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Wildlife Toxicology: Environmental Contaminants and Their National and International Regulation

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WILDLIFE TOXICOLOGY

Environmental Contaminants and Their National and International Regulation

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Wildlife toxicology is the study of potentially harmful effects of toxic agents in wild animals, focusing on amphibians, reptiles, birds, and mammals. Fish and aquatic invertebrates are not usually included as part of wildlife toxicology since they fall within the field of aquatic toxicology, but collectively both disciplines often provide insight into one another and both are integral parts of ecotoxicology (Hoffman et al. 2003). It entails monitoring, hypothesis testing, forensics, and risk assessment; encompasses molecular through ecosystem responses and various research venues (laboratory, mesocosm, field); and has been shaped by chemical use and misuse, ecological mishaps, and biomedical research. While human toxicology can be traced to ancient Egypt, wildlife toxicology dates back to the late 19th century, when unintentional poisoning of birds from ingestion of lead shot and predator control agents, alkali poisoning, and die-offs from oil spills appeared in the popular and scientific literature (Rattner 2009).

By the 1930s, about 30 pesticides were commonly available (Sheail 1985), and crop-dusting aircraft facilitated their use. With the discovery of dichlorodiphenyltrichloroethane (DDT) in 1939, and related compounds shortly thereafter, use of pesticides increased exponentially. Between 1945 and 1960, wildlife mortality events were documented following pesticide application in agricultural and forest habitats. Field and laboratory studies described effects on reproduction, survival, tissue residues, and toxicity thresholds in birds. The widespread hazards of spent lead shot, and mercurials from fungicides and industrial activities became apparent.

Scientific observations and the publication of *Silent Spring* (Carson 1962) led to contaminant monitoring programs in the United States, United Kingdom, and Canada during the 1970s. Research highlights of this era included bioaccumulation of organochlorines in food chains, exposure of diverse species (e.g., bats, marine mammals), and avian mortality due to accumulation of lethal pesticide residues. Eggshell thinning and population declines in raptorial and fish-eating birds were attributed to DDT (and its metabolite DDE), and polychlorinated biphenyls (PCB) were detected and linked to reproductive problems in mink. Screening programs were launched to examine chemical toxicity and repellency to birds and mammals.

By the 1980s, heavy metal pollution from mining and smelting activities, agrichemical practices and non-target effects, selenium toxicosis, PCB pollution, die-offs related to anticholinesterase pesticides,

and environmental disasters (e.g., Chernobyl, *Exxon Valdez*) were at the forefront of ecotoxicology. Molecular biomarkers, endocrine disruption, population modeling, and studies with amphibians and reptiles dominated the 1990s. With the turn of the century, interests shifted toward pharmaceuticals, flame retardants, and surfactants; toxicogenomics; inter-specific extrapolation of toxicity data; and interconnections between wildlife toxicology, ecological integrity, and human health (Rattner 2009).

Mechanisms of Action and Changes Over Time

Chemicals pose risks to organisms due to a combination of factors that are intrinsic to the compound, particular species, and/or from interaction with extrinsic factors (e.g., habitat, ambient temperature), and other chemicals. The myriad physiological, behavioral, and life history characteristics of different organisms result in unique exposure pathways and unusual susceptibilities. For example, physical and chemical properties of some contaminants may cause them to preferentially accumulate in water, sediment, or soil, habitats, or ecosystems, or may cause particular toxicity to certain species. Species and individuals can be affected by contaminants directly and indirectly (see Chapter 24 in this volume). Also, individuals and populations are rarely exposed to single contaminants, and the effects of exposure to mixtures may differ from the effects of a single chemical through additive, synergistic, antagonistic, or delayed effects.

Over the past century, discoveries concerning how chemicals move through the environment and the effects they can have on wildlife and people have changed the types and properties of synthetic chemicals. Within the past decade, chemical-induced climate change and discoveries of pesticides and industrial chemicals in pristine locations have resulted in international regulation to restrict chemical manufacture and use to those with the least risk to human health and the environment. As early as the 1990s, the U.S. Environmental Protection Agency (USEPA) initiated a "Design for the Environment Program" that sought to develop cleaner product processes and reduce pollution. One goal of the program is to "minimize environmental damage and maximize efficiency during the life of the product" (www.epa.gov/dfe/pubs/comp-dic/factsheet/). The program promotes use of nontoxic manufacturing processes with minimal emissions, and recyclable materials that have few harmful effects on the environment. Characteristics of newer replacement compounds include short environmental half-lives, limited potential for bioaccumulation, and mechanisms of action that do not evoke toxic effects in non-target animals.

MAJOR ENVIRONMENTAL CONTAMINANT CLASSES

The most widely recognized classes of contaminants that have demonstrated effects or pose risk to wildlife and human populations include pesticides, industrial chemicals, fossil and mineral fuels, pharmaceuticals (human and veterinary) and personal care products, metals, and fertilizers (Table 25.1).

Pesticides

The vast majority of synthetic chemical substances are industrial in nature (80,000 to 100,000 registered). Even though there are only about 1,200 active pesticide compounds, their volume of use is significant. Annually, more than 5 billion pounds of pesticides are used worldwide, with the United States accounting for 20% to 30% of global usage (USEPA 2001). As of 2007, pesticides were detectable in most surface water samples, major aquifers, and fish species in the United States; they sometimes exceeded water-quality benchmarks for aquatic or fish-eating wildlife (Gilliom 2007).

