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Water Resource Impacts

from Medicines and Other Biologically Active Substances

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Introduction

A wide variety of substances affects the chemical quality of water resources. Commonly studied contaminants to streams, lakes and aquifers are sediments, organic matter, nutrients, pesticides and salts. Recent advances in laboratory techniques and equipment have opened the path for study of bioactive chemicals related specifically to the control of human and/or animal disease and human endocrinology.

Most of these chemicals are organic (carbon-based) with some also classed as pesticides because of their use for controlling pests. These chemicals include pharmaceuticals (human and veterinary medicines) and substances that disrupt the functions of the human endocrine system (endocrine disruptors).

Most of these chemicals are of man-made origin and manufactured for a specific purpose; however, many of the endocrine disruptors are of natural origin.

Pharmaceutical use has been significant for many years. The Centers for Disease Control and Prevention (CDC) has estimated that approximately 25,000 tons of antibiotics are produced annually in the United States, with 10,000 tons for the animal production industry (9). This number may be substantially greater (7), with one annual estimate of livestock producers' use of antibiotics for nontherapeutic purposes alone at 12,300 tons.

In the European Union, approximately 5,000 tons of antibiotics were used for animal production in 1999 (13). One study estimated that for ibuprofen alone, 105 tons/year were prescribed in Germany (12).

The number of different active compounds marketed as pharmaceuticals is enormous. Nearly 1,000 different compounds are marketed in Denmark (11). In the United States, the lists of approved drugs for humans and animals are extensive and may be found on the U.S. Food and Drug Administration (FDA) Web site *(www.fda.gov)*.

For approximately the last 30 years, the U.S. FDA has been required under the National Environmental Policy Act (NEPA) to consider environmental risks associated with the manufacture, use, and distribution of both human and animal medicines.

The environmental fate of bioactive chemicals classed as medicines or endocrine disruptors has not been studied to a great extent until recently. A number of reasons account for this apparent lack of attention.

Although these substances are used regularly, their potential environmental concentrations are comparatively low. For example, critical levels of nutrients in water resources are in the mg/l or parts-per-million (ppm) range. The highest environmental concentrations of bioactive chemicals are present at levels expressed as mg/l or parts per billion, and more commonly at levels expressed as ng/l (parts per trillion) or even pg/l (parts per quadrillion).

Usually medicines are readily degraded through metabolism and waste treatment processes after excretion. Several groups that have studied this issue all have concluded that the concentrations of bioactive chemicals in the environment are small, but in some situations their presence has become ubiquitous (2,3, 8,14).

The extremely low environmental concentrations of bioactive substances have acted as a deterrent to environmental investigations in two ways. First, these concentrations are below the levels where acute toxicity effects are observed in laboratory animals. This does not rule out chronic effects, but they are much more challenging to demonstrate. Second, the equipment and laboratory techniques to determine minute quantities of bioactive chemicals accurately were not available until recently.

Researchers in the late 1990s combined gas and high-performance liquid chromatography with mass spectrometry, which allows for accurate detection and quantification of estrogenic and polar pharmaceutical compounds in the lower parts-per-trillion range (10).

The scientific community appears to have reached a consensus about the need for continued research to fully understand the environmental fate and impact of bioactive chemicals. Reviews of the issue conducted in Denmark (3,4), the United Kingdom (1,5), and the United States (8, 14) all come to the same conclusion regarding the continued need for research.

The recent U.S. Geological Survey reconnaissance study (6) confirms the presence of a host of bioactive substances in the nation's rivers. This study has provided support for other studies that clarify "cause and effect" relationships.

A daunting reality of this type of research is that the hundreds of bioactive substances being marketed all have different chemical, physical and biological properties.

The Problem

The positive consequences of using bioactive compounds for disease and pest control are substantial. The unanticipated negative effects combined with their widespread presence in some geographic areas are what have generated concern about their use.

The scientific community has identified three legitimate general effects related to the release of bioactive chemicals into the environment: 1) Endocrine system disruption (4, 5); 2) Biocidal effects on nontarget organisms (2,3); and 3) Antibiotic resistance (1,2,3). Whether an organism actually is affected depends on the concentration of the chemical, exposure time and amount of chemical internalized (dose).

Under controlled laboratory experiments, a variety of effects has been observed. Many chemical and biological processes that may contribute to environmental problems have been proven in a general sense. However, extrapolation of environmental "cause and effect" relationships from proven biological processes is not a simple task. Scientists are faced with the challenge of realistically determining environmental concentrations, organism exposure times and dose of individual chemicals often found in a complex chemical soup.

Further, environmental studies cannot be designed with the rigid control that is typical for most laboratory studies. An additional challenge to scientists is determining the chronic impacts resulting from long-term exposures to low chemical concentrations. Sorting through the many factors that contribute to "cause and effect" relationships in the environment requires a rigorous experimental design and a commitment to long-term studies.

What Do We Know About Endocrine Disruption?

Fish

The challenges of studying bioactive chemicals in the environment notwithstanding, we have learned some things about their secondary impacts. Studies in Germany, Italy and Brazil show that sewage treatment systems can remove 10 percent to 100 percent of bioactive chemicals (1,7,13).

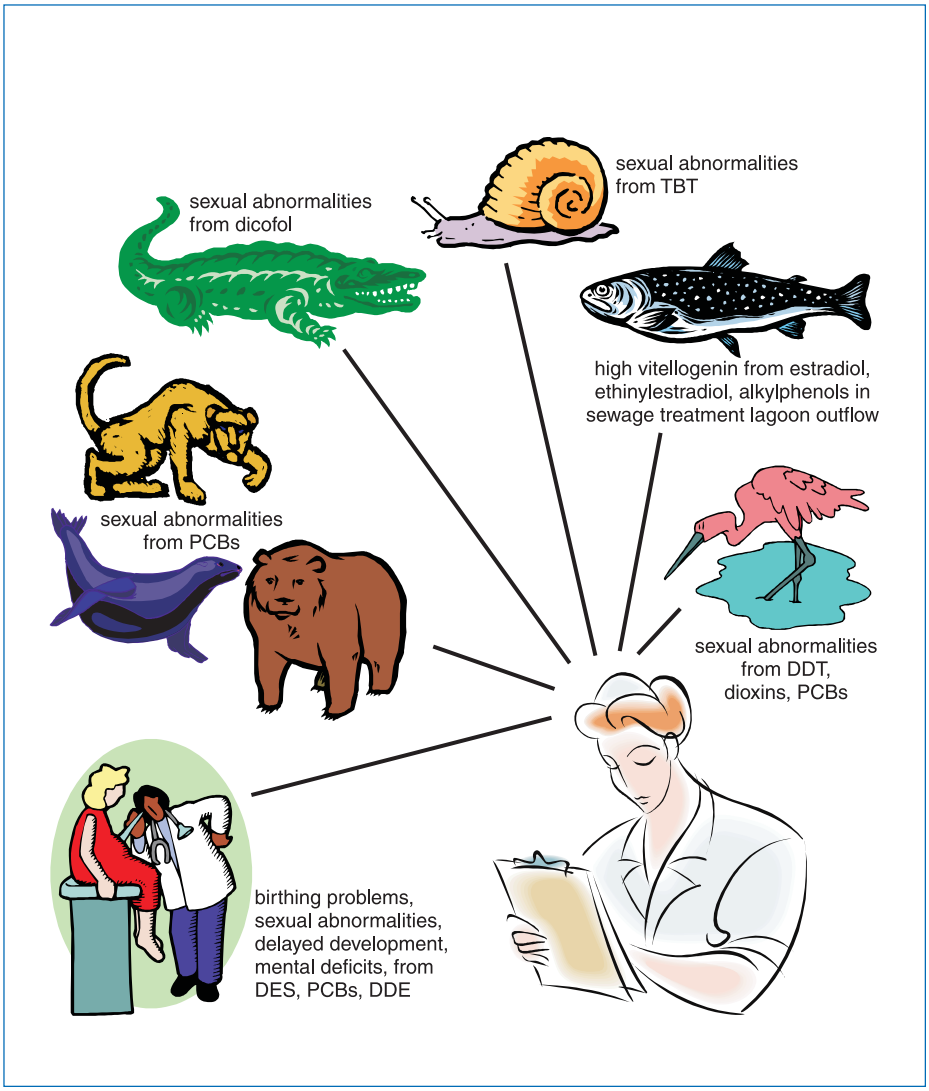

Figure 1. Observed effects of endocrine disruptors.

In United Kingdom, United States, Germany and France, links have been established between the occurrence of reproductive abnormalities in wild fish and their proximity to effluent outflow from sewage treatment systems (3,8,10,12,13,14).

The reproductive abnormalities range from the production of vitellogenin, a female specific protein, in male fish to physical defects that would affect reproduction. The link between these abnormalities and specific estrogenic chemicals is not clear.

