Chapter 4
Organic Compounds

4.1 Pesticides

Pesticides are substances, or mixtures of substances, intended to prevent, destroy, repel, or mitigate any pest. They may be chemical substances, biological agents (such as viruses or bacteria), antimicrobial and disinfectant agents, or other devices. The term *pest* includes insects, plant pathogens, weeds, mollusks, birds, mammals, fish, nematodes (roundworms), and microbes that compete with humans for food, destroy property, spread or are a vector for disease, or are a nuisance (EPA 2006). Pests have attacked and destroyed crops, and pesticides have been developed, as long as agriculture has been practiced. Some historical examples include selection of seed from resistant plants in Neolithic times (~7000 BC; Ordish 2007), sulfur dusting by the Sumerians (~2500 BC), and over 800 recipes in the Ebers Papyrus, the oldest known medical document (dated around 1550 BC), which describes recognizable substances that were used as poisons and pesticides. More recently, during the fifteenth century, arsenic, mercury, and lead were used to fight pests. The first book to deal with pests in a scientific way was John Curtis's *Farm Insects*, published in 1860, but massive production and application of pesticides only began around World War II. The major development at that time was the discovery of the insecticidal properties of DDT by P. H. Muller in 1942, who received the Nobel Prize (medicine) for his discovery in 1948.

From this point on, many millions of tons of active ingredients have been released intentionally each year to the environment, spreading around the globe. An illustration of the amounts of active-ingredient pesticides applied is shown in Fig. 4.1, where total annual amounts used in the USA surpass billions of pounds for the period from 1982 to 2001.

In contrast to all other groups of contaminants mentioned in Part II, pesticides are released to the environment in staggering quantities, even though they are designed to suppress the normal biological growth of different pests. Pesticides are formulated specifically to be toxic to living organisms, and as such, they are usually hazardous to humans. In fact, most pesticides used today are acutely toxic

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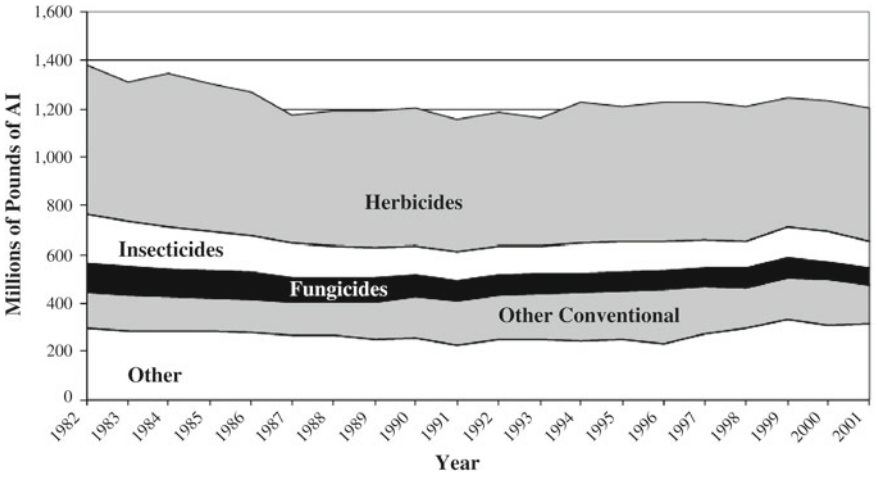

Fig. 4.1 Annual amount of pesticide active ingredients used in the USA, by pesticide type, from 1982 to 2001; estimates are for all market sectors (Kiely et al. 2004)

to humans, causing poisonings and deaths every year. Annual poisoning from pesticides, in the USA alone, is estimated to range between 10,000 and 40,000 diagnosed illnesses and injuries among agricultural workers (Blondell 1997). Chronic health effects from pesticides also have been reported, including neurological effects, reproductive problems, interference with infant development, and cancer. The effect of exposure to various pesticides can induce, on the longer term, shortened attention span and reduced coordination (Rosenstock et al. 1991); a more drastic outcome of such exposure includes increased risk of early onset of Parkinson's disease (Butterfield et al. 1993; Gorell et al. 1998). Moreover, from animal studies, it appears that developing brains during the cell division stage (i.e., during early infancy) are more susceptible to destructive impact of some pesticides, which may lead to long-term abnormal behavior (Chanda and Pope 1996; Eriksson 1996).

Increased risk of various cancers (e.g., lymphatics, blood, stomach, prostate, testes, brain, and soft tissues) was reported upon exposure to pesticides (Zahm and Blair 1993; Hayes et al. 1995; Zahm et al. 1997). Children's cancer including brain tumors, leukemia, non-Hodgkin's lymphoma, sarcoma, and Wilms' tumor due to direct or parental exposure to pesticides also has been determined (Fear et al. 1998; Kristensen et al. 1996; Pogoda and Preston-Martin 1997; Sharpe et al. 1995; Buckley et al. 1994). Often, the risk of cancer due to exposure to pesticides has been higher in children than in adults (Zahm and Ward 1998). Moreover, birth defects, including limb-reduction defects, have been linked to exposures to pesticides (Restrepo et al. 1990; Schwartz and LoGerfo 1988; Lin et al. 1994), as has a higher-than-normal risk of stillborn births (Pastore et al. 1997).

Usually, only small fractions of applied pesticides reach the target organisms, the majority of the chemicals being distributed to the air, soil, and water. On such

release, many nontarget organisms can be affected severely. Pesticide residues and their degradation products are toxic to many components of ecological systems, either by being lethal to certain living forms or by changing environmental conditions that in turn alter and usually decrease biodiversity in these systems. In some cases, pesticides can have synergistic effects with other contaminants, thus increasing overall toxicity. Exposure routes of pesticides include direct intake of pesticide residues through, for example, digestion of pesticides adsorbed on crops or dissolved in water and indirect paths through intake of pesticides or their degradation products that have been concentrated in food chains and intake of other environmental mediators.

Official lists of pesticides contain over 1,500 substances (Wood 2006). Pesticides are divided into several major groups (e.g., herbicides, fungicides, insecticides), which are subdivided into chemical or other classes (e.g., chloroacetanilide herbicides or auxins). These compounds may be arranged according to their toxicity (WHO 2005), chemical structure, and/or activity. Here, we briefly discuss only a few of the more common groups of pesticides; the interested reader should consult readily available references (e.g., Barbash 2003; Matthews 2006; Milne 1995; Briggs 1992) as a primary source of more detailed information.