Use of cyclodiene insecticides (e.g., DDT, aldrin, dieldrin, lindane, and chlorodecone) became widespread after World War II. The half-lives of these chemicals are on the order of 30 years. They are very hydrophobic and accumulate in lipids within animals and humans. Consequently, these compounds biomagnify in the food chain, resulting in very high exposure to top predators and insectivorous birds. Cyclodienes cause toxicity by inhibiting ATPases, antagonizing neurotransmitters, and depolarizing nerves by interfering with calcium fluxes both along the axon and at the neuronal junctions. The neurological effects are universal across all animal species, resulting in very nonspecific insecticides. Toxic effects can occur in non-neural tissues; for example, inhibition of calcium ATPase in the shell gland of birds

Table 25.1 Common Chemical Classes Affecting Wildlife and Human Health

Chemical Class	Most Common Sub-Classes or Types Found in the Environment	Unifying characteristic
Pesticides	Herbicides/fungicides/algaecides Insecticides/nematicides/molluscicides Avicides/rodenticides Growth regulators (plant and insect)	Designed to kill, repel, or alter physiological mechanisms in target organisms
Industrial Chemicals	Volatiles (e.g., household products including paints, paint strippers, wood preservatives, aerosol sprays, cleansers and disinfectants, moth repellents, air fresheners, stored fuels, automotive products, hobby supplies, dry-cleaned clothing) Semi-volatiles (e.g., industrial plasticizers (phthalates), byproducts of incomplete combustion of fossil fuels (benzo(a)pyrene), dioxins, PCBs, brominated flame retardants, lubricants) Solvents (e.g., acetone, ethanol, hexane, carbon tetrachloride, ether, etc.) and surfactants Nanomaterials Explosives and energetic compounds	The largest class of synthetic chemicals with no definable common characteristics but used in the household, in work areas, and industrial processes
Fossil and Mineral Fuels	Oil/petroleum Coal Natural gas Naturally occurring energetic compounds (e.g., perchlorate)	Natural resources that primarily consist of carbon and hydrogen, are burned to produce energy, or are used to develop consumer items (e.g., plastics)
Pharmaceuticals (Human and Veterinary)	Hormone agonists/antagonists (e.g., birth control pills, thyroid medications, cholesterol synthesis blockers, both synthetic and natural) Antimicrobials (e.g., antibiotics, antiparasitics, antifungals, antivirals) Analgesics/Neuroleptics/Anesthetics Antidepressants/Antianxiety medications Controlled substances (illicit) Antihypertensives	Designed to be biologically active and are often introduced into the environment at steady rates through sewage treatment plants, concentrated animal feeding operations and widespread biosolid dispersal
Personal Care Products	Nutraceuticals Food additives (e.g., caffeine) Cosmetics, fragrances, soaps, and everyday use items	Individual consumer use introduced into the environment at steady rates primarily through sewage and water treatment plants
Metals	Heavy and/or inorganic metals Metalloids (e.g., mercury, selenium, arsenic) and organotins	Non-biodegradable, cannot decompose into less harmful components, can biomagnify
Fertilizers	Natural (e.g., manure, water-treatment sludge) Inorganic fertilizers	Chemicals used by agro-businesses to improve crop production

causes eggshell thinning (Lundholm 1987, 1997). Cyclodienes were very effective pesticides precisely because of their persistence (a single application provided long-term effects) and their toxicity to pests of both economic and epidemiological importance. They have been, for example, instrumental in controlling mosquitoes that transmit malaria, a disease that is responsible for infecting 350 million to 500 million people annually (http://www.cdc.gov/malaria/), and DDT still is used inside homes in tropical countries for this purpose. Dieldrin was very effective in controlling cotton pests and was of considerable economic benefit in the southern United States. However, Rachel Carson's book *Silent Spring* raised the alarm about the threats that uncontrolled use of these chemicals posed to wildlife and the environment. The USEPA banned the use of DDT in the United States in 1972, confirming that continued massive use of it posed unacceptable risks to the environment and potential harm to human health (http://www.epa.gov/history/topics/ddt/01.htm). Dieldrin was banned as an agricultural pesticide in 1974 and from other uses (e.g., termite control) in 1987 (http://www.epa.gov/pbt/pubs/aldrin.htm). Even prior to the ban on the cyclodiene pesticides, neurotoxic chemicals in the organophosphorus and carbamate classes were available for use as pesticides. These chemicals were developed initially as nerve agents during World War II and gained widespread use as insecticides in the 1950s and 1960s. They principally act by inhibiting acetylcholinesterase at neuromuscular junctions, which also is a universal property among all animal species. However, mammals contain *a*-esterases that rapidly metabolize these compounds, making them much less toxic to humans than to insects (Mineau 1991). Unfortunately, birds do not have such an enzyme in blood, so they remain more vulnerable to non-target effects of the cholinesterase inhibitors. Some organophosphorus pesticides act through an alternate mechanism causing degeneration of the myelin sheath and inducing a delayed neuropathy. After the ban of DDT, dieldrin, and other cyclodiene pesticides, the cholinesterase inhibitors gained popularity due to their low toxicity to mammals and short half-life in the environment (less than 1 month to a year in soils, depending upon the formulation). They vary widely in regard to toxicity to birds and non-target species, from the highly toxic parathion and methyl parathion (no longer registered for use in the United States) to the relatively nontoxic malathion, which is still used as a fogging agent for mosquito control. However, many of these chemicals are sufficiently toxic to people, wildlife, and the environment so that they can be used only by a licensed pesticide applicator.