Natural (estradiol) and synthetic (ethinylestradiol) hormones have been detected at low concentrations in sewage treatment system effluent. Laboratory evidence indicates that low concentrations of hormones comparable to the levels found in sewage treatment effluent can induce the observed effects.

Alkylphenolic compounds that are commonly used as cleaning products for a variety of industrial, agricultural and household applications also can be found in most sewage treatment effluents. Many of these compounds possess estrogenic activity, although substantially weaker than the natural estrogen hormones. Also, additive and/or synergistic effects from several compounds in sewage treatment effluent may be responsible for the observed fish abnormalities.

Although no specific study on sewage treatment effluents exists to substantiate this theory, additivity and/or synergism have been demonstrated in other studies that measured biologic effects of multiple estrogenic compounds (2, 9).

Marine mollusks

Sexual abnormalities caused severe effects in the population of dog whelk, a type of marine snail, off the coast of the North Sea in France and Ireland (6,16). A strong link was established between the observed effects and the endocrine disrupting chemical tributyltin (TBT). TBT is used as an anti-foulant on ship hulls, and the sexual abnormalities were most prevalent near sites of intense shipping traffic.

In this case, determining "cause and effect" was the basis for regulatory action that reduced the use of TBT in Ireland. The practical result has been a substantial decrease of sexual abnormalties in the dog whelk population.

Reptiles

A strong relationship exists between a decrease in the alligator population in Lake Apopka in Florida because of reproductive disorders and a spill of dicofol and sulfuric acid in the 1980s. Data that was gathered supports a connection between elevated concentrations of dicofol metabolites (DDD, DDE, and chloro-DDT) and the alteration of alligator gonads still in the egg.

Birds

Since the 1960s, scientific evidence has linked reproductive disorders in certain bird populations with endocrine disruptors such as DDT and its metabolites, dioxins and PCBs (4,6,16). In the Great Lakes area, these chemicals have been linked to eggshell thinning in certain species of gulls and terns. Poor reproductive success of gulls and terns also has been associated with endocrine disrupting chemicals along the Pacific coast of the United States.

Peregrine falcons and white-tailed sea eagles are other bird populations that have seen dramatic impacts from exposure to endocrine-disrupting chemicals.

Populations of some of the affected bird species, such as cormorants and gulls, have rebounded substantially as a result of regulations that have reduced the environmental concentrations of DDT and its metabolites and PCBs. However, several species of terns continue to show declines in their populations because of sexual disorders.

Mammals

Wild populations of certain mammals have developed reproductive abnormalities that may be linked to endocrine disruption from PCBs (6,16). The Florida panther, black and grizzly bears in Canada, and several species of seals in the Baltic and Wadden Seas may be affected. However, a clear "cause and effect" relationship has not been established.

Humans

Some recent trends in human health are suspected to be linked to endocrine-disrupting chemicals in the environment (6,11,15). Trends that have received the greatest attention are the following: 1) increased rates of breast and endometrial cancer in women; 2) increased rates of testicular and prostate cancer in men; and 3) reduced sperm concentrations in men. Laboratory studies indicate that certain tissues are quite sensitive to endocrine disruption. However, definite "cause and effect" relationships between these

human health trends and environmental concentrations of endocrine disruptors do not exist.

The most compelling evidence for the connection between human health and endocrine disruptors appears to be on unborn children. In the period between 1947 and 1971, approximately 4 million women exposed their fetuses to regular doses of diethylstilbestrol (DES) in the United States alone (11).

DES is a potent estrogenic chemical used as a therapy to prevent premature labor. Studies have shown that children, particularly female, of the women who used this therapy have a significantly higher incidence of diseases and abnormal conditions related to the genital tract.

Other studies from the United States and other countries have shown that populations with a high consumption of fish contaminated with PCBs and/or DDE have higher than normal reproductive abnormalities in unborn children. Additionally, children exposed to higher levels of these chemicals via the placenta are more likely to have shorter gestations, lower birthweights, delayed neuromuscular development and IQ/memory deficits.

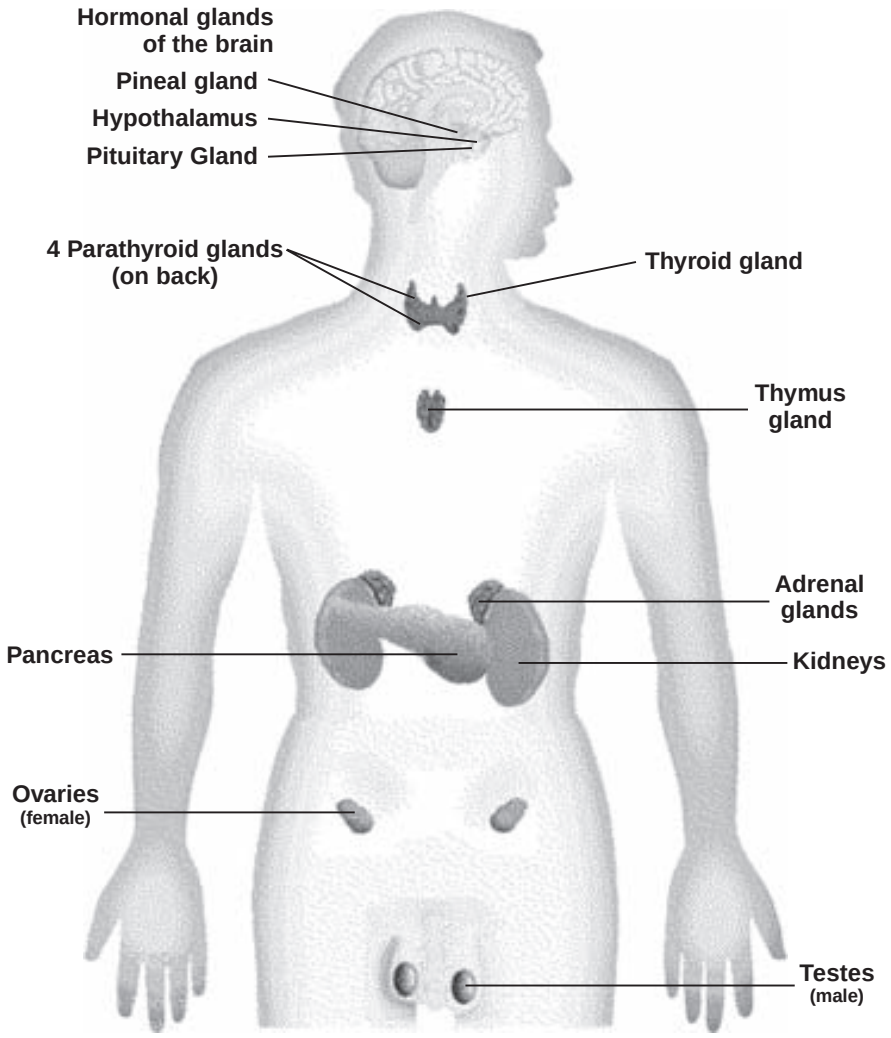

Figure 2. The human endocrine system.

Important endocrine disrupting chemicals

The endocrine system in humans and other animals is made up of glands that manufacture and secrete hormones (6,11,15). Hormones relay the message to start or stop many basic biological functions required for survival. They are involved in determining sleep/wake cycles, stimulating or stopping growth, regulating blood pressure, and determining gender, sexual maturation and reproductive capacity. The endocrine and nervous systems regulate body functions in response to environmental conditions.

Hormones convey messages by being excreted from specific cells, moving through the body and attaching to specific receptor sites in the target cells. Certain chemicals may disrupt this orderly process in several different ways. They may damage the glands that create and excrete certain hormones. They may degrade the hormone itself, thus not allowing receptor sites to receive the message.

Many chemicals mimic hormones because they have similar molecular structure and are able to attach to the receptor site. Hormone mimics can cause the body to overreact either by prematurely

decreasing hormone production during a time when a response is needed (antagonistic) or causing an exaggerated response when no response is required (agonistic).

Determination of endocrine-disrupting chemicals begins with testing on laboratory animals. These laboratory analyses can determine which chemicals are endocrine disruptors and their potency. They cannot establish "cause and effect" relationships between wild species and environmental levels of certain chemicals. As a broad group, the list of these chemicals is composed of both synthetic (man-made) and natural compounds. Endocrine disruptors that impact the sexual function of humans and animals have received the greatest attention in terms of suspected environmental effects.

Most of the observed endocrine-system disruptions appear to be related to estrogens, or "female" hormones. Estrogens are extremely potent hormones with a steroidal molecular structure that occur naturally as estradiol, estrone and estriol. Estrogenic disruptors are rated by comparing their potency to that of estradiol. In general, organisms must be exposed to substantially higher concentrations of estrogenic disruptors compared with estradiol to cause an equivalent biologic reaction.

Endocrine disrupting chemicals can be placed in 10 broad categories (16). They all have observed impacts on the endocrine system that controls sexual definition and function. Eight of these categories are composed of compounds that cause estrogenic disruption; the other two cause disruption of the production, distribution or delivery of androgens or hormones responsible for "male" characteristics. The 10 groups of endocrine-disrupting chemicals are listed in **Table 1**.