4.1.1 Organochlorine Insecticides

Organochlorine insecticides (e.g., DDT, aldrin, dieldrin, heptachlor, mirex, chlordecone, and chlordane) were used commonly in the past, but many have been removed from the market due to their negative health and environmental effects and their persistence. However, insecticides of this group are in some cases still used as active ingredients in various pest control products, such as gamma-hexachlorocyclohexane (lindane). Lindane also is used as the active agent in the medicine Kwell®, used for human ectoparasitic disease, although it has been associated with acute neurological toxicity either from ingestion or in persons treated for scabies or lice. The general chemical structures of some of the organochlorine insecticides are given in Fig. 4.2. These compounds are characterized by cyclic structures, a relatively large number of chlorine atoms on the molecule, and low volatility. As a result, they usually are resistant to natural degradation processes and thus stable for very long periods after release to the environment.

Organochlorines are absorbed in the body through ingestion, inhalation, and across the skin. These substances tend to concentrate in fatty tissues following exposure. The chief acute toxic action of organochlorine pesticides is on the nervous system, where these compounds induce a hyperexcitable state in the brain (Joy 1985; Reigart and Roberts 1999). This effect is manifested mainly as convulsions, sometimes limited to myoclonic jerking, but often expressed as violent seizures. Other less severe signs of neurological toxicity, such as paresthesias, tremor, ataxia, and hyperreflexia, also are characteristic of acute organochlorine poisoning. Convulsions may cause death by interfering with pulmonary gas

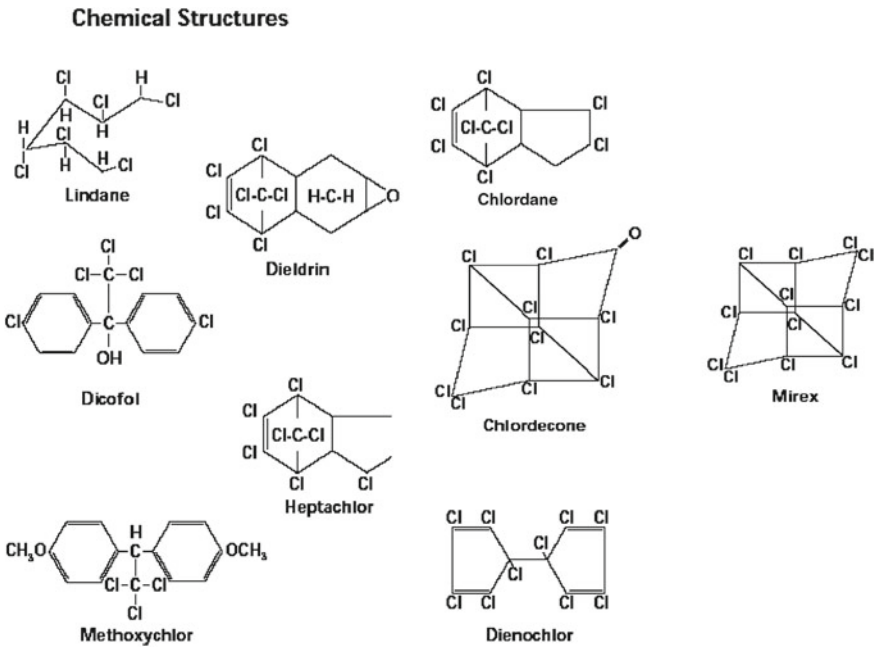

Fig. 4.2 General chemical structures of some organochlorine insecticides

exchange and generating severe metabolic acidosis. High tissue concentrations of organochlorines increase myocardial irritability, predisposing to cardiac arrhythmia. Human absorption of organochlorine sufficient to cause enzyme induction is likely to occur only as a result of prolonged intensive exposure.

There has been considerable interest recently in the interaction of organochlorines with endocrine receptors, particularly estrogen and androgen receptors. In vitro studies and animal experimentation support the view that the function of the endocrine system may be altered by these interactions. This in turn may alter the reproductive development and success of animals and humans. The International Association for Research on Cancer evaluated organochlorine insecticides as being either possibly carcinogenic to humans (DDT, chlordane, heptachlor, toxaphene) or not classifiable as to carcinogenicity (aldrin, dieldrin, lindane) (IARC 1987, 1991, 2001). Inconclusive epidemiological studies linked organochlorine insecticides to increased risks of soft tissue sarcoma, non-Hodgkin's lymphoma, leukemia, and prostate, lung, pancreas, and breast cancers (Purdue et al. 2006). Due to evidence of their toxicity and carcinogenic potential, some organochlorines have been banned or restricted for use. Several organochlorine pesticides, including DDT, methoxychlor, endosulfan, and dicofol, mimic estrogen (Gillette et al. 1994; Cummings 1997). Lindane, which is sometimes used to treat head lice in children, acts as an antiestrogen and is toxic to the nervous system (Cooper et al. 1989).

4.1.2 Organophosphates

The general chemical structure of organophosphate pesticides is shown in Fig. 4.3. The functional group R usually is either ethyl or methyl. Pesticides with double-bonded sulfur moieties are organothiophosphates but are converted to organophosphates in the liver. Phosphonate contains an alkyl (R–) in place of one alkoxy group (RO). The "leaving group" is the principal metabolite for a specific identification.

Acute pesticide poisonings frequently involve organophosphate pesticides; these pesticides were originally derived from chemical warfare agents developed during World War II. Some common organophosphates in use today include chlorpyrifos, diazinon, azinphos-methyl, malathion, and methyl-parathion, all of which apparently share a common mechanism of cholinesterase inhibition and cause similar health effects. Organophosphates poison insects and mammals primarily by phosphorylation of the acetylcholinesterase enzyme (AChE) at nerve endings. The result is a loss of available AChE so that the affected organ becomes overstimulated by the excess acetylcholine (ACh, the impulse-transmitting substance) in the nerve ending. The enzyme is critical to normal control of nerve impulse transmission from nerve fibers to smooth and skeletal muscle cells, glandular cells, and autonomic ganglia, as well as within the central nervous system.

4.1.3 N-methyl Carbamate

The general chemical structure of *N*-methyl carbamate is shown in Fig. 4.4. Common *N*-methyl carbamates in use today include aldicarb, carbofuran, methiocarb, oxamyl, and carbaryl. *N*-methyl carbamates share with organophosphates the capacity to inhibit cholinesterase enzymes and, therefore, share similar symptomatology during acute and chronic exposure.