The pyrethroid pesticides, developed in the late 1960s and 1970s in Britain (http://www.rothamsted.bbsrc.ac.uk/notebook/words/pyrethroids.htm), are synthetic analogs of pyrethrin, an insecticidal chemical found in flowers of plants in the genus *Chrysanthemum* (http://extoxnet.orst.edu/pips/pyrethri.htm). They are neurotoxins, opening sodium channels in nerve membranes and causing prolonged depolarization. Because the length of time the sodium channels are open is inversely related to temperature (i.e., shorter time of opening at higher temperatures), pyrethroids are much more toxic to invertebrates than to homeotherms such as birds and mammals (Narahashi et al. 1998). Pyrethroids also are rapidly metabolized in homeotherms and have a short (12 day) half-life in soils (http://npic.orst.edu/factsheets/pyrethrins.pdf). Therefore, these chemicals appear to be more environmentally benign than the organophosphorus or carbamate pesticides, although they are relatively toxic to some aquatic invertebrates, fish and tadpoles. They remain a common household pesticide used to control insects in lawns and in and around house foundations.

Other pesticide classes affect the nervous system in different ways (Brown 2006). Avermectins (abamectin) and phenyl pyrazoles (fipronil) are systemic insecticides used for flea control that block the action of the gamma-aminobutyric acid (GABA) receptor. Because GABA is an inhibitory enzyme, the nerves remain stimulated. Imidacloprid is a neonicotinoid insecticide that mimics the action of acetylcholine, also resulting in prolonged nerve stimulation. It is a more specific agonist in insects, affecting nicotinic acetylcholine receptors, than in birds or mammals, giving it greater target specificity than the older cholinesterase-inhibiting insecticides, although there is some evidence that their use may result in greater impacts on pollinator insects. Several classes of insecticides act through disruption of energy production (uncoupling of oxidative phosphorylation) and require activation within the insects. These include compounds such as hydramethylnon, sulfuryl fluoride, chlorfenapyr, and sulfluramid that may be toxic to birds, have a half-life of approximately 1 year,

and can bioaccumulate in the food chain (Brown 2006).

As all animals share similar nerve physiology and energy metabolism, pesticide development has targeted insect-specific physiological mechanisms (Brown 2006). Some insect growth regulators mimic juvenile hormone, causing insects to remain in the juvenile instar and not molt into adults. These are used as mosquito control agents in some locations but are considerably more expensive than conventional pesticides (e.g., malathion, DDT). Chitin synthesis inhibitors block the production of chitin, an important component of the insect exoskeleton. Because insects need to synthesize chitin at each molt, they cannot molt or reach adult stage and eventually die without reproducing. However, some non-target organisms, such as shellfish and other crustaceans, also require chitin and can be adversely affected by these compounds.

Although most pesticides target invertebrates, there are several products directed at vertebrate pests, particularly rodents. Rodenticides include strychnine and zinc phosphide that are systemic poisons for birds and mammals. Anticoagulant baits include coumarins that kill animals after ingesting only a single dose. Indandiones (e.g., diphacinone) usually require several doses to cause death. These chemicals interfere with the synthesis of vitamin K required for post-translational processing of clotting factors and hemostasis. They increase the permeability of capillaries, allowing blood to extravasate into the body cavity. Secondary poisoning of hawks, owls, foxes, and other predators that eat poisoned rodents may be a problem in some areas. The USEPA recently restricted the use of some anticoagulant rodenticides (http://www.epa.gov/oppsrrd1/reregistration/rodenticides/finalrisk-decision.htm). It remains difficult to develop poisons for targeted wildlife pests that are sufficiently specific to reduce non-target mortality.

Herbicides are a group of pesticides that target weeds and invasive plants. They act through mechanisms specific to plants, such as disruption of photosynthesis or production of amino acids not shared by animals. Some kill on contact, whereas others are systemic and are taken up from the soil by the roots or translocated throughout the plant following a foliar spray. They may be used either pre-emergence (to inhibit seed germination and below-ground growth) or post-emergence on the above-ground plant, and can be broad-spectrum or specific to grasses or to broadleaf plants. General classes of herbicides include phenoxy acids (e.g., 2,4-D), triazine herbicides (e.g., atrazine), benzoic acids (dicamba), dinitroanilines (trifluralin), bipyrdyliums (diquat), substituted ureas (linuron), arsenicals, pyridines, and others including the widely used glyphosate and glufosinate. Historically, herbicides were considered to be minimally hazardous to people and wildlife. However, atrazine, which is widely used on corn, has been detected in groundwater throughout the Midwest, and concerns have been raised about potential exposure and toxicity to humans consuming well water. Multiple studies suggest that environmentally realistic concentrations of atrazine may affect amphibian development and reproduction (Giddings et al. 2005), although a recent critical review suggests that atrazine is not adversely affecting frogs (Solomon et al. 2008). In general, there is less concern about the potential environmental harm of herbicides than insecticides, with the possible exception of those applied directly to water for the control of vegetation (e.g., pondweed, duckweed, and *Hydrilla*). In the 1990s technological advances minimized the use of pesticides in agriculture. Some of these practices include biological pest control, crop rotation, mechanical controls and barriers that minimize pest damage, and genetically modified crops that impart disease and pest resistance. These practices can be more labor-intensive and expensive to implement. Genetically engineered crops have the potential to transfer genes to native species that may confer selective advantage and change the dynamics of natural plant communities (Ellstrand 2003). Furthermore, because of patents on insecticidal genes, farmers are prohibited from saving back seeds from one year's crop to start the next, making farming with genetically modified crops more expensive and making farmers more dependent upon agro-companies.