Table 1. Categorization and characteristics of endocrine-disrupting chemicals (16).

Endocrine disruptor group	Chemical use	Sexual effect (Estradiol potency index)	Concentration causing effects in lab animals	Observed aquatic concentrations
Organochlorine pesticides (DDT, DDE, methoxychlor, lindane, kepone	Insect pest control	Estrogenic (100 – 100,000 X < potent)	>32 µg/l	0 – 2.8 µg/l
Polychlorinated biphenyls (PCB)	Applications related to electrical and heat transfer, hydraulic equipment, plasticizers, pigments	Estrogenic (50 – 500 X < potent)		
Dioxins (PCDD, TCDD)	Result of burning organic compounds	Estrogenic	0.1 – 1 µg/l	0 – 40 µg/l
Alkylphenols (APE)	Manufacture of plastics, elastomers, ag chemicals, pulping and industrial detergents	Estrogenic (2,000 – 100,000 X < potent)	0.32 – 10 µg/l	
Polycarbonate-derived products and epoxy resins (BPA)	Coating for containers and pipes	Estrogenic (2,000 X < potent)	> 10 µg/l	0 – 1 µg/l
Phthalates (DBP, DEHP)	Manufacture of plastics, repellents, cosmetics, inks, oils	Estrogenic	> 320 µg/l	0 – 30 µg/l
Vinclozolin	Control of fungal disease	Androgenic		
Organotin compounds (TBT)	Anti-foulant for ship hulls	Androgenic	1 – 5 ng/l	0 – 30 ng/l
Synthetic estrogens (EE_2)	Birth control	Estrogenic (0.7 X < potent)	0.1 – 10 ng/l	0 – 7 ng/l
Natural estrogens (estradiol, estrone, etriol, isoflavonoids, coumestrol, enterlactone)		Estrogenic	0.002 – .003 pg/l (in blood)	1 – 80 ng/l

What Do We Know About Antibiotics in the Environment?

The potential impact on the environment from antibiotics is related to practices used to produce, distribute and dispose of medicines and/or drugs within the two major industries of human health care and animal production. Although many of the same medicines are used in both industries, there are significant differences in the potential for environmental impacts.

First, the pathway between the site of drug use and the environment is quite different between humans and animals (12). Second, although the FDA has the regulatory authority to ensure minimal environmental impact from drugs used in both of these industries, the environmental assessment protocol is quite different (6).

Figure 3. Pathways of entry into the environment for medicines found in human and animal wastes.

Environmental pathways

Human medicines are excreted or washed off as the original drug or a degraded product, metabolite, of the original drug. These chemicals then enter the human waste stream via the plumbing system. Unused drugs in their original potent form also will enter the waste stream when disposed of either via the plumbing or solid-waste garbage disposal systems.

In the United States, at least one level of treatment interrupts the human waste stream before it reaches the environment. In the case of solid waste, the treatment is minimal, but so is the potential for entry into the environment. In the case of fluid waste, the treatment and potential for entry into the environment are substantially greater.

Human drugs have been detected in groundwater below landfills (8,16) and in effluent from sewage treatment lagoons in several countries (14,30,31). The other mechanism for entry into the environment is from fields that have received sludge applications from sewage treatment lagoons.

The pathways that veterinary drugs take to enter the environment are quite different than for human medicines. The three major pathways are related to aquaculture (fish farms), animals as groups and animals as individuals.

Drugs are administered to fish raised in aquaculture systems by incorporation in the food, so they are applied directly to the aquatic system. Drugs administered to livestock or poultry in confined areas are excreted in waste that is applied to fields. Free-range

livestock receive drug applications that are excreted or washed onto the fields in which they graze.

In all cases, the opportunity for degradation before entry into the environment is substantially less, compared with the drugs that humans use. The differences between the treatment of the human and animal waste streams probably explain, to some extent, the different approaches the FDA requires in assessing environmental impacts of human and veterinary drugs.

Of course, the chemical and physical properties of each type of compound will combine with the pathway and influence whether environmental impacts actually occur. Some general observations from environmental and drug studies help us understand the possible fate and impacts of some drugs. Most drugs are transformed into metabolites that have more or less different properties than the original drug. Often the metabolite is more water soluble than the parent drug and therefore more mobile, but probably less potent.

However, microorganisms in sewage lagoons or other environments may change many metabolites back to the original parent drug. The less soluble but more potent parent compound tends to associate with organic matter in sediments and soils and may have negative effects on organisms that contact these materials. The mechanism described contributes to the observation of biologically active drugs in aquatic environments beyond the zone of treatment.

The chemical nature of almost all drugs is organic, just like many other manufactured chemicals such as pesticides. The large organic molecules that compose organic matter in sediments and soil tend to attract and adsorb nonpolar organic chemicals, such as many pesticides. This relationship has been used to predict the environmental behavior of many pesticides in the environment.

However, because of the polar nature of many drug metabolites, the ion exchange capacity of different organic and nonorganic (i.e., clay and sesquioxides) substances in sediments and soil substantially affects their adsorption (23,32).

Studies in Demark show significant differences in antibiotic adsorption to manure. The order of adsorption in pig manure was metronidazole < olaquindox << tylosin A < oxytetracyline. Predicting drug behavior in sediments and soils is much more complicated than applying a simple relationship with organic matter.

The potential for environmental impacts from antibiotics also depends on their persistence in the environment after they are released. Antibiotic activity in various mixtures is measured to determine the range of persistence over common environmental conditions. For antibiotic activity losses from a soil-and-chicken-manure mixture for a group of commonly used antibiotics in animal production, see **Table 2** (9).

The loss of antibiotic activity in environmental materials such as mixtures of soils, sediments and manure is related to both chemical degradation and adsorption (11). As indicated previously, much of the observed loss may be the result of adsorption. For example, tylosin, a widely used antibiotic in swine production, has been shown to be completely lost within as little as two days when mixed with pig manure in either aerobic or anaerobic lagoons in Denmark (22).

Adsorption of tylosin to manure must play an important role in this observation because other studies have shown that the degradation half-life of tylosin is between 10 and 40 days under similar conditions (18). Apparently, undegraded tylosin remains adsorbed in the system, but is not biologically active.

Table 2. Antibiotic activity loss from a soil-manure mixture (9).

Antibiotic	Incubation temp	Incubation time	Loss
	(C)	(days)	(%)
Chlortetracycline	30°	30	66
Bacitracin	30°	12	50
Tylosin	30°	30	100
Erythromycin	30°	30	100
Bambermycin	30°	30	100
Penicillin	30°	0.125	98.7
Streptomycin	30°	immediate	100

The processes of adsorption and biodegradation play an important role in hindering antibiotic movement into the environment. One study in Germany found little if any indication that many commonly used antibiotics, such as penicillins or tetracyclines, had moved into aquatic or groundwater systems (15).

However, if the rate of antibiotic input exceeds the rate of degradation, the antibiotics can build up on the soil sorption sites. Detachment or desorption of adsorbed antibiotics over time can lead to environmental impacts, where desorbed antibiotics are translocated to aquatic and groundwater systems.

Another study in Germany found that cefotiam, ciprofloxacin, meropenem, penicillin G and sulfamethoxazole were not readily biodegradable in mixtures from sewage treatment plants (2). The adsorbed antibiotics were found to be toxic to bacteria necessary for waste treatment.

Finally, another German study found residues of tetracycline in the upper foot of soils because liquid pig manure was applied in quantities that exceeded the biodegradation rate of tetracycline (13).

Biocidal impacts to nontarget organisms

When biocides (antibiotics, pesticides, etc.) enter the environment, a potential exists for unintended impacts to organisms other than those targeted. Biocides released into the environment pose a risk to a wide range of fauna, including microorganisms (2, 3, 10, 17, 21, 28, 29, 37, 38, 39).

These populations of different fauna perform critical functions related to cycling of minerals and energy, such as organic matter decomposition and nitrification.

Of course, the dose-response relationship is an important aspect that must be assessed continually. Monitoring studies indicate that environmental concentrations of most biocides, such as antibiotics, are extremely low. Generally, environmental concentrations of antibiotics are at least an order of magnitude less than concentrations that are toxic to microorganisms in the laboratory.

Veterinary drugs have been rated for their potential to cause impacts to nontarget organisms in the United Kingdom (4). The rating protocol is a two-step process.

The first step considered estimates of the amounts of drugs used and their potential to enter the environment.

The second step began by determining the ecotoxicity of those compounds identified as having a high potential to enter the environment in substantial quantities. The ecotoxicity was determined for both aquatic and terrestrial systems and was called the "hazard assessment." To complete the second step, 56 compounds **(Table 3)** were ranked as having a high priority for further risk analyses.

Unfortunately, sufficient information was available to rank only 11 of the 56 compounds with confidence. The other 45 compounds are considered as high priority on a provisional basis.

