. Agric. Food Chem.* **1984,** *32,* 94–102.

(35) Velagaleti, R. R.; Davis, M. L.; O'Brien, G. K. The Bioavailability of C-14 Sarafloxin Hydrochloride in 3 Soils and a Marine Sediment as Determined by Biodegradation and Sorption Desorption Parameters. In *Abstracts of American Chemical Society Meetings*, **1993,** *205*, 92.

(36) Halley, B. A.; VanHeuval, W. J. A.; Wislocki, P. G. *Vet. Parasitol*. **1993,** *49*, 109–125.

(37) Holten-Lützhøft, H. C.; Halling-Sørensen, B.; Jorgensen, S. E. *Arch. Environ. Contam. Toxicol*. **1999**, *36,* 1–6.

(38) Pfizer. *Environmental Assessment: Doramectin 1% Injectable Solution for Treatment of Parasitic Infection in Cattle;* Report No. 141-061EA; 1996; on USFDA website, www.fda.gov/cvm/efoi/ea/ea.htm.

(39) Kruger, K.; Lukhele, O. M.; Scholtz, C. H. *Bull. Entomol. Res.* **1999,** *89,* 543–548.

(40) Wardhaugh, K. G.; Holter, P.; Longstaff, B. *Aust. Vet. J.* **2001,** *79*, 125–132.

(41) Burhenne, J.; Ludwig, M. *Environ. Sci. Pollut. Res.* **1997,** *4,* 61–67.

(42) Westergaard, K.; Muller, A. K.; Christensen, S.; Bloem, J.; Sorensen, S. J. *Soil Biol. Biochem.* **2001,** *33,* 2061–2071.

(43) Sommer, C.; Bibby, B. M. *Euro. J. Soil Biol.* **2002,** *38,* 155–159.

(44) Pro, J.; Ortiz, J. A.; Boleas, S.; Fernandez, C.; Carbonell, G.; Tarazona, J. V. *Bull. Environ. Contam. Toxicol.* **2003,** *70*, 290–295.

(45) Strong, L. *Vet. Parasitol.* **1993,** *48,* 3–17.

(46) Strong, L.; Brown, T. A. *Bull. Entomol. Res.* **1987,** *77,* 357–389.

(47) McCracken, D. I. *Vet. Parasitol.* **1993,** *48,* 273–280.

(48) DuPont, H. L.; Steele, J. H. *Rev. Infect. Dis.* **1987,** *9,* 447–460.

(49) Smith, K. E.; et al. *N. Engl. J. Med.* **1999,** *340,* 1525–1532.

(50) Rhodes, G.; et al. *Appl. Environ. Microbiol*. **2000,** *66,* 3883–3890.

(51) Schmidt, A. S.; Bruun, M. S.; Dalsgaard, I.; Pedersen, K.; Larsen, J. L. *Appl. Environ. Microbiol*. **2000,** *66,* 4908–4915.

(52) Sengeløv, G.; Agersø, Y.; Halling-Sørensen, B.; Baloda, S. B.; Andersen, J. S.; Jensen, L. B. *Environ. Intl.* **2003,** *28,* 587–595.

(53) Top, E.; Desmet, I.; Verstraete, W.; Dijkmans, R.; Mergeay, M. *Appl. Environ. Microbiol.* **1994,** *60,* 831–839.

(54) Van Elsas, J. D.; Trevors, J. T.; Starodub, M. E. *Science* **1988,** *264,* 375–382.

(55) Mach, P. A.; Grimes, D. J. *Appl. Environ. Microbiol*. **1982,** *44,* 1395–1403.

(56) Chee-Sanford, J. C.; Aminov, R. I.; Krapac, I. J.; Garrigues-Jeanjean, N.; Mackie, R. I. *Appl. Environ. Microbiol*. **2001,** *67,* 1494–1502.

(57) Barnes, K. K.; et al. *U.S. Geol. Surv. Open File Rep. 02-94;* **2002**.

(58) Solomon, K. R.; Sanderson, H.; Sibley, P. K.; Mabury, S. A. Abstract submitted for the ENVIRPHARMA meeting, Lyons, France, April 13–16, 2003.

Alistair Boxall is an environmental chemist at the Cranfield Centre for EcoChemistry. Dana Kolpin is a research hydrologist at the U.S. Geological Survey in Iowa City, Iowa. Bent Halling-Sørensen is an associate professor at the Danish University of Pharmaceutical Sciences, and Johannes Tolls is an ecotoxicologist with an interest in fate of an exposure to organic chemicals. He recently moved from the University of Utrecht in The Netherlands to Henkel KGaA in Germany. Address correspondence to Boxall at a.boxall@cranfield.ac.uk.