Mechanical means of controlling pests include silica aerogels and diatomaceous earth, which scratch through the waxy protective layer and absorb the protective oils on the insect's cuticle, causing water loss, dehydration, and death. Boric acid, which can be applied topically, also disrupts water balance in insects but has similar consequences in non-target organisms. Biopesticides include viruses and bacteria that are highly specific to certain insect species, as well as pesticidal products incorporated into plants through genetic engineering such as the insecticidal toxin from

the bacterium *Bacillus thuringiensis* (http://www.epa.gov/pesticides/biopesticides/). Some biopesticides have been linked to delayed development or decreased growth in some pollinator species—for example, monarch butterfly (*Danaus plexippus*) larvae (Dively et al. 2004)—although it is not clear if there are long-term effects on populations. It is assumed that adverse effects would be less than those associated with exposure to traditional pesticides. Integrated pest management also uses a combination of strategies, with insect growth regulators and pesticides as a last resort.

Industrial Chemicals

Compared to pesticides, much less is known about the modes of action and effects of industrial chemicals on fish, wildlife, and the environment. Industrial chemicals were not regulated until the late 1970s. At that time nearly 62,000 chemicals were put on the Toxic Substances Control Act (TSCA) Chemical Substance Inventory in the United States without requiring any information on their environmental or human health effects (http://www.epa.gov/lawsregs/laws/tsca.html). There are now over 83,000 chemicals in the TSCA Inventory, some of which have been assessed for safety, primarily through the use of structure–activity relationships (Auer et al. 1990) that compare the structures of new chemicals with those that have already been studied. Remarkably, health and environmental effects data are incomplete for over 2,000 high production volume (HPV) chemicals commonly used in the United States and elsewhere (http://www.epa.gov/HPV/pubs/general/basicinfo.htm), although considerable progress has been made to address data gaps.

The reporting of serious incidents in the media fostered public awareness of the hazards of industrial chemicals to the environment. Improper chemical disposal was highlighted at Love Canal, New York, where drums of chemical waste were dumped into ditches, covered over, and forgotten until people living in the area developed cancer and other symptoms of toxicity during the 1970s; the area was declared a state disaster area in 1978. The fire on the Cuyahoga River in Ohio in 1969 highlighted the consequences of discharging industrial wastes into rivers and other water bodies. Discovery in the 1980s of toxaphene and other organochlorine pesticides in Arctic species (Muir et al. 1988) and PCBs in breast milk of indigenous people in the region (Dewailly et al. 1989) raised concern about the potential for long-range transport of persistent bioaccumulative chemicals.

Polychlorinated and polybrominated biphenyls (PCBs and PBBs) belong to a class of halogenated chemicals that have been used since the 1940s as flame retardants. Their mode of action is similar to that of dioxins, one of the most toxic chemicals known to humans. The USEPA banned the use of PCBs in 1979 (http://www.epa.gov/history/topics/pcbs/01.htm), and PBBs a few years later following an incident in which cattle feed was accidentally contaminated with PBBs, causing human illness by its passage through milk. Polybrominated diphenyl ethers (PBDEs) were substituted for use as flame retardants, although recently these were discovered to evoke some toxic effects in wildlife and biomagnify in the human food chain (Sjödin et al. 2004). Many are now banned from use in Europe and are being phased out elsewhere.

During the late 1990s, the potential for chemicals to cause reproductive dysfunction in people and wildlife at relatively low environmental concentrations through actions on the endocrine system was publicly highlighted (Colburn 1997). Subsequent environmental studies have demonstrated estrogenic effects in fish from streams contaminated with pulp and paper mill discharges (Mellanen et al. 1999, Tyler et al. 1998). Bisphenol A and phthalates used in plastics and nonylphenols used as surfactants in common detergents have been implicated as endocrine disruptors (Patisaul 2010), leading to their ban in Europe and certain locations in the United States. Regulatory agencies in North America and Europe are now beginning the process of screening chemicals for potential endocrine activity; for example, the USEPA issued a data call in to screen 67 pesticides in October 2009, but at the time of this writing there is no formal registry of endocrine-active chemicals.

Most plastics are high-molecular-weight synthetic polymers with carbon, hydrogen, and some with oxygen, nitrogen, chlorine, and sulfur in the backbone. Because of their strength, durability, and ease of manufacture, they are ubiquitous in modern society and have become a serious environmental issue. Although pure plastics have low toxicity, some contain additives (e.g., phthalates, bisphenol A) that may have endocrine-disruptive properties, among other toxic effects. Also, there are extensive data

demonstrating that the plastic debris from finished products is harmful to wildlife through entanglement and by ingestion of litter, possibly mistaken as food items (Derraik 2002).

Nanoparticles, defined as matter that has at least one dimension in the 1- to 100-nm range (U.S. National Nanotechnology Initiative, http://www.nano.gov/), are emerging groups of industrial chemicals that have numerous applications (e.g., sunscreens, electronics, fabric coatings). Engineered nanoparticles are becoming more abundant in the environment, and the risks posed to wildlife and human health could be substantial. Toxicological studies with titanium dioxide have demonstrated effects on the respiratory and immune systems in laboratory rodents. Controlled exposure studies in fish have documented increased peroxidation of neural tissue in brain and glutathione depletion in gill tissue (Oberdörster 2004), cell cycle defects, and neurotoxicity (Smith et al. 2007). Data on potential effects in amphibians, reptiles, and higher wild vertebrates are lacking altogether (Handy et al. 2008).