Aquaculture

Although aquaculture facilities attempt to achieve substantial drug uptake, the majority of drugs applied is unused, resulting in substantial amounts that may enter the environment (4,12). Emamectin benzoate, oxolinic acid and oxytetracycline have been detected in the sediments beneath fish farm cages in the tissues of wild fish and crustaceans, such as the bleak,

Table 3. High priority veterinary drugs for risk assessment (4).

High Priority compounds			
Amoxicillin	Cypermethrin	Oxytetracycline	Tetracycline
Apramycin	Diazinon	Sarafloxin	Tylosin
Chlortetracycline	Dihydrostreptomycin	Sulphadiazine	
Provisional High Priority Compounds			
Amitraz	Dimethicone	Levamisole	Poloxalene
Amprolium	Emamectin benzoate	Lincomycin	Procaine benzyl penicillin
Antiseptics	Enrofloxacin	Lido/ligocaine HCL	Procaine penicillin
Baquiloprim	Fenbendazole	Maduramicin	Robenidine hydrochloride
Cephalexin	Flavomycin	Monensin	Salinomycin sodium
Clavulanic acid	Flavophospolipol	Moraniel	Tiamulin
Clindamycin	Florfenicol	Neomycin	Tilmicosin
Clopidol	Flumethrin	Nicarbazin	Toltrazuril
Cypromazine	Immunological products	Nitroxynil	Triclabendazole
Decoquinate	Ivermectin	Oxolinic acid	Trimethoprim
Deltamethrin	Lasalocid sodium	Phosmet	
Diclazuril		Pipcronyl butoxide	

roach, dog fish, crabs and mussels. Oxytetracycline was detected in a national monitoring project of U.S. streams (20).

Laboratory studies indicate that both marine and freshwater algae are sensitive to a number of common antibiotics (10,17,21). Blue-green algae, compared with green algae, were found to be much more sensitive to several antibiotics used for fish production. Amoxicillin and sarafloxacin hydrochloride were the most toxic.

The evidence demonstrates that veterinary drugs reach the environment via the aquaculture pathway, but adverse direct effects on wild species have not been reported. However, indirect effects on these species may be expected where toxic effects from certain antibiotics diminish their food sources, such as algae.

Livestock

Studies show that at least two chemicals used in sheep-dipping treatments, diazinon and cypermethrin, are quite toxic to nontarget species. Diazinon is highly toxic to soil-dwelling earthworms and saprophytic isopods (5). Diazinon and cypermethrin are toxic to honey bees. Diazinon and cypermethrin have been detected in surface and groundwater in the United Kingdom. Of the veterinary drugs detected, diazinon was of greatest frequency.

Avermectins are used to control a variety of insect parasites. Studies show that other insect species important to manure degradation are sensitive to avermectins excreted in the manure from treated animals. Measured degradation rates are significantly slower in manure containing avermectins because of the decreased numbers of dung beetles (28,29,37).

Two commonly antibiotics, oxytetracycline and tylosin, used in livestock production were studied to determine their impact on certain soil fauna (earthworms, springtails and enchyraeids) (3). The low level of toxicity observed had little direct effect on these soil-dwelling organisms. In another study on the effects of tylosin on soil microflora, direct impacts on the bacterial community were observed, but little impact to protozoa or fungi occurred (38). As noted before, indirect effects on higher-order soil organisms likely are to be observed when direct impacts occur to their food sources, such as bacteria.

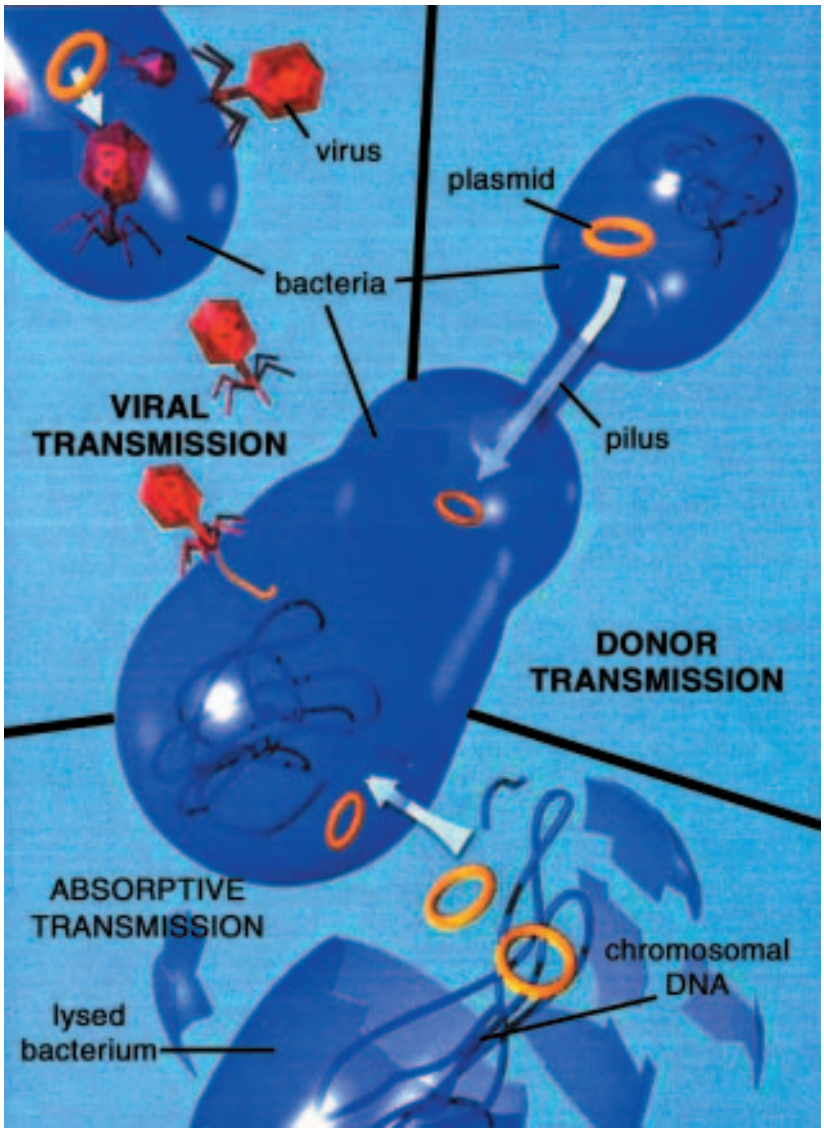

Figure 4. Transfer of genetic material containing antibiotic resistance. *(After Khachatourians, 1998)*

Antibiotic resistance

Penicillin was the first antibiotic discovered, in 1928. It was not generally used for therapeutic purposes until 1940 (1). Penicillinase, an enzyme that imparts antibiotic resistance to Escherichia coli (E. coli) also was described in 1928.

Antibiotic resistance clearly existed prior to the first therapeutic use of antibiotics by humans. However, worldwide use of antibiotics in the last 64 years has had substantial impacts on the existence and distribution of resistant strains of microbes.

Antibiotic use and resistance have been locked together as an inseparable issue ever since the initial scientific breakthrough. The importance of antibiotic resistance cannot be overstated because of the obvious implications to human health. The National Foundation for Infectious Diseases has estimated the cost of antibiotic resistance in terms of human health to be $4 billion annually.

Research since the discovery of penicillin has provided scientists with a good understanding of how antibiotic resistance works at the cellular level. Scientists also have a good understanding of how antibiotic resistance is imparted to individual cells. The processes of antibiotic resistance are quite complex. However, a few general observations help define the issue and provide some direction for reasonable approaches to management.

Antibiotic mechanisms of action

Antibiotics impede or stop the growth and reproduction of the target organism by inhibiting at least one of the following: 1) cell wall synthesis; 2) nucleic acid replication; 3) protein synthesis; and 4) folate metabolism (1). The mode of action, in part, organizes the major classes of antibiotics.

Antibiotic resistance is related to other cellular mechanisms that resist the four growth-inhibiting actions. Resistance mechanisms are organized into the following categories: 1) alteration of the antibiotic's target receptor; 2) deterring chemical entry into the cell or enhancing its removal; 3) destruction or inactivation of the antibiotic; and 4) creation of new metabolic pathway that the antibiotic does not affect.

For a given bacterial species, the mechanism of resistance is highly specific to a particular antibiotic. Depending on the natural mechanism of resistance that each bacterial species possesses, each species is more or less sensitive to different types of antibiotics.

When a bacterial population is exposed to an antibiotic, the individual organisms that possess the specific mechanism to resist that antibiotic will survive. Thus, antibiotic resistance is passed to their offspring through the process of natural selection, allowing a resistant population to grow.

Compared with the human cycle of reproduction and growth, the bacterial cycle is extremely rapid; therefore, resistant bacterial populations may become serious problems within very short periods of time.