The *N*-methyl carbamate esters cause reversible carbamylation of the acetylcholinesterase enzyme, allowing accumulation of acetylcholine, the neuromediator substance, at parasympathetic neuroeffector junctions (muscarinic effects), at skeletal muscle myoneural junctions and autonomic ganglia (nicotinic effects), and in the brain (CNS effects). The carbamyl–acetylcholinesterase combination dissociates more readily than the phosphoryl–acetylcholinesterase complex produced by organophosphate compounds. This property has several important consequences:

1. It tends to limit the duration of *N*-methyl carbamate poisoning.
2. It accounts for the greater span between symptom-producing and lethal doses than most organophosphate compounds.
3. It frequently invalidates the measurement of blood cholinesterase activity as a diagnostic index of poisoning.

N-methyl carbamates are absorbed by inhalation and ingestion, and somewhat by skin penetration, although the last tends to be a less toxic route.

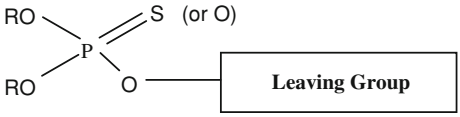

Fig. 4.3 General structure of organophosphate pesticides

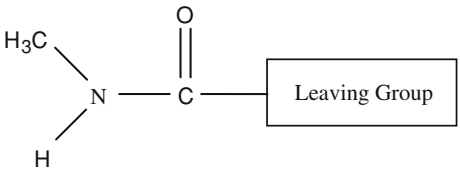

Fig. 4.4 General structure of *N*-methyl carbamate

4.1.4 Triazines

Triazine pesticides and their metabolites are a group of closely related herbicides used widely on agricultural and nonagricultural sites; they are inhibitors of electron transport in photosynthesis. As a family, their chemical structures are heterocyclic, composed of carbon and nitrogen in their rings. Most, except for metribuzin, are symmetrical with their altering carbon and nitrogen atoms. Herbicide members in this family include atrazine, hexazinone, metribuzin, prometon, prometryn, simazine, and their degradates. Atrazine is used widely in corn production and is estimated to have been the most often-used pesticide in the USA during the late 1990s. Its toxic effects may include disruption of ovarian function, generation of mammary (breast) tumors in animals, and interference with the binding of steroid hormones and the breakdown pathway of estrogen (Bradlow et al. 1995; Cooper et al. 1996; Danzo 1997). Some uses of atrazine are classified as restricted because of groundwater and surface water concerns. Many of the triazines show acute and chronic toxicities at low concentrations (Letterman 1999; Montgomery 1993), and they generally are known or suspected to be carcinogenic, mutagenic, and/or teratogenic (Newman 1995; Letterman 1999; Montgomery 1993; C&EN 2000, 2002). Recent evidence (Reeder et al. 1998; Renner 2002; Tavera-Mendoza et al. 2002a, b) implicated specific triazines and/or their degradation products as endocrine disruptors and teratogens in amphibians.

4.1.5 Paraquat and Diquat

Paraquat (1,1′-dimethyl, 4,4′-bipyridyl) is a nonselective contact herbicide. It is used almost exclusively as a dichloride salt and usually is formulated to contain surfactants. Both its herbicidal and toxicological properties are dependent on the ability of the parent cation to undergo a single-electron addition, to form a free radical that reacts with molecular oxygen to reform the cation and concomitantly

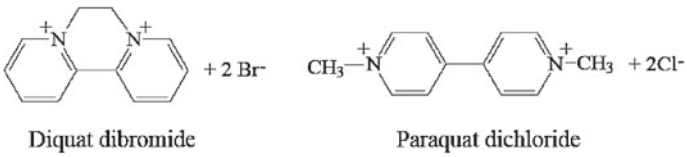

Fig. 4.5 General chemical structures of paraquat and diquat

produce a superoxide anion. This oxygen radical may directly or indirectly cause cell death. Diquat, 1,1′-ethylene-2,2′-dipyridylium, is a charged quaternary ammonium compound often found as the dibromide salt. The structure of diquat dibromide and that of the closely related herbicide paraquat is shown in Fig. 4.5.

Paraquat and diquat are nonselective contact herbicides that are relatively widely used and highly toxic. Paraquat has life-threatening effects on the gastrointestinal (GI) tract, kidney, liver, heart, and other organs. The LD50 (lethal dose to 50 % of the population) in humans is approximately 3–5 mg/kg. The lung is the primary target organ of paraquat, and pulmonary effects represent the most lethal and least treatable manifestation of toxicity (Pond 1990; Giulivi et al. 1995). However, toxicity from inhalation is rare. Both types I and II pneumatocytes appear to selectively accumulate paraquat. Biotransformation of paraquat in these cells results in free-radical production with resulting lipid peroxidation and cell injury (Pond 1990; Giulivi et al. 1995; Honore et al. 1994). There is a progressive decline in arterial oxygen tension and CO_2 diffusion capacity. Such a severe impairment of gas exchange causes progressive proliferation of fibrous connective tissue in the alveoli and eventual death from asphyxia and tissue anoxia (Harsany et al. 1987). Local skin damage includes contact dermatitis. Prolonged contact produces erythema, blistering, abrasion and ulceration, and fingernail changes (Tungsanga et al. 1983; Vale et al. 1987).

Following ingestion of the substance, the GI tract is the site of initial or phase I toxicity to the mucosal surfaces. This toxicity is manifested by swelling, edema, and painful ulceration of the mouth, pharynx, esophagus, stomach, and intestine. With higher levels, other GI toxicity includes centrizonal hepatocellular injury, which can cause elevated bilirubin, and hepatocellular enzyme levels such as AST, ALT, and LDH.

Diquat poisoning is much less common than paraquat poisoning, so that human reports and animal experimental data for diquat poisoning are less extensive than for paraquat. However, diquat has severe toxic effects on the central nervous system (CNS) that are not typical of paraquat poisoning (Vanholder et al. 1981; Olson 1994).

4.2 Synthetic Halogenated Organic Substances

Halogenated hydrocarbons constitute a widely used family of products. Some of the more common halogenated hydrocarbons are brominated flame retardants and the chlorinated derivatives of methane, ethane, and benzene, which are used mainly as solvents and chemical intermediates. Broad production and use of these compounds began in the early 1900s when chlorinated solvents replaced other flammable substances in a variety of industrial process. These compounds became popular because the progressive halogenation of a hydrocarbon molecule yields a succession of liquids or solids of increasing density, viscosity, and improved solubility for a large number of inorganic and organic materials. Other physical properties such as flammability, specific heat, dielectric constant, and water solubility decrease with increasing halogen content (Marshall 2003).