Recent efforts have resulted in the replacement of commonly used hazardous chemicals with less-toxic alternatives. In the past decade, the concept of "green chemistry" has come to the forefront, entailing the use of chemicals and chemical processes designed to reduce or eliminate environmental impacts by applying contemporary processes that use nontoxic components and reduced waste production (Anastas and Warner 1998). Consumer awareness and choice are key driving elements in this change, which engages the entire supply chain for consumable products.

Some toxic compounds have been removed altogether from consumer use. Contemporary examples include some chlorofluorocarbon refrigerants linked to depletion of the ozone layer; perfluorooctane sulfonate and related perfluorinated surfactants that were detected in chemical plant workers and bioaccumulate in wildlife on a global scale; penta- and octa-brominated diphenyl ether flame retardants due to bioaccumulation in wildlife and humans; and in Europe nonylphenol, due to endocrine-disruptive characteristics. Other compounds are undergoing rigorous testing evaluation to better determine if regulatory action is in order.

Metals

Metals are known to adversely affect wildlife and humans, especially mercury, lead, cadmium, and selenium. Their mechanisms of action, sources, and distributions in the environment are relatively well understood. Wildlife and humans continue to be exposed to and affected by metals through many sources, including mining operations, atmospheric deposition from industrial processes, and exposure through spent lead shot for hunting game.

The toxic effects of lead have been recognized for centuries, and its biocidal properties date back to ancient Egypt. Its presence in lead pipes, cosmetics, pottery, and wine preparation has been hypothesized to contribute to the fall of the Roman Empire. Lead use increased dramatically during the Industrial Revolution, with adverse effects noted in lead trade workers and miners, and it continued to be widely used in paint and as an anti-knock gasoline additive through much of the 20th century. Lead is toxic to multiple organ systems, inducing anemia, neurological impairment, nephrotoxicity, hypertension, and reproductive and endocrine system toxicity (Goyer 1986). Uses of lead that result in widespread contamination (tetraethyl lead in gasoline, water pipes, solder in food cans, paints, and ammunition for hunting) are being phased out (ATSDR 2007). There is substantial evidence that ingestion by reptiles, birds, and mammals of spent shot and bullets, lost fishing sinkers and tackle, and related lead fragments is accompanied by a range of effects (molecular to behavioral) that historically may have contributed to the population decline of some species (e.g., waterfowl, eagles, condors). Restrictions on the use of lead ammunition for hunting waterfowl (~1986), and to a lesser degree lead fishing tackle (~1987), have been instituted in many countries (Rattner et al. 2008). Safe replacements for lead used in hunting of waterfowl and for fishing tackle have been developed and approved for use, and there is evidence of reduced lead poisoning in waterfowl. Unfortunately, some alternatives to lead have also resulted in environmental problems. For example, fuel oxygenates such as methyl-*tert*-butyl ether (MTBE) were introduced in the 1980s to replace lead and enhance octane ratings in gasoline. This additive results in fuel burning more cleanly in cold weather. However, leaks and spills at pumping stations have significantly contaminated groundwater with MTBE. Human health effects have been difficult to establish unequivocally; nevertheless, reports of nausea, dizziness, and headaches and perhaps an increased potential for carcinogenesis

at high exposures (e.g., from drinking contaminated groundwater) resulted in a ban on MTBE by 2004.

Mercury use by humans dates back some 2,000 years (Weiner et al. 2003), and emissions have resulted in its worldwide distribution. The environmental fate of mercury is complex in that both natural and industrial processes release various forms; it may be chemically inter-converted, metabolized by microorganisms into organic and inorganic forms, and demethylated in the liver of higher vertebrates (viz., wildlife) (Rattner et al. 2010). Today, over 50% of the waterways in the United States have fish consumption advisories related to mercury. From an ecotoxicological perspective, in the 1950s and 1960s granivorous birds and small mammals were poisoned by eating agricultural seeds coated with a mercurial fungicide (Borg et al. 1969). At about the same time, poisoning of scavenging and fish-eating birds, and humans, related to the industrial release of methyl mercury was reported in Minamata Bay, Japan (Doi et al. 1984). Pulp mills and chloralkali plants are also sources of mercury release into the environment. Affected wildlife included mink (*Mustela vison*), otter (*Lutra canadensis*), and piscivorous birds (Wobeser and Swift 1976; Wren 1985). Toxicological effects include overt neurotoxicity, reproductive failure, histopathological lesions, and outright mortality. Field and controlled dosing studies have determined tissue and dietary concentrations that cause overt toxicity or reproductive impairment. Although total mercury concentrations in liver and kidney of about 20 μg/g wet weight may be lethal, some studies have documented much greater concentrations in apparently healthy animals (e.g., ringed seal [*Pusa hispida*] and bearded seal [*Erignathus barbatus*], Smith and Armstrong 1975; wandering albatross [*Diomedea exulans*], Thompson and Furness 1989), which may be attributable to demethylation (Scheuhammer et al. 2008). Adverse effects of methylmercury on egg hatchability in birds have been noted at 1 μg/g wet weight or less (Heinz et al. 2006, 2009). Because of demethylation and the accumulation of relatively nontoxic mercury–selenium complexes in biota, toxicological field assessments cannot rely on total mercury concentration alone (Heinz et al. 2006, 2009). Concentrations of mercury in some habitats (e.g., historic mining sites and point sources, acid-affected lakes) continue to be of contemporary concern to wildlife (Wiener et al. 2003; Scheuhammer et al. 2008).