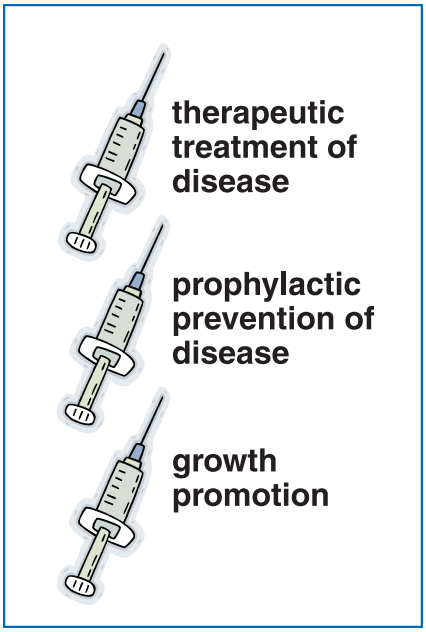

Figure 5. Antibiotic use in the animal production industry.

Traits for resistance may be acquired through random mutation or exchange of genetic material. Transfer of resistance via genetic material may occur in ways other than normal cell division during reproduction (19). Small pieces of DNA called plasmids or transporons may be transferred through a conduit between individual bacterium called a pilus. Plasmids and transporons also may be transferred to different bacterial species either through viral attacks or when they are adsorbed after the cell wall is ruptured. Transfer of antibiotic resistance between different species of bacteria is of particular importance because of the similarity between antibiotics used to treat humans and animals.

Antibiotic resistance and animal production

Antibiotic resistance is related to exposure of microorganisms to antibiotics used for both human and animal care. However, the focus of attention in recent years has been on animal production for several reasons.

First, usage estimates indicate that considerably greater quantities of antibiotics are used on animals compared with humans. One study estimated that the quantity of antibiotics used for nontherapeutic use in animal production (12,300 tons/year) was eight times greater than the amount used for human health care (1,500 tons/year) (24).

Antibiotics are used in animal production as therapeutics for managing disease, prophylactics at subtherapeutic amounts and as growth promoters (1). Second, considerably less control exists in dispensing and applying antibiotics for animal production compared with human health care. The nontherapeutic use of antibiotics as feed additives has been called into question and actually banned in some countries.

Finally, because of large differences between human and animal waste handling and treatment, a greater potential exists for antibiotic release into the environment from animal production. The antibiotics approved for both therapeutic and nontherapeutic uses in animal production appear in **Table 4**.

Table 4. Antibiotics, chemotherapeutics, sulfonamides and coccidiostats approved by the U.S. Food and Drug Administration (FDA) for use in animal production (36).

x = Approved

Antibiotic	Cattle	Pigs	Sheep	Poultry
amoxicillin	x	x		
ampicillin	x	x		
amprolium				x
arsanilate sodium		x		x
apramycin		x		
arsanilic acid		x		
bacitracin	x	x		x
bambermycins		x		x
buquinolate				x
carbadox		x		
ceftiofur	x			
chlortetracycline	x	x	x	x
clopindol				x
dequinate				x
dihydrostreptomycin	x			
efrotomycin		x		x
erythromycin	x	x	x	
fluoroquinolones				x
furamazone	x			
gentamycin	x	x		x
lasalocid	x			x
lincomycin		x		
maduramycin				x
monesin	x			x
narasin				x
nequinate				x
neomycin	x	x	x	x
nicarbazin				x
novobicin				x
oleandomycin		x		x
oxytetracycline	x	x	x	x
penicillin	x	x	x	x
robenidine				x
roxarsone		x		x
salinomycin				x
spectinomycin		x		x
streptomycin	x	x	x	x
sulfabromomethazine	x			
sulfachloropyzasine				x
sulfachlorpyridazine	x	x		
sulfadimethoxine	x			x
sulfaethoxypyridazine	x	x		
sulfamethazine	x	x		x
sulfamethoxine	x			
sulfamyxin				x
sulfanitran				x
sulfaquinoxaline				x
sulfathiazone		x		
tetracycline	x	x		x
tiamulin		x		
tilmicosin	x			
tylosin	x	x		x
virginiamycin		x		x
zoalene				x

Links among animal production, human disease and antibiotic resistance

Salmonella and *Escherichia coli (E. coli)* bacteria are the two most important pathogens in livestock. They also cause foodborne illness in humans (1).

The Centers for Disease Control and Prevention (CDC) estimates that 1.4 million cases, with 600 deaths, occur every year from illnesses that *Salmonella* causes. *Salmonella* has more than 2,300 serotypes.

The proportion of antibiotic-resistant strains of *Salmonella* associated with human infections increased between 1980 and 1990 from 17 percent to 31 percent (19). Resistance to ampicillin, chloramphenicol, fluoroquinolone, streptomycin, sulfonamides, tetracycline and trimethoprim have been reported, with many strains exhibiting multidrug resistance.

In particular, illness involving multidrug-resistant *Salmonella typhimurium* increased from nearly 260 human cases in 1990 to more than 3,800 cases in 1995 in the United Kingdom. *Salmonella typhimurium* has been found in all four of the major types of livestock.

A 1994 USDA National Animal Health Monitoring System (NAHMS) survey of livestock operations detected *S. typhimurium* regularly in dairy calves but not in beef cattle. The same study found three of the serotypes of *Salmonella* in samples from swine operations also were on the CDC's top five list of *Salmonella* serotypes found in humans.

E. coli is a common inhabitant of mammalian intestinal systems that may cause diarrhea (scours) and edema in young pigs, dysentery and septicemia in young calves, and mastitis in adult cattle. About 150 to 200 different serotypes of *E. coli exist*; one in particular, *O157:H7*, is associated with human disease.

Several national surveys of animal production facilities conducted in the 1990s (33,34,35) found the *O157:H7* serotype of *E .coli* in samples from dairy cows, calves and feedlot cattle. An antibiotic-resistant form of *O157:H7* was observed during a study conducted on dairy farms in Wisconsin (26). *E. coli* resistance to apramycin, gentamicin and nourseothricin related to swine production has been reported in the United Kingdom and Europe.

Enterococcos faecalis and *Campylobacter jejuni* also contribute to gastrointestinal illness in humans. Strains of *Enterococcos faecalis* with observed resistance to avoparcin and vancomycin have been reported in the United Kingdom and Europe. Studies have shown that the exhibited traits for resistance have been transferred to other species of *Enterococcos* and *Listeria monocytogenes*.

Campylobacter jejuni is the most commonly recognized cause of gastroenteritis in the United States (27) and poultry is the major source of infections. Significant increases in quinolone-resistant strains of *C. jejuni* taken from infected humans were reported during the 1990s in United Kingdom, Europe and Mexico. This increase correlates positively with the introduction of quinolones for poultry production in these countries.

Antibiotic resistance and water resources

The discussion above establishes that transfer of antibiotic resistance occurs within and among bacterial species. The development of antibiotic resistance does not necessarily follow the introduction of a new antibiotic, although this is a distinct possibility. Discontinued use of an antibiotic in some cases has been correlated with decreased populations of antibiotic-resistant organisms.

However, this is not a universal observation for all cases of antibiotic resistance. The concern related to development of antibiotic resistance from the indirect release of antibiotics into the environment is justified. Development of antibiotic resistance is a natural process that potentially is initiated whenever a bacterial population is exposed to an antibiotic. Whether significant antibiotic resistance actually develops is another matter.

Water resources play an important role in the transfer of antibiotics and genetic material for resistance. Monitoring for both antibiotics and DNA in environmental materials (i.e., water, soil and sediments) requires sophisticated techniques and instrumentation that have been developed only recently. Some studies and monitoring projects are

beginning to provide information about the relationship between environmental levels of antibiotics and resistant genetic material.

Monitoring studies in the United States (20) and Germany (15) demonstrate that certain antibiotics do contaminate water resources. Fourteen out of 22 antibiotics tested were detected in U.S. streams **(Table 5)**. Seven out of 18 antibiotics tested were detected in German water resources **(Table 5)**.

Whether water resource contamination with antibiotics significantly contributes to antibiotic resistance still needs to be determined. In Denmark, a study of pig manure applications to farmland showed that antibiotic resistance to tetracycline, streptomycin, erythromycin and lincomycin was significant in the manure slurry (25). After manure application, antibiotic resistance of soil bacteria increased for a short period of time, but returned to normal levels in less than five months.

There appears to be a period of time that transport of antibiotic-resistant genetic material could occur through runoff from treated soils.

In Illinois, a group of researchers (7) found evidence of the translocation of genetic material carrying specific resistance to tetracycline. DNA analyses on water samples from a shallow water table directly in the path of groundwater flow from two hog waste lagoons revealed the presence of tetracycline-resistant genes. In this case, leaky waste lagoons were a source for the transmission of antibiotic resistance via groundwater flow.

Table 5. Detection of antibiotics in U.S. (20) and German (15) water resources.