In addition to use as dry-cleaning and degreasing solvents, many of the halogenated organic solvents have been used in adhesives, pharmaceuticals, and textile processing; as extraction solvents, paint solvents, and coating solvents; and as feedstocks for production of other chemicals. The widespread use and subsequent disposal of chlorinated solvents has led to their being among the most commonly found contaminants at hazardous waste disposal sites. In general, these compounds are considered persistent in the environment, having long half-lives in soil, air, and water in comparison with other, nonhalogenated hydrocarbons. The health effects of these compounds have been studied extensively, as a result of concerns raised about their toxicity and their carcinogenic nature. Due to the large diversity of this group, only a few major ubiquitous substances are discussed further.

4.2.1 Chlorinated Hydrocarbons

Chlorinated derivatives of methane include methyl chloride, methylene chloride, chloroform, carbon tetrachloride, and several chlorofluorohydrocarbons (CFCs). We discuss carbon tetrachloride (CT) as a representative example of this group. CT was originally prepared in 1839 and was one of the first organic chemicals to be produced on a large scale by the end of the nineteenth century and beginning of the twentieth century. CT is the most toxic of the chloromethanes and the most unstable on thermal oxidation (Holbrook 2000).

In the past, the main uses of CT were for dry-cleaning, fabric-spotting, and fire extinguisher fluids; as a grain fumigant; and as a solvent in various chemical processes (DeShon 1979). Until recently, CT was used as a solvent for the recovery of tin in tin-plating waste, for metal degreasing, in the manufacture of semiconductors, as a petrol additive and a refrigerant, as a catalyst in the production of polymers, and as a chemical intermediate in the production of fluorocarbons and some pesticides (HSDB 1995).

Acute inhalation and oral exposure to high levels of CT have been observed primarily to damage the liver (swollen, tender liver; changes in enzyme levels; and jaundice) and kidneys (nephritis, nephrosis, proteinuria) of humans. Depression of the CNS also has been reported. Symptoms of acute exposure in humans include headache, weakness, lethargy, nausea, and vomiting (EPA 2000a). Occasional reports have noted the occurrence of liver cancer in workers exposed to CT by inhalation; however, the data are not sufficient to establish a cause-and-effect relationship. Liver tumors have developed in rats and mice exposed to CT, by experimentally placing the chemical in their stomachs (ATSDR 1994; IARC 1972, 1982). The EPA has classified CT as a Group B2, probable human carcinogen (EPA 2000a).

Chlorinated ethanes and ethylenes comprise ethyl chloride, ethylene dichloride (EDC) (1,2-dichloroethane), vinyl chloride, trichloroethylene (TCE), perchloroethylene (PCE, also called tetrachloroethylene), and several CFCs. Some of the major uses of these compounds are as degreasing agents, dry-cleaning solvents, building blocks for manufacturing of polymers (e.g., PVC, ethyl cellulose), and raw material for the production of tetraethyl lead and CFCs. We discuss EDC, TCE, and PCE as examples of this group.

EDC is used primarily in the production of vinyl chloride monomer (HSDB 2000). It also is an intermediate in the manufacture of trichloroethane and fluorocarbons and used as a solvent. In the past, EDC was used as a gasoline additive and a soil fumigant. The reported toxicological effects on exposure of workers to levels of 10–37 ppm were nausea, vomiting, dizziness, and unspecified blood changes (Brzozowski et al. 1954). In other studies, adverse CNS and liver effects were reported in workers occupationally exposed to concentrations of 16 ppm EDC (Kozik 1957) and less than 25 ppm (Rosenbaum 1947). EDC is reasonably anticipated to be a human carcinogen based on experiments on animals (IARC 1987). When administered by gavage, 1,2-dichloroethane increased the incidence of hepatocellular carcinomas in male mice, mammary gland adenocarcinomas and endometrial stromal neoplasms of the uterus in female mice, and lung adenomas in mice of both sexes. Furthermore, gavage administration of 1,2-dichloroethane increased the incidence of squamous cell carcinomas of the forestomach, subcutaneous fibromas, and hemangiosarcomas in male rats and mammary gland adenocarcinomas in female rats. No adequate data were available to evaluate the carcinogenicity of 1,2-dichloroethane in humans (IARC 1987).

The first documented synthesis of TCE was in 1864, and by the early 1900s, a manufacturing process was initiated, becoming a full industrial process by the 1920s (Mertens 2000). The main use of TCE is metal degreasing (over 90 % of production and consumption). TCE also was used extensively for dry cleaning and, in the past, as an extraction solvent for natural fats and oils for food, cosmetic, and drug production (e.g., extraction of palm, coconut, and soybean oils; decaffeination of coffee; isolation of spice oleoresins) (Doherty 2000a; Linak et al. 1990). Additional applications of TCE are as components in adhesive and paint stripping formulations, as a low-temperature heat-transfer medium, as a nonflammable solvent carrier in industrial paint systems, and as a solvent base for metal

phosphatizing systems. TCE is used in the textile industry as a carrier solvent for spotting fluids and as a solvent in waterless preparation dying and finishing operations (Mertens 2000; Doherty 2000a).

TCE is now a common contaminant at hazardous waste sites and many federal facilities in the USA. TCE has been identified in at least 1,500 hazardous waste sites regulated under Superfund or the Resource Conservation and Recovery Act (EPA 2005). TCE can enter surface waters via direct discharges and groundwater through leaching from disposal operations and Superfund sites; the maximum contaminant level for TCE in drinking water is 5 ppb. TCE can be released to indoor air from use of consumer products that contain it, vapor intrusion through underground walls and floors, and volatilization from the water supply.

On acute exposure, TCE is considered toxic, primarily because of its anesthetic effect on the central nervous system. Exposure to high vapor concentrations is likely to cause headache, vertigo, tremors, nausea and vomiting, fatigue, intoxication, unconsciousness, and even death. Ingestion of large amounts of TCE may cause liver damage, kidney malfunction, cardiac arrhythmia, and coma (Mertens 2000; EPA 2000b). TCE is anticipated to be a human carcinogen, based on limited studies on humans and evidence from studies of animals (NTP 2002). Studies have found that occupational exposures to TCE are associated with excess in liver cancer, non-Hodgkin's lymphoma, prostate cancer, and multiple myeloma, with the strongest evidence for the first three cancers (Wartenberg et al. 2000).