Pharmaceuticals and Personal Care Products

As a group, pharmaceuticals and personal care products (PPCPs) have, until the past decade, been largely overlooked as active environmental contaminants. The past 100 years has been the most active in terms of drug development, beginning with the discovery of penicillin as an antibiotic in 1938. Controversy over PPCPs has primarily been generated by the release of steroids and antimicrobials into the environment from sewage treatment plants, concentrated animal feeding operations, and through widespread biosolid dispersal (Daughton and Ternes 1999). Environmentally, the most notable developments were oral contraceptives in the 1950s, several classes of antibiotics that have been associated with drug resistance, and drugs for depression and pain management. Both veterinary and human pharmaceuticals pose risks to wildlife since they are designed for their bioactive properties. Personal care products, on the other hand, such as nutraceuticals (i.e., food or food products that provide health or medical benefit), food additives, and fragrances, are not necessarily designed to be biologically active. However, like pharmaceuticals, they pose risks through the continual introduction to the environment through sewage treatment and biosolid dispersal on food crops and fields adjacent to waterways.

Few large-scale environmental catastrophes have been associated with the use of single pharmaceuticals, but the potential for such effects is demonstrated by the use of diclofenac, a nonsteroidal anti-inflammatory drug (NSAID) used extensively by veterinarians for the treatment of inflammation, fever, and pain in domestic livestock. Diclofenac appears to have been the principal cause of a population crash of Old World vultures (Genus *Gyps*) in India, Pakistan, and Nepal (Oaks et al. 2004; Green et al. 2004; Schultz et al. 2004). Vultures unintentionally ingested diclofenac when scavenging carcasses of treated livestock. It was discovered that diclofenac is extremely toxic to *Gyps* vultures (LD_{50} of about 0.1 to 0.2 mg/kg), evoking visceral gout, renal necrosis, and mortality within a few days of exposure (Swan et al. 2006a). This is the best-documented instance of a pharmaceutical resulting in

an adverse population-level response in non-target free-ranging wildlife. More recently another commonly used NSAID, ketoprofen, has been discovered to be causing the death of vultures in Asia (Naidoo et al. 2009b). Controlled exposure studies identified meloxicam (Swan et al. 2006b, Swarup et al. 2007) as a safe alternative, and veterinary use of diclofenac in India is being phased out. Regrettably, the sale and widespread use of diclofenac continues in Africa and elsewhere (Naidoo et al. 2009a). Recently, staggering declines of several raptor species, including vultures, have been documented in Africa. Specifically, the decline of *Gyps* spp. populations, especially during the migration season, has been linked to human activities such as poisoning of carcasses (Virani et al. 2010).

Fossil and Mineral Fuels

The fossil and mineral fuel class includes petroleum hydrocarbons, polycyclic aromatic hydrocarbons (PAHs), coal, natural gas, and other associated chemicals. Many of these are carcinogenic compounds and also contribute to wildlife mortality from petrochemical spills in marine environments (Albers 2003). In some instances, adverse effects can be both toxicological and physical. For example, petroleum contamination reduces the insulating properties of fur and feathers, resulting in hypothermia and death. Risks from spills or burning of fossil fuels occur during exploration, drilling, refinement, transport, storage, and use, such as occurred after the explosion on April 20, 2010, of the Deepwater Horizon oil drilling platform in the Gulf of Mexico (http://www.restorethegulf.gov/). Coal poses risks to wildlife from mining operations as well as through combustion byproducts. Some coal ash contains high levels of mercury, selenium, and arsenic that have contaminated ponds and wetlands near coal-fired power plants (Hopkins et al. 2000). Energetic compounds in this class, such as perchlorate, can affect functions of the thyroid gland and have contaminated groundwater and drinking water wells (York et al. 2001). Nitroaromatic munitions such as trinitrotoluene (TNT) and hexahyro-1,3,5-trinitro-1,3,4-triazine (RDX) are commonly found on military installations or areas where explosive devices have been detonated. These are moderately toxic to birds and amphibians when incidentally ingested (Talmage et al. 1999).

REGULATION OF CHEMICALS

Knowing the Pertinent Regulations and Legislation

Individuals should familiarize themselves with the general regulatory requirements of chemical use for the country in which they are located. This is particularly important for the purchase and use of pesticides, but also is applicable to chemical disposal. Chemicals should be stored properly to reduce the potential for spills or for unintentional exposure of children or animals. Sending chemicals through the mail or by courier, either within or between countries, may be illegal and requires special labeling, packaging, and handling. The Globally Harmonized System of Classification and Labeling of Chemicals (GHS) is an internationally agreed-upon approach for classifying chemicals as nonhazardous, hazardous, or extremely hazardous for shipping. It includes provisions for standardized shipping labels and safety data sheets (http://www.unece.org/trans/danger/publi/ghs/ghs_welcome_e.html). Capacity building and training for chemicals management is available through the UN Institute for Training and Research (UNITAR): http://www.unitar.org/chemicals-and-waste-management-at-unitar.