Antibiotic	U.S. Streams	German Streams	German Sewage Treatment Plant Effluent	German Groundwater
chloramphenicol	*not tested*	**DETECTED**	**DETECTED**	not detected
chlortetracycline	**DETECTED**	not detected	not detected	not detected
ciprofloxacin	**DETECTED**	*not tested*	*not tested*	*not tested*
clarithromycin	*not tested*	**DETECTED**	**DETECTED**	not detected
erythromycin	**DETECTED**	**DETECTED**	**DETECTED**	not detected
lincomycin	**DETECTED**	*not tested*	*not tested*	*not tested*
norfloxacin	**DETECTED**	*not tested*	*not tested*	*not tested*
oxytetracycline	**DETECTED**	not detected	not detected	not detected
roxithromycin	**DETECTED**	**DETECTED**	**DETECTED**	not detected
sulfadimethoxine	**DETECTED**	*not tested*	*not tested*	*not tested*
sulfamethazine	**DETECTED**	not detected	not detected	**DETECTED**
sulfamethizole	**DETECTED**	*not tested*	*not tested*	*not tested*
sulfamethoxazole	**DETECTED**	**DETECTED**	**DETECTED**	**DETECTED**
tetracycline	**DETECTED**	not detected	not detected	not detected
trimethoprim	**DETECTED**	**DETECTED**	**DETECTED**	not detected
tylosin	**DETECTED**	*not tested*	*not tested*	*not tested*

Management of Bioactive Chemicals for Water Resource Protection

Notwithstanding considerable gaps in our knowledge of the environmental fate of bioactive chemicals, we know enough to formulate some management strategies. The U.S. EPA has outlined treatment methods designed to remove specific endocrine disruptors from municipal water supplies (13). Management practices designed for specific situations are beyond the scope of this discussion, but considering strategies that eventually will be composed of many individual practices is appropriate.

Screening and monitoring for endocrine disruptors

The extremely small concentrations of bioactive chemicals in the environment and the complexity of "cause and effect" relationships challenge our ability to develop management strategies.

Development of screening models and monitoring techniques for endocrine disruptors that provide consistent and meaningful quantification of environmental concentrations is essential before effective management strategies can be implemented. However, the use of a single screening or monitoring method is not recommended because of the complexity of the problem. Single and/or simple models likely would cause false negative or positive results with inappropriate safety factors (10).

The Committee on Hormonally Active Agents in the Environment for the National Research Councils

(NRC) has made the following recommendations regarding monitoring (10):

1. A battery of short-term tests that are rapid and inexpensive need to be developed for endocrine disruptors. They need to reflect the range of endocrine disruption known to occur.
2. Indicators or biomarkers of exposure to endocrine-disrupting chemicals (e.g., vitellogenin in fish) need to be incorporated into screening procedures.
3. Monitoring protocols need to be robust enough to adequately account for the significant differences in response to endocrine disruptors related to the age of individuals exposed.
4. Work should continue to identify sensitive wildlife species to serve as environmental sentinels. Populations of these sentinel species should be monitored regularly for change that would be the first indicator of elevated levels of certain endocrine-disrupting chemicals.
5. Observed environmental concentrations of endocrine disruptors continually need to be placed into the context of actual biologic toxicity and dose-response relationships. Measurable quantities of endocrine-disrupting chemicals in the environment do not necessarily constitute significant impacts.

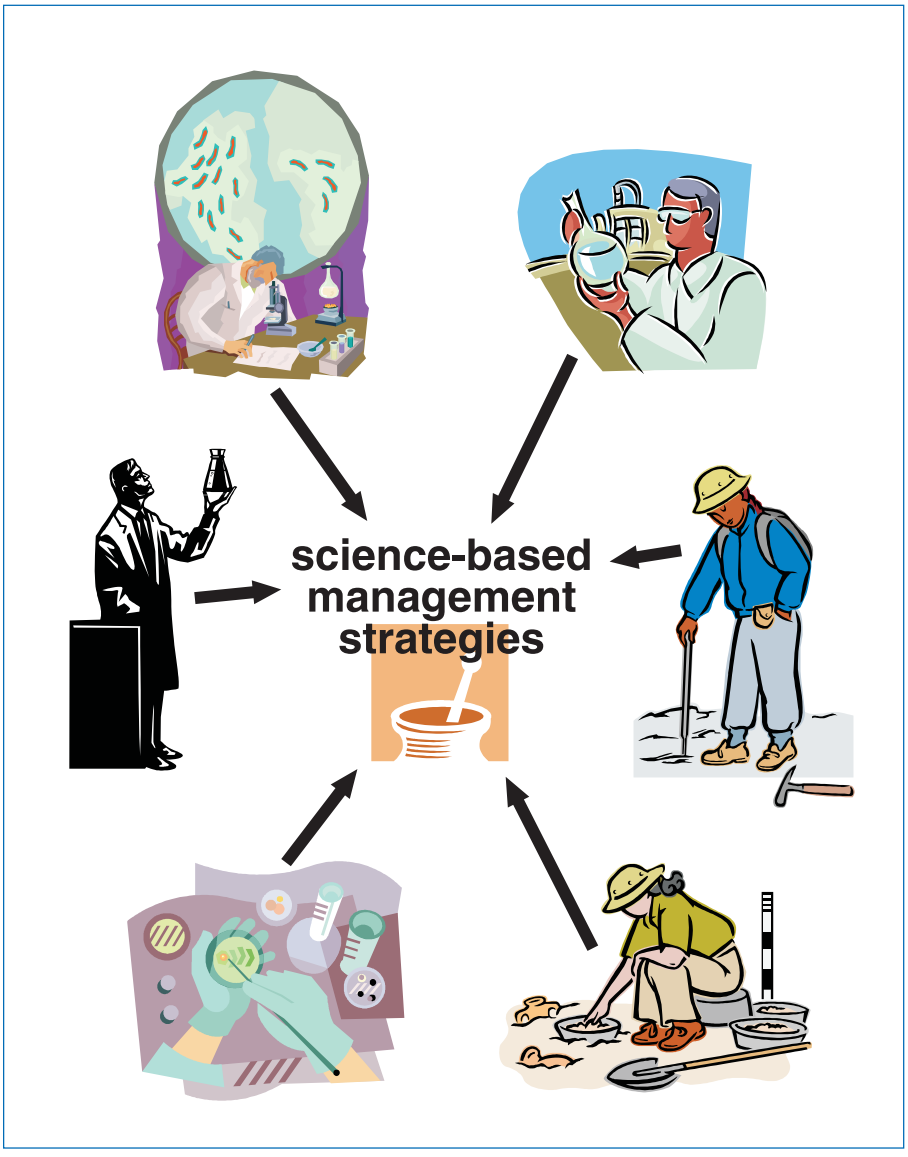

Figure 6. Screening and monitoring are needed for effective management strategies.

Monitoring for antibiotic resistance

Monitoring for antibiotic resistance needs to track both resistant organisms and antibiotic use. In the United States, three USDA agencies (APHIS, ARS and FSIS) are involved in the National Antimicrobial Resistance Monitoring System (NARMS). The enteric bacteria *Salmonella, Campylobacter* and *E. coli* are the focus of the monitoring effort. NARMS collects and analyzes samples from livestock operations from various surveys and studies around the nation. The samples are analyzed and results stored in a national database at the Richard Russell Research Center in Athens, Ga.

Requirements for records of antibiotic use are not the same for human and animal drugs. Point-of-sale records for human drugs are obtainable, but not for animal drugs. Many groups have suggested (8) that requirements for detailed information regarding potency and use characteristics of antibiotics in the livestock industry need to be obtained in a more rigorous and regular fashion.

Waste management recommendations to reduce estrogen losses

Both humans and animals continually excrete estrogens (natural and manufactured). A potential exists for contamination of water resources when excreted wastes are applied to the land.

Estradiol and its degradation products have been shown to have a high affinity to organic matter (6). The rate of mineralization or degradation of estradiol after adsorption has been shown to be extremely rapid in both sewage treatment plants (7) and soils (2,3,4).

However, some studies showed increased levels of estrogen and testosterone in runoff from fields where animal manure had been applied (5,12).

Estrogen and testosterone concentrations were inversely correlated with the length of time between the manure application and the first runoff event. Increased levels of estrogen in spring water also were positively correlated to runoff events in an area of heavy manure applications (11).

In one study (9), a significant decrease of estrogen concentration was observed when runoff was diverted from a manured pasture through a tall fescue filter strip between 20 and 60 feet wide. Based on these observations, manure likely can be applied to fields using practices that greatly reduce or eliminate the translocation of estrogen to water resources.

Here are some management recommendations that can help accomplish reductions in estrogen translocation:

1. Land-applied manure or sewage sludge should be incorporated into the soil immediately.
2. Manure or sewage sludge should be applied in fields that are least likely to generate significant runoff or groundwater recharge. Soils with greater than 6 percent slopes should be avoided. Sandy or gravelly soils that serve as aquifer recharge sites also should be avoided.
3. Manure or sewage sludge applications should be timed to avoid significant runoff events.
4. A vegetated filter strip no less than 20 feet wide should border fields that receive regular applications of manure or sludge.
5. Allowing manure to age before land application will promote greater degradation of estrogen and a substantial reduction in loading.