PCE was first prepared in 1821, but industrial production of PCE reportedly began in the first decade of the twentieth century (Gerhartz 1986); significant use began only about 100 years after its discovery (Doherty 2000b). The main use of PCE is in the dry-cleaning industry. It is also used as a feedstock for chlorofluorocarbon production, for metal cleaning, as a transformer insulating fluid, in chemical masking formulations, and as a process solvent for desulfurizing coal (Hickman 2000).

Overexposure to tetrachloroethylene by inhalation affects the CNS and the liver. Dizziness, headache, confusion, nausea, and eye and mucous tissue irritation occur during prolonged exposure to vapor concentrations of 200 ppm (Rowe et al. 1952). These effects are intensified and include lack of coordination and drunkenness at concentrations in excess of 600 ppm. At concentrations in excess of 1,000 ppm, anesthetic and respiratory depression effects can cause unconsciousness and death (Hickman 2000).

PCE inhalation may affect the CNS and the liver. At higher concentrations, the effects become more pronounced, and at high concentrations, PCE was used as an anesthetic substance, which also can cause depression, difficulty in speaking and walking, respiratory system damage, unconsciousness, and death (Hickman 2000). The International Agency for Research on Cancer determined that PCE probably is carcinogenic to humans. Results of animal studies, conducted with amounts much higher than those to which most people are exposed, show that tetrachloroethylene can cause liver and kidney damage and liver and kidney cancers, even though the relevance to people is unclear (ATSDR 2006a).

Chlorinated aromatics, including monochlorobenzene (MCB), *o*-dichlorobenzene (*o*-DCB), and *p*-dichlorobenzene (*p*-DCB), are the major chlorinated aromatic species produced on an industrial scale. MCB is used as both a chemical intermediate and a solvent. As an intermediate, it is used to produce chloronitrobenzene, pesticides, and pharmaceutical products. In solvent applications, MCB is used in the manufacture of isocyanates. Its high solvency allows it to be used with many types of resins, adhesives, and coatings. The *o*-DCB is used primarily for organic synthesis, especially in the production of 3,4-dichloroaniline herbicides. Like MCB, it can be used as a solvent, especially in the production of isocyanates. It is also used in motor oil and paint formulations. The *p*-DCB is used as a moth repellent and for the control of mildew and fungi. It also is used for odor control. It is a chemical intermediate for the manufacture of pharmaceuticals and other organic chemicals.

4.2.2 Brominated Flame Retardants

The term *brominated flame retardant* (BFR) incorporates more than 175 different types of substances, which form the largest class of flame retardants; other classes are phosphorus-containing, nitrogen-containing, and inorganic flame retardants (Birnbaum and Sttaskal 2004). The major BFR substances in use today (depicted in Fig. 4.6) are tetrabromobisphenol A (TBBPA), hexabromocyclododecane (HBCD), and mixtures of polybrominated diphenyl ethers (PBDEs) (namely, decabromodiphenyl ether (DBDE), octabromodiphenyl ether (OBDE), and pentabromodiphenyl ether (pentaBDE)).

BFRs have been added to various products (e.g., electrical appliances, building materials, vehicle parts, textiles, furnishings) since the 1960s, in growing rates (15-fold from the mid-1960s to 2003; DePierre 2003). BFRs usually are classified as semivolatile and hydrophobic, but these properties vary due to the large diversity of this group of compounds.

BFRs tend to accumulate in organic-rich media, such as soils and sediments, and lipid-rich biotic tissues and are expected to biomagnify in food chains (DePierre 2003). Two incidents in the 1970s brought attention to the toxic potential of BFR. The first incident was in a farm in Michigan in 1974, where polybrominated biphenyls were mixed accidentally with animal feed. As a result, individuals living on affected farms and consumers of contaminated farm products were exposed to these compounds for months before the mistake was discovered. The outcomes of the contamination were loss of livestock and long-term impact on the health of farm families (Birnbaum and Sttaskal 2004; Dunckel 1975). The second case involved tris(2,3-dibromopropyl)phosphate (tris-BP), which is a mutagen and causes cancer and sterility in animals; it was found to be absorbed from fabric by people (Blum et al. 1978). These two BFRs were phased out, as a consequence (Birnbaum and Sttaskal 2004).

The potential toxicity of these compounds is considered here for the PBDE group and HBCD, which are among the most ubiquitous BFRs to date. PBDEs

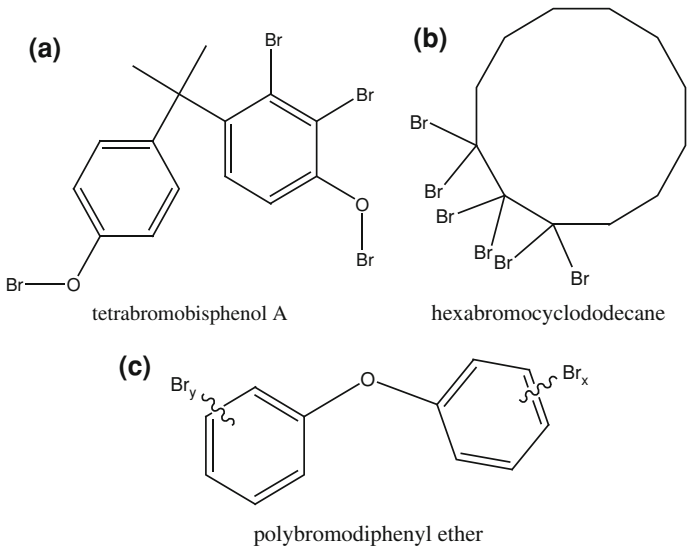

Fig. 4.6 Chemical structures of **a** tetrabromobisphenol A (*TBBPA*), **b** hexabromocyclododecane (*HBCD*), and **c** polybrominated diphenyl ethers (*PBDEs*)

have been associated with a wide variety of toxic effects, affecting (1) thyroid hormone balance, which can cause hypothyroidism and tumors; (2) the central nervous system, which may manifest abnormalities in development dysfunction; (3) hepatic functions, which may cause increased activities of a number of enzymes, including cytochrome P-450, reduction in vitamin A levels, and tumors; (4) disturbances to the estrogen balance; and (5) in utero development, which can cause increased embryo mortality and delayed skeletal formation (e.g., DePierre 2003; EPA 2000c; EU 1997; Hooper and McDonald 2000; Meerts et al. 2000). Exposure to PBDEs disrupts the thyroid hormone both in humans (Bahn et al. 1980) and in animals (Hallgren and Darnerud 1998, 2002; Hallgren et al. 2001). It should be further noted that such effects on the thyroid hormone and its regulatory functions may cause brain developmental abnormalities, especially in children exposed in utero or through breast-feeding. PBDEs were found to bind the Ah receptor in experiments on rats, which in turn regulate several enzymes, including the cytochrome P-450 system (Hooper and McDonald 2000). Due to similarities in their chemical structure and physical properties with other toxic compounds such as PCBs, dioxins, and several pesticides such as DDT, PBDEs are suspected of sharing some toxicological properties as well (DePierre 2003).