All chemicals in commerce are required to have a Materials Safety Data Sheet (MSDS) available to the public, which contains information on toxicity, flammability, solubility, vaporization, and other facts important to safe handling. These should be reviewed whenever chemicals are purchased and can be found online for most substances. Table 25.2 provides links to websites with information about occupational health and safety related to chemical use or transport.

Who Is Responsible for What Regulations?

International treaties, negotiated and enforced through the UN, regulate international commerce of chemicals and contaminated waste. Specific regulations for individual countries can be found through a search of the Internet (suggested search words: environmental legislation [country of interest]) and is summarized for the United States in Fairbrother (2009).

Pesticides are regulated separately from industrial chemicals. Pesticides are tested for efficacy and target

Table 25.2 Worldwide Web-Based Links to Chemical Management Safety and Labeling Programs in Various Countries (Accessed August 2010)

ASEAN Occupational Safety and Health Network (ASEAN OSH-NET)
www.aseanoshnet.net
Asia-Pacific Economic Cooperation (APEC) Chemical Dialogue
www.apec.org/apec/apec_groups/committee_on_trade/chemical_dialogue.html
Chemical Hazards Communication Society
www.chcs.org.uk
Germany: Deutsche Gesellschaft für Technische Zusammenarbeit (GTZ) GmbH
www.gtz.de/en/themen/laendliche-entwicklung/7720.htm
Globally Harmonized System of Classification and Labelling of Chemicals (GHS)—official text
www.osha.europa.eu/en/news/ghs_entered_into_force_01.04022009
Globally Harmonized System of Classification and Labelling of Chemicals (GHS)—all countries' regulations
www.unece.org/trans/danger/publi/ghs/implementation_e.html
Health Canada: GHS
www.hc-sc.gc.ca/ahc-asc/intactiv/ghs-sgh/index-eng.php
ILO Safework: Programme on Safety and Health at Work and the Environment (SAFEWORK)
www.ilo.org/safework/lang—en/index.htm
International Programme on Chemical Safety (IPCS)
www.who.int/ipcs/capacity_building/ghs_statement/en/*and* www.inchem.org/pages/about.html
Japan Ministry of Environment
www.env.go.jp/chemi/ghs/ (site in Japanese)
New Zealand, Hazardous Substances
www.ermanz.govt.nz
Pan American Health Organization (PAHO)
www.paho.org
Society for Chemical Hazard Communication
www.schc.org/home.php
U.S. Department of Labor, Occupational Health and Safety Agency (OSHA)
www.osha.gov
U.S. Environmental Protection Agency (US EPA)
www.epa.gov
WSSD Global Partnership for Capacity Building to Implement the GHS
www2.unitar.org/cwm/ghs_partnership/index.htm

specificity, and large-scale use (as for agriculture) is restricted to licensed applicators. However, home use of the same products is not regulated except through detailed labeling, although intentional poisoning of fish or wildlife is prohibited (Fairbrother 2009). In the United States, pesticides are regulated by the USEPA under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). The European Union (EU), Japan, Australia, and other industrialized nations have similar pesticide use laws and guidelines for developing data required for product registration. These guidelines are harmonized through the Organization for Economic Cooperation and Development (OECD).

Other chemicals in commerce are registered prior to use in manufacturing, and are reviewed for their potential to affect the health of factory workers (under industrial hygiene laws), consumers, and the environment. In the United States, this regulation falls under TSCA. Most developed countries maintain

similar lists, such as Canada's Domestic Substances List (http://www.ec.gc.ca/substances/ese/eng/DSL/DSLprog.cfm) and the Chinese Inventory of Toxic Substances (http://english.mep.gov.cn/inventory/). The UN Environment Program (UNEP) maintains a database of toxicity and environmental fate information on HPV chemicals (http://www.chem.unep.ch/irptc/sids/OECDSIDS/sidspub.html). The EU regulates chemical use through the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) legislation that came into force in 2007. It requires manufacturers and importers of all chemicals and products into the EU to provide information about environmental transport and fate, as well as effects on people and the aquatic environment. HPV chemicals require information on toxicity to terrestrial systems to be authorized for sale. The European Chemicals Agency (EChA) handles the data submissions and hazard assessments on all registered products. The intent is to find substitutions and to phase out the most hazardous substances.

Countries also are responsible for the disposal of hazardous waste within their borders. In the United States, the Resource Conservation and Recovery Act (RCRA) defines what is meant by "hazardous waste" and regulates how it is handled and disposed. The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA, also known as the Superfund Law) provides for emergency cleanup, assessment, and compensation for improper discharge or disposal of toxic substances. Some countries, such as Germany, require manufacturers to collect and properly dispose of used products containing hazardous materials (e.g., electronics).

Most developed countries have laws against uncontrolled discharge into water bodies of chemicals or other waste (such as raw sewage) (Fairbrother 2009). These laws define what is meant by "clean water" and require the maintenance of a healthy aquatic community. The Clean Water Act in the United States and the Water Framework Directive in the EU are two examples of this type of legislation. It is recognized that clean water for drinking and bathing is essential for public health, and necessary for environmental sustainability. There is no similar legislation for clean soils, although some countries, such as the Netherlands, Canada, and Germany, have clean soil standards that define allowable limits of soil contamination. Clean air is addressed in most countries but only in relation to human health, not in terms of environmental protection, except for ozone (Fairbrother 2009).