Figure 7. Feeding colustrum to calves is an effective practice that helps maintain a robust immune system.

Recommendations for reduced antibiotic use

Theoretically, reduced use of an antibiotic also reduces the indirect exposure of other (nontarget) bacterial populations. The result is less environmental pressure that would lead to the development and maintenance of resistant strains of bacteria to a given antibiotic. Recommendations designed to reduce the overall use of antibiotics for animal production can be categorized into the following groups of management strategies (1):

1. A simple but important recommendation is that veterinarians, as with physicians, practice greater restraint in prescribing antibiotic treatments.
2. The incidence of disease obviously correlates positively with the use of antibiotics; therefore, practices that reduce the potential for disease also contribute to less need for antibiotics. The basic hygienic practice of waste separation from the living area has had enormous impact on the reduction of disease in the human population. This simple practice has the same impact on animal health. All livestock facilities regularly should use practices that maintain a clean, healthy environment for all animals.
3. The introduction of new diseases to which individuals have no natural immunity has been a problem throughout human history. The decimation of Native Americans by the small pox virus that European explorers carried is a case in point.

   Prevention of disease transfer by "foreign" intruders is referred to as "biosecurity" and is just as important to animal health. All livestock operations should formulate and implement an active biosecurity plan.
4. Practices that maintain a healthy immune system should be used regularly. Maintenance of a robust immune system gives individuals within a population the natural ability to fight and overcome disease before antibiotic drugs are necessary. This is true for both humans and animals.

   The regular application of vaccinations can provide immunity to many common diseases. The administration of colostrum to newborn calves is a specific practice that has been effective in cattle. The antibodies carried in colostrum have been shown to impart immunity for weeks to months. Proper nutrition, including mineral supplements, also contributes to a strong, resilient immune system.
5. If possible, avoid the application of antibiotics in feed as prophylactics or growth promoters. This is a controversial recommendation because the subtherapeutic administration of antibiotics as feed additives has been shown to improve livestock growth to the extent that it is a profitable practice.

   The subtherapeutic use of antibiotics in animal production has no human medical analogy. The discovery of the positive effects of low levels of antibiotics on the growth of chickens came in the early 1950s and expanded quickly to other types of animals. Evidence indicates that the regular low levels of antibiotics in animal feed function as a prophylactic in certain diseases, such as swine dysentery. However, a secondary benefit is not fully understood.

   Subtherapeutic levels of antibiotics also exhibit an apparent modulating effect on intestinal microflora that results in more efficient digestion and consequent improvements in animal growth. Because of the lack of good information regarding the actual sale and use of subtherapeutic antibiotics, a wide range in estimates of use exists.

   One group claims that the use of antibiotics as growth promoters is significantly greater than the therapeutic use for both humans and animals combined (8). Some groups have proposed a complete ban on the subtherapeutic use of antibiotics. Sweden actually implemented such as ban in 1986. By 1996 the total amount of antibiotics used in Sweden had decreased by 55 percent.

   The Swedish Animal Health Service has concluded that the ban has provided evidence that poultry, calves and pigs can be raised without the use of subtherapeutic levels of antibiotics if production practices such as improved hygiene are maximized.

   Recent research on "probiotic" chemicals that improve antibody levels or strengthen the immune system through vitamin supplements demonstrates one alternative to the subtherapeutic use of antibiotics.

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Glossary of Terms and Acronyms

- **abiotic degradation**
  decomposition of organic chemicals through processes not associated with organism metabolism, such as hydrolysis or photolysis

- **adsorption isotherm**
  describes the mathematical relationship between the concentration of chemical in solution and adsorbed to a solid phase material such as soil or sediment. The simplest relationship is described is the Nernst partitioning equation $K_d = C_s/C_w$, where K_d is the partition coefficient, C_s is the chemical concentration adsorbed to the solid and C_w is the chemical concentration in solution. The Freundlich isotherm equation includes a linearity parameter (n) and the Langmuir isotherm equation includes parameters that describe sorption interactions with a finite number of sorption sites.

- **agonist**
  endocrine-disrupting chemical that causes an exaggerated response by the body

- **androgen**
  steroidal molecules secreted primarily by the interstitial Leydig cells of the testes and are responsible for male sexual determination, differentiation and development. The main androgen chemicals in most vertebrates are testosterone and 5α-dihydrotestosterone. In fish the main androgen is 11-ketotestosterone.

- **antagonist**
  endocrine-disrupting chemical that causes the body to respond incorrectly or in a limited way

- **antibiotic**
  a substance produced by microorganisms that kills or suppresses multiplication or growth of other microorganisms. Tetracycline is an example of an antibiotic. Antibiotics are a subclass of antimicrobial chemicals that are produced naturally.

- **antimicrobial**
  a synthetic or natural substance that kills or suppresses multiplication or growth of microorganisms. Sulfonamide is an example of a synthetic antimicrobial. Antibiotics are a subclass of natural antimicrobial chemicals.

- **APE**
  alkylphenol ethoxylate, an endocrine disruptor used as a nonionic surfactant in the manufacture of plastics, elastomers, agricultural chemicals and pulping detergent

- **APHIS**
  Animal and Plant Health Inspection Service of the U.S. Department of Agriculture

- **BBP**
  butyl benzyl phthalate

- **beta lactams**
  class of antimicrobial chemicals, including amoxicillin, ampicillin, cefotaxime, cloxacillin, oxacillin, penicillin G and penicillin V

- **bioaccumulation**
  accumulation of chemicals in biologic tissue. Organic chemicals that are lipophylic or that have log K_{ow} most likely will bioaccumulate.

- **biomarker**
  chemical used to as an indicator of endocrine system disruption (e.g., vitellogenin in male fish)

- **biotic degradation**
  decomposition of organic chemicals through processes associated with organism metabolism resulting in degradation products called metabolites

- **BPA**
  bisphenol A (4,4'-isopropylidenediphenol), an endocrine disruptor used in the production of polycarbonate for the manufacture of plastic products

- ***Campylobacter jejuni***
  bacteria that causes intestinal diseases in animals and humans. Some strains have antibiotic resistance to the antibiotic quinolone.

- **CEAH**
  Centers for Epidemiology and Animal Health of the U.S. epartment of Agriculture

- **CLLE**
  continuous liquid; liquid extraction

- **coccidiostat (antiprotozoal)**
  a chemical used to control single-cell parasites (protozoans) (e.g., amprolium, clopidol, dimetridazole, narasin and nicarbazin)

- **companion animal**
  pet

- **conjugation**
  metabolic process that changes a drug's chemical structure to a conjugated form (glucoronide) through the process of glucuronation that is more water soluble but less bioactive than the unconjugated parent drug. Bacterial action in STPs change many conjugated metabolites back to the bioactive unconjugated form.

- **Daphnia magna**
  species of water flea frequently used as a test organism to determine ecotoxicity in an aquatic environment

- **DBP**
  dibutyl phthalate di-n-butyl-phthalate), the most commonly found phthalate in aquatic environments

- **DDD**
  1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethane, degradation product of DDT

- **DDE**
  1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene, an endocrine disruptor that is a degradation product of DDT

- **DDT**
  dichlorodiphenyltrichloroethane, an endocrine disruptor used as a pesticide

- **DES**
  diethylstilbestrol, a xenoestrogen responsible for genitourinary tract abnormalities in second-generation children

- **dioxin**
  a group of several hundred chemical compounds that are members of three closely related chemical families: the chlorinated dibenzo-r-dioxins (CDD), chlorinated dienzofurans (CDF) and certain polychlorinated biphenyls (PCB). CDDs and CDFs are not created intentionally, but are produced inadvertently by a number of human activities. Many dioxins are the result of burning waste and fuels.

- **DOM**
  dissolved organic matter

- **E1**
  estrone, a natural estrogen

- **E2**
  estradiol, a natural estrogen

- **E3**
  estriol, a natural estrogen

- **EE2**
  17a-ethynlestradiol, a synthetic estrogen

- **EC_{50}**
  50 percent immbilization of test organism concentration

- **ecotoxicity**
  toxic impact of chemicals on the environment. Generally, the impacts are divided into terrestrial and aquatic environments. Select species include algae, insects, crustaceans and fish as test organisms to determine EC_{50} and LC_{50} for each chemical in the aquatic environment. To determine terrestrial toxicity, test species include microbes, plants, earthworms and insects.