HBCD distribution in the environment and its effects on humans were discussed in a review by Covaci et al. (2006). HBCD was reported to be capable of inducing cancer by a nonmutagenic mechanism (Helleday et al. 1999; Yamada-Okabe et al. 2005). Similar to the BPDEs, HBCD is considered capable of disrupting the thyroid hormone system (Yamada-Okabe et al. 2005). Following neonatal

exposure experiments in rats, developmental neurotoxic effects can be induced, such as aberrations in spontaneous behavior, learning, and memory function (Eriksson et al. 2002). HBCDs can also alter the normal uptake of neurotransmitters in rat brains (Mariussen and Fonnum 2003).

4.3 Petroleum Hydrocarbons and Fuel Additives

Petroleum hydrocarbons (PHs) constitute a group of compounds characterized by complex mixtures of hydrocarbons. Overall, hundreds to thousands of individual compounds can be found in the different mixtures, although information about their physical and chemical properties is available only for approximately 250 of these compounds, and substantial toxicological data exist for just a small fraction ($\sim$10 %) of the identified substances (Vorhees et al. 1999). Often these compounds are referred to in the literature as light nonaqueous-phase liquids (LNAPLs), when they exist as a separate phase. In terms of volumes of contaminants released to the environment, the contamination of land surface, partially saturated zone, and groundwater by PHs generally is one of the most serious. This is due to the staggering amounts of PHs used mainly as energy sources for electricity, transportation, and heating around the world. Leaking underground and aboveground storage tanks, improper disposal of petroleum wastes, and accidental spills are major routes of soil and groundwater contamination by petroleum products (Nadim et al. 2000).

Upon release to the environment, the bulk phase migrates downward by gravity. As the NAPL moves through the partially saturated zone, a fraction of the PH is retained by capillary forces as residual globules in the soil pores, thereby depleting the contiguous PH mass until movement ceases. If sufficient PH is released, it will migrate until it encounters a physical barrier (e.g., low-permeability stratum) or is affected by buoyancy forces near the water table. Additionally, PH vapors migrate in the porous matrix creating a larger impact zone. Once the capillary fringe is reached, the PH may move laterally as a continuous, free-phase layer along the upper boundary of the water-saturated zone, due to gravity and capillary forces. On contact with water in the saturated or partially saturated zone, dissolution of compounds from the PH mixture begins. A schematic description of PH distribution patterns in the subsurface is given in Fig. 4.7.

There are different approaches to estimating the toxicity of various PHs. One method is to examine the known individual compounds in each PH fraction, based on the data collected for a limited number of compounds and assuming that the known materials are representative of the entire mixture. A second method is to divide the mixture into several fractions that contain substances with similar chemical and physical properties, which therefore are considered to have comparable toxicity. A third approach is to consider the entire mixture. The actual content of each mixture depends mainly on the origin of the PH and the distillate fractions.

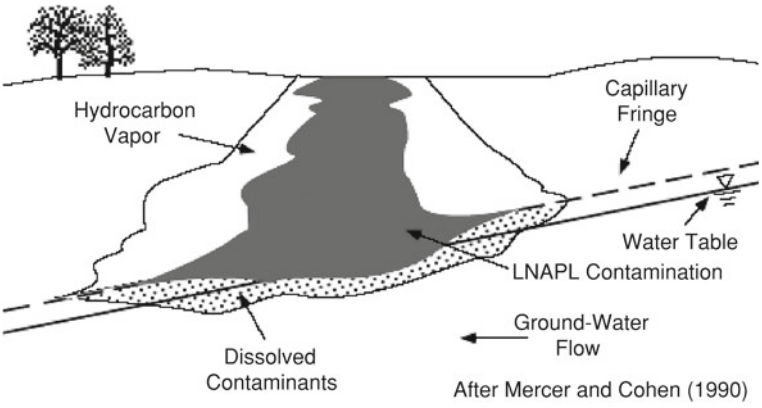

Fig. 4.7 Simplified conceptual model for light nonaqueous-phase liquid (*LNAPL*) release and migration. Reprinted from Mercer and Cohen (1990). Copyright 1990 with permission from Elsevier

The direct exposure pathways of humans to PH following a leak are described in Fig. 4.8. Once released to the surface and subsurface environment, PHs can reach humans directly as vapors, solutes, or adsorbed on particles.

Here, we briefly discuss several individual compounds that are common constituents of different PH mixtures, the main groups being (1) small aromatic compounds, mostly benzene derivatives (e.g., benzene, toluene, ethylbenzene, and xylenes), which are considered slightly soluble (150–1,800 mg/L); (2) branched and linear aliphatics (e.g., *n*-dodecane and *n*-heptane), which are characterized by relatively low water solubility; and (3) polar hydrocarbons and petroleum additives (e.g., methyl tertiary-butyl ether (MTBE) and alcohols), which are highly soluble. The weight percentage of three selected compounds in various commercial petroleum products is given in Table 4.1.

Benzene is important from an environmental point of view, as it is an important component of various petroleum products. Its weight fraction ranges from practically zero for the heavy distillates to 3.5 % for gasoline, as shown in Table 4.1. Its solubility is 1,780 mg/L, and it is very volatile (vapor pressure 100 torr at 26.1 °C). The acute (short-term) effects of benzene toxicity include dizziness, headache, nausea, vomiting, and drowsiness; with higher levels of benzene toxicity come the threat of convulsions, coma, and death. The long-term or chronic results of benzene toxicity include reproductive damage, chromosomal aberrations, immunodeficiencies, and several types of leukemia (ATSDR 2006b).