Responsive (Vertical) and Precautionary Regulation

Fairbrother and Fairbrother (2009) describe two schools of thought in environmental legislation. The traditional model is known as a "vertical" approach as it regulates both the manufacturing process and the end use of products. The burden of proof is on the regulators (the government) to identify potential risks. Minimal information is required and the approach assumes that market incentives will result in safe products; damage to human or environmental health will have negative feedback through consumer choices and expensive litigation. Monitoring of products in use is an important aspect of this approach to identify threats after a product reaches the market, at which time regulations are implemented. This approach looks for a balance between environmental protection and support of business and commerce, and is used by the USEPA to regulate chemicals in commerce under TSCA.

The EU takes a more precautionary approach to environmental regulation as required under the European Community Treaty, which stipulates that a high level of environmental protection be based on the precautionary principle as stated in the Rio Declaration on Environment and Development (UNCED 1992). This puts the burden of proof of safety on the manufacturer or seller of goods and assumes new materials are inherently harmful until demonstrated otherwise. The precautionary approach views science as informative rather than decisional as is the case in the vertical approach.

Most countries incorporate precaution into policy decision-making (Fairbrother and Fairbrother 2009). Pesticide legislation, for example, has historically put the burden of proof for safety on the manufacturer since pesticides are, by their very design, toxic to organisms in the environment. The Food, Drug, and Cosmetic Act in the United States that regulates PPCPs also is precautionary, and puts the burden of proof on the manufacturer of the products. Pesticide and pharmaceutical regulations both include cost–benefit analyses, as there are times when the benefits that accrue to human wellbeing may outweigh temporary environmental costs.

International Approaches

Because pollution knows no boundaries and disputes over transboundary pollution have intensified, the UN has negotiated several international treaties to control trafficking and dumping of chemicals. The earliest recognition of the universal responsibility for marine pollution included the "London Convention and Protocol" that prohibits dumping of waste in the ocean (http://www.imo.org/OurWork/Environment/SpecialProgrammesAndInitiatives/Pages/LondonConvention.aspx). The Basel Convention of 1993 prohibits industrialized countries from indiscriminate waste disposal in developing countries (http://www.basel.int/). However, the international trade on e-waste (from disposal and dismantling of electronic equipment) is not covered by the Basel Convention and has been recognized as a serious international problem. The Rotterdam Convention of 2004 established codes of conduct and information exchange procedures for chemicals and pesticides in commerce, in recognition of the need to standardize datasets among countries to reduce the financial burden on chemical companies. The Stockholm Convention on Persistent Organic Pollutants (POPs) of 2004 established a process to review all persistent, bioaccumulative, and toxic substances with the intention of banning the most hazardous and finding suitable substitutes for those that are less dangerous (http://chm.pops.int/). The UN Convention on Climate Change, as embodied in the Kyoto Protocol (adopted in 1997), was the first international effort to reduce greenhouse gas emissions (http://unfccc.int/kyoto_protocol/items/2830.php). The UN Conference on Climate Change in Copenhagen in 2009 was expected to provide the framework for extension and intensification of the targets for reducing emissions that were set in Kyoto. It concluded with a nonbinding agreement with nations promising to meet future pollution reduction targets and with $30 billion over three years pledged to aid developing nations reduce pollution while still growing their economies.

Developing World Versus Developed World

In 2006, an international conference sponsored by the UN adopted the Strategic Approach to International Chemicals Management (SAICM). The purpose of SAICM is to ensure that the goal agreed to at the 2002 Johannesburg World Summit on Sustainable Development is met, such that by the year 2020, chemicals are produced and used in ways that minimize significant adverse impacts on the environment and human health. There are five official SAICM regional focal points: Argentina, Japan, Nigeria, Romania, and the United Kingdom. SAICM identified the critical emerging issues in chemical management, particularly for developing countries, to be lead in paint, chemicals in products, commerce in e-waste, nanotechnology, and perfluorinated hydrocarbons (http://www.ipen.org/ipenweb/firstlevel/saicm.html).

WHAT SHOULD YOU DO IN THE CASE OF ENVIRONMENTAL CONTAMINATION?

In the United States, chemical or petroleum spills are managed by the National Response Center (NRC). Observation of a chemical or petroleum spill or any other indication that a hazardous substance may be causing illness or death to plants, fish, or wildlife should be reported immediately to the NRC (http://www.nrc.uscg.mil/nrchp.html) or appropriate authorities in other countries. These can be located on the Internet using the search term "environmental protection agency [country]." Scientists performing field investigations are directed to Sheffield et al. (2005), who describe the procedures taken if animals (including fish) are found dead and poisoning is suspected. Several large databases exist that contain data on chemical characteristics, toxicity and effects in wildlife species, and fate of chemicals in the environment that are useful for contaminant investigations. The "Whole Wildlife Toxicology Catalog" (http://www.pwrc.usgs.gov/wwtc/) provides a portal to many of the databases that are Web-accessible.

REDUCING ANTHROPOGENIC EFFECTS ON THE ENVIRONMENT

Consumer choices to buy and use less-toxic products can drive changes in the manufacturing and use of chemicals in the household and workplace.

These choices have significant impacts on the release of chemicals into the environment, potentially before governmental regulations can be set into place. Ultimately, common sense and knowledge about the resources used to develop a household and/or occupational product can be the most effective means of choosing among options—for example, taking into account the energy consumed during manufacture and shipping, the ingredients in the product and their sources, options available for disposal, and whether its use is really necessary. Participation in community decisions and thoughtful personal choices can change the impetus for the discipline of wildlife toxicology from response to environmental catastrophe to an approach based on sound science and responsible foresight.

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