- **ectoparasiticide**
  chemical agent used to control external parasites such as mites, blowfly, lice ticks, headfly and keds (e.g., diazinon and pyrethroids)

- **EIC**
  xpected introductory concentration based on an estimate of the amount of chemical manufactured per year and the amount of liquid entering a typical STP per year

- **endectocides**
  anti-parasitic agents used to control internal and external parasites, such as gastrotintestinal worms, liver flukes and lung worms (e.g., ivermectin, pyrantel, triclabendazole)

- **endocrine disruptor**
  a chemical substance that interferes with, or has adverse effects on, the production, distribution or function of hormones

- **endocrine modulator**
  a chemical substance that causes subtle change without dramatic impact to the production distribution or function of hormones

- ***Enterococcus***
  a genus of bacteria found in the intestinal tract of animals and humans. Some strains of *E. faecium* have multidrug resistance.

- **environmental compartment**
  soil, air, surface water, groundwater, sediment and biota

- ***Escherichia coli***
  E. coli, bacteria that reside in the intestinal tracts of humans and animals. Some strains are pathogenic and responsible for various types of intestinal disease. E. coli O157:H7 is of particular concern because of its virulence toward humans and its resistance to many antibiotics.

- **estrogen**
  steroidal molecules secreted primarily by follicle cells surrounding the oocytes of the ovary and are responsible for female sexual determination, differentiation and development. The main estrogen chemicals in all classes of vertebrates are 17β-estradiol, estrone and estriol.

- **fluoroquinolones**
  antibiotics that are derivatives of quinolones used for both human and animal diseases

- **GC/MS**
  gas chromatography/mass spectrometry analytical method

- **GC/MS-MS**
  gas chromatography/tandem mass spectrometry analytical method

- **growth promoter**
  an antibiotic used as a feed additive at subtherapeutic concentrations to enhance animal growth and production (e.g., spiramycin, tylosin, carbadox, virginiamycin and monesnin)

- **HAA**
  hormonally active agent

- **HAH**
  halogenated aromatic hydrocarbon

- **hormone**
  a chemical messenger that starts or stops a specific biologic function. It is manufactured and secreted by an internal gland.

- **HPLC**
  high-pressure liquid chromatography analytical method

- **hydrophilic**
  organic chemical that associates with water and would be considered water soluble. The polar nature of many pharmaceutical drugs makes them hydrophilic.

- ***in vitro***
  biological processes determined by testing outside the body of an organism under laboratory conditions

- ***in vivo***
  iological processes determined by testing within the body of an organism under laboratory or environmental conditions

- **K_{ow}**
  octanol/water partition coefficient

- **K_d**
  solid/water partition coefficient

- **K_{oc}**
  organic carbon/water partition coefficient

- **LC_{50}**
  50 percent lethal to test organism concentration

- **LC/MS-ESI**
  liquid chromatography/mass spectroscopy — positive-ion electrospray analytical method

- **Lipophilic**
  organic chemical that associates with lipids (fats) and is therefore not water soluble (solubility < 100 mg/l)

- **LOD**
  limit of detection

- **LOEC**
  lowest observed effect on test organism concentration

- **macrolides**
  class of antimicrobials, including erythromycin, lincomycin, ormetoprim, roxithromycin, trimethoprim, tylosin and virginiamycin

- **metabolite**
  product of chemical degradation via the processes of biologic metabolism. Phase I metabolites are the result of oxidation, reduction, hydroxylation, hydrolysis or glucuronation reactions. Phase II metabolites are the result of conjugation.

- **MIC**
  minimum inhibitory concentration, the lowest concentration of an antibiotic that will inhibit the growth of a bacterium *in vitro*

- **monodrug resistant**
  resistance to one antibiotic

- **multidrug resistant**
  resistance to more than one antibiotic

- **mycoestrogen**
  type of estrogen produced by fungi (e.g., zearalenone)

- **NAHMS**
  ational Animal Health Monitoring System of the U.S. Department of Agriculture

- **NEPA**
  National Environmental Policy Act

- **NP**
  nonylphenol, a degradation product of APEs

- **NOEC**
  no observed effect concentration
- **NOEL**
  no observed effect level
- **NPE**
  nonylphenol ethoxylate, a type of APE that accounts for more than 80 percent of the APEs produced
- **OWC**
  organic waste water contaminants, including veterinary and human antibiotics, prescription drugs, nonprescription drugs, deodorizers, anti-oxidants, anti-corrosives, plasticizers, PAHs, pesticides, detergents, degreasers, fire retardants, steroids and hormones
- **PAH**
  polycyclic aromatic hydrocarbon
- **PCB**
  polychlorinated biphenyl, an endocrine disruptor created for many industrial purposes, such as insulation, hydraulics and paint plasticizers
- **PEC**
  predicted environmental concentration based on the amount of chemical sold, the number of inhabitants, waste-water quantity and dilution
- **PhAC**
  pharmaceutically active compound
- **phthalates**
  a type of manufactured chemical used to impart flexibility to plastics. They are the most abundant man-made chemical found in the environment and some are endocrine disruptors.
- **phytoestrogen**
  type of estrogen produced by plants, particularly legumes (e.g., coumestrol)
- **pK_a**
  negative log of the acid dissociation constant. The formula for this constant describes the mathematical relationship between the concentration of charged species that result when a chemical that exhibits incomplete or weak dissociation in water is dissolved. The hydronium ion $[H^+]$ is one of the charged species, so the negative log of its concentration (pH), along with the pK_a, influences the concentration of the other charged species. Most organic compounds exhibit weak dissociation, so the pK_a may be used to predict which charged species will be present at a given pH and how this may influence adsorption on solid materials such as organic matter, clays, and oxides of iron and aluminum.
- **PNEC**
  predicted no environmental effect concentration
- **ppb**
  parts per billion, microgram per liter (mg/l)
- **PPCP**
  pharmaceutical and personal care products
- **ppm**
  parts per million, milligram per liter (mg/l)
- **ppq**
  parts per quadrillion, picogram per liter (pg/l)
- **ppt**
  parts per trillion, nanogram per liter (ng/l)
- **prophylactic**
  the use of antibiotics as a treatment to prevent disease. The concentrations for prophylactic treatment are below (subtherapeutic) those for therapeutic applications, generally < 200 g/ton.
- **QSAR**
  quantitative structure-activity relationships
- **quinolones**
  class of anti-microbials that target DNA gyrase, an essential bacterial enzyme that is responsible for introducing superhelical twists into the DNA, which include flumequine, norfloxacin, oxolinic acid, sarafloxacin, ciprofloxacin, ofloxacin, lomefloxacin and clinafloxacin
- **R-type**
  resistance type
- ***Salmonella***
  a genus of bacteria responsible for many types of intestinal diseases in animals and humans. Infected beef, dairy, pork, poultry and seafood may transfer the disease to humans.
- ***Serpuolina hyodysenteriae***
  bacteria responsible for swine dysentery
- **SIM**
  selected ion monitoring analytical method
- **SLRA**
  creening level risk assessment

- **sludge**
  digested solids originating from the bottom of municipal sewage treatment lagoons. Maintenance of the lagoon requires that the sludge be removed intermittently. Disposal of removed sewage sludge may include land application.

- **SPE**
  solid-phase extraction

- **STP**
  sewage treatment plant

- **STW**
  sewage treatment works

- **sulfonamides**
  class of anti-microbials that includes sulfachlorpyridazine, sulfadiazine, sulfadimethoxine, sulfamerazine, sulfamethazine, sulfamethoxazole and sulfathiazole

- **$T_{1/2}$**
  half-life, time (days) for one-half of the original amount of organic chemical to be degraded. Half-life may vary from days to years, depending on the chemical properties and environmental conditions.

- **TBT**
  tributyltin, an endocrine disruptor used as an anti-fouling (biocide) compound in paints for ship hulls

- **TCB**
  tetrachlorobiphenyl

- **TCDD**
  2,3,7,8-tetrachlorodibenzo-*p*-dioxin, an endocrine disruptor and one of the most toxic and studied dioxins

- **tetracylines**
  class of antimicrobials that includes chlorotetracycline, doxycycline, minocycline, oxytetracycline, tetracycline, and degradation products anhydrochlortetracycline, anhydrotetracycline and demecloycline

- **therapeutic**
  the use of antibiotics to treat an existing disease as opposed to nontherapeutic uses for prophylaxis or growth promotion

- **vinclozolin**
  VTG, 3-(3,5-dichlorophenyl)-5-methyl-5-vinyl-oxazolidine-2,4-dione, an endocrine disruptor used a a dicarboxidide fungicide on grapes, fruits, vegetables and hops

- **vitellogenin**
  a female lipoprotein that functions as a yolk-precursor in fish eggs

- **VS**
  Veterinary Services of the U.S. Department of Agriculture

- **VP**
  veterinary pharmaceuticals

- **xenobiotics**
  chemicals created for control of biota or biologic processes

- **xenoestrogen**
  estrogenic chemical produced artificially outside the body (e.g., 17α-ethynylestradiol used oral contraceptives)

The positive consequences of using bioactive compounds for disease and pest control are substantial.

The unanticipated negative effects combined with their widespread presence in some geographic areas are what have generated concern about their use.

For more information on this and other topics, see: www.ag.ndsu.nodak.edu

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