Xylene belongs to the group of small aromatic compounds with relatively higher solubility, like benzene. Exposure to toluene causes CNS depression (Faust 1994). Short-term exposure effects include fatigue, confusion, lack of coordination, impaired reaction time, perception, and motor control and function (NTP 1990). Exposure to high concentrations results in narcosis and death (WHO 1985). Prolonged abuse of toluene or solvent mixtures containing toluene has led to permanent

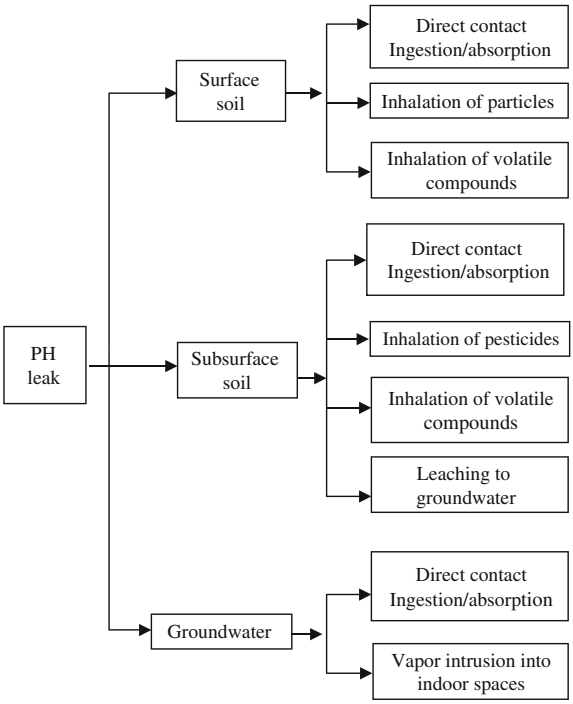

Fig. 4.8 Pathways of direct human exposure to petroleum hydrocarbons following release to the surface and subsurface environment (Vorhees et al. 1999)

Table 4.1 Fraction range (in wt.%) of three hydrocarbons in selected commercial petroleum products, based on data from Gustafson et al. (1997)

	Crude oil	Diesel	Fuel oil #2	Gasoline	JP-4
Benzene	0.04–0.4	0.003–0.10	<0.125	0.12–3.50	0.5
Toluene	0.09–2.5	0.007–0.70	0.025–0.110	2.73–21.80	1.33
n-Octane	0.9–1.9	0.1	0.1	0.36–1.43	3.8

CNS effects. Hepatomegaly and impaired liver and kidney function have been reported in some humans chronically exposed to toluene (Greenburg et al. 1942).

Hexane represents the aliphatic group. Most of the aliphatic compounds are branched, but the same trend of low solubility that decreases with increasing C number is typical of all substances in this group. Due to their very low solubility, these compounds hardly partition to water and migrate mainly as vapors, as a separate phase, or adsorbed on particulate matter. In very high concentrations (thousands of ppm), hexane is a lethal narcotic to humans (HCN 2005). High-level exposure affects several enzyme functions, which lead to increased liver weight. No data on octane toxicity are available, and it is considered nontoxic.

MTBE is an octane enhancer; that is, it promotes more complete burning of gasoline and thereby reduces carbon monoxide and ozone levels. MTBE is very soluble, and once released, it moves through soil and into water more rapidly than other chemical compounds present in gasoline. In groundwater, it is slow to biodegrade and more persistent than other gasoline-related compounds. Exposure to vapors may result in several health effects including dizziness, nausea, sore eyes, and respiratory irritation (McCarthy and Tiemann 2001). The US EPA concluded that MTBE poses a potential for carcinogenicity to humans at high doses; however, because of uncertainties and limitations in available data, the EPA has been unable to reliably estimate the risk at low exposure levels (EPA 1997). Based on this, several wells contaminated with MTBE have been closed, but because MTBE is an additive, its effect should be considered against other alternatives, which usually are more problematic.

In general, because of the combination of solubility and toxicity characteristics, aromatic compounds are the major group of PH contaminants in groundwater. However, due to the large amounts of PH released to the environment and lack of information, much more research is needed to understand the behavior and toxicity of these complex mixtures and their potential effect on the subsurface environment.

4.4 Pharmaceuticals and Personal Care Products

A large class of chemicals gaining attention in recent years comprises pharmaceutical, veterinary, and illicit ("recreational") drugs and the ingredients in cosmetics, food supplements, and other personal care products, together with their respective metabolites and transformation products; they are collectively referred to as *pharmaceuticals and personal care products* (PPCPs). PPCPs are used in large amounts throughout the world, and some studies demonstrated their occurrence in aquatic environments in Austria, Brazil, Canada, Croatia, Denmark, England, Germany, Greece, Italy, Spain, Switzerland, the Netherlands, and the USA (Heberer et al. 2002; Daughton and Ternes 1999; Erickson 2002).

Most PPCPs are disposed of or discharged into the environment on a continuous basis via domestic and industrial sewage systems and wet weather runoff. In many instances, untreated sewage is discharged into receiving waters (e.g., flood overload events, domestic "straight piping," or sewage waters lacking municipal treatment). A scheme of possible pathways for the occurrence of PPCP residues in aquatic environments is depicted in Fig. 4.9. The bioactive ingredients are first subjected to metabolism by the dosed user; the excreted metabolites and unaltered parent compounds then can be subjected to further transformations in sewage treatment facilities. The literature shows, however, that many of these compounds survive biodegradation, eventually being discharged into receiving waters. Many of these PPCPs and their metabolites are ubiquitous and display persistence in, and bioconcentration from, surface waters. Additionally, by way of continuous

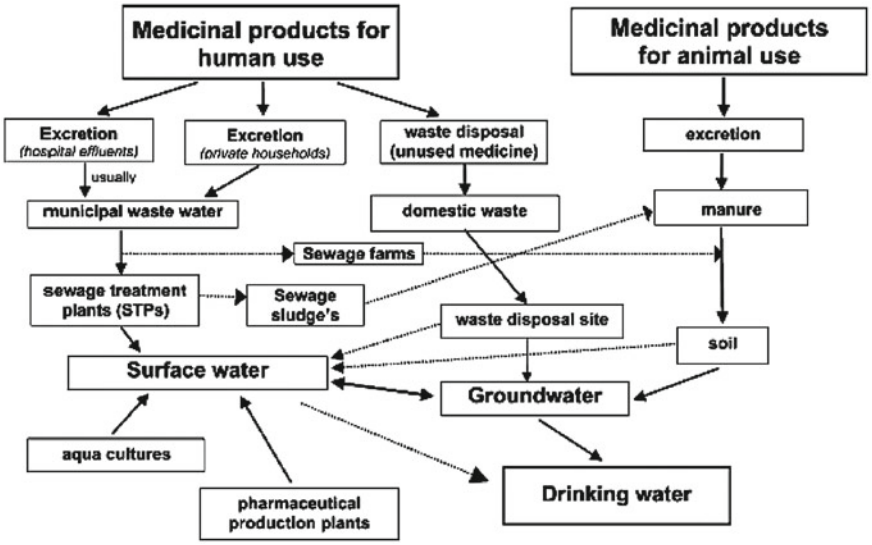

Fig. 4.9 Scheme showing possible sources and pathways for the occurrence of pharmaceutical residues in the aquatic environment. Reprinted from Heberer T (2002). Copyright 2002 with permission from Elsevier

infusion into the aquatic environment, those PPCPs that might have low persistence can display the same exposure potential as truly persistent pollutants, because their transformation and removal rates can be compensated by their replacement rates. While the concentration of individual drugs in the aquatic environment often is low (subparts per billion or subnanomolar, often referred to as *micropollutants*), the presence of numerous drugs sharing a specific mode of action could lead to significant effects through additive exposures.

Many PPCPs are used on a daily basis for very long periods, sometimes a good portion of the user's lifetime. Although drugs are usually designed with a specific mode of action in mind, they also can have numerous effects on nontarget, or as yet unknown receptors, and possibly cause side effects in the target organism. Furthermore and of equal importance, nontarget organisms can have receptors, or receptor tissue distributions, that do not exist in the target organisms, and therefore, unexpected effects can result from unintentional exposure. Often PPCPs are released to the environment in low concentrations for long periods, which in turn may cause genetic selection of the more resistant pathogens that can reduce the effectiveness of current medications.

Some studies (Migliore et al. 1995) demonstrated that drugs alter the normal post-germinative development of plants and the growth of roots, hypocotyls, and leaves. This effect becomes more important with time, so it is more evident in structures produced later. In other cases, drugs such as natural and synthetic estrogens that reach the environment have been shown to produce deleterious

effects in aquatic organisms, such as feminization and hermaphroditism. The presence of ethinyl estradiol, the most potent synthetic estrogen known, in a river sediment has been associated with a striking incidence of carp species with both macroscopically developed male and female reproductive organs (Gross-Sorokin et al. 2006).

Traditionally, drugs were rarely viewed as potential environmental pollutants; there was seldom serious consideration as to their fates once they were excreted from the user. On the other hand, until the 1990s, any concerted efforts to search for drugs in the environment would have met with limited success, because the requisite chemical analysis tools with sufficiently high separatory efficiencies to resolve the drugs from the plethora of other (native and anthropogenic) substances and with sufficiently low detection limits (i.e., nanograms per liter or parts per trillion) were not commonly available. Examples of major groups of PPCPs found in the environment follow.

4.4.1 Analgesics and Anti-inflammatory Drugs

This group refers mainly to drugs used primarily as painkillers, although they may also have anti-inflammatory and antipyretic properties. Drugs in this group are sold in large quantities by prescription and even larger amounts without prescription, as so-called over-the-counter (OTC) drugs. Acetaminophen (paracetamol) and acetylsalicylic acid (ASA, aspirin) are the two most popular painkillers sold as OTC drugs. In Germany, the total quantities of ASA sold per year have been estimated at >500 tons (Heberer et al. 2002; Ternes 2001).

Other examples of analgesics or their metabolites that have been found in the environment include 4-aminoantipyrine, aminophenazone, codeine, fenoprofen, hydrocodone, indomethacin, ketoprofen, mefenamic acid, naproxen, propyphenazone, diclofenac, ibuprofen, phenazone, gentisic acid and *N*-methyl phenacetin. Many studies have identified these compounds in various locations around the world and in different water resources (e.g., Heberer et al. 1997, 2001a, b; Ternes 2001; Stumpf et al. 1999; Ahrer et al. 2001; Sedlak and Pinkston 2001; Holm et al. 1995; Ahel and Jelicic 2001; Sacher et al. 2001).

4.4.2 Hormones

Synthetic steroids, especially estrogenic drugs, are used extensively in estrogen-replacement therapy and oral contraceptives, in veterinary medicine for growth enhancement, and in athletic performance enhancement. In general, large portions of these endocrine disruptors, used by humans as well as for stimulating beef, poultry, and fish production, are excreted unchanged in feces and urine. Synthetic steroids have been found in the environment in very low concentrations (usually

less than 5 ng/L). Furthermore, the physicochemical properties (lipophilicity) of such hormones are expected to allow removal via sorption processes in sewage treatment facilities or adsorption to subsurface soil. However, even the low concentrations found in different water bodies (e.g., sewage, surface water, and groundwater) (Daughton and Ternes 1999; Heberer et al. 2002) may pose a threat for ecosystems. For example, exposure of wild male fish to only 0.1 ng/L of xenoestrogens may provoke feminization in some species.

4.4.3 Antibacterial Drugs

Antibacterial drugs (i.e., antibiotic and bacteriostatic drugs) have received considerable attention because of their heavy use and their potential hazardous effect on ecosystems. Antibiotics used to treat infections are an invaluable tool, and their introduction has revolutionized the treatment of infectious diseases. Because of their widespread use, it is not surprising that antibiotics have been found in liquid waste at animal feedlots and spread into many surface water and groundwater supplies. In general, large portions of antibiotics used by humans, as well as for beef and poultry production, are excreted unchanged in feces and urine. With increasingly wide use of antibiotics, resistant strains of bacteria are replacing antibiotic-susceptible bacteria. Furthermore, resistant bacteria in one environment may not be confined to that specific environment and can be carried over distances of thousands of kilometers by wind, water, animals, food, or people. And, most important, antibiotic-resistant organisms that develop in animals, fruits, or vegetables can be passed to humans through the food chain and environment. All these factors have had the effect of changing the balance between antibiotic-susceptible and antibiotic-resistant bacteria in ecosystems, both locally and globally.

Macrolide antibiotics (clarithromycin, dehydroerythromycin (a metabolite of erythromycin), roxithromycin, lincomycin, sulfonamides (sulfamethoxazole, sulfadimethoxine, sulfamethazine, sulfathiazole), fluoroquinolones (ciprofloxacin, norfloxacin, enrofloxacin), chloramphenicol, tylosin, and trimethoprim) have been found up to low μg/L levels in sewage and surface water samples. Sacher et al. (2001) reported the occurrence of sulfamethoxazole (up to 410 ng/L) and dehydroerythromycin (up to 49 ng/L) in groundwater samples in Baden-Wurttemberg, Germany. Sulfamethoxazole and sulfamethazine have also been detected at low concentrations in several groundwater samples in the USA and Germany (e.g. Hartig et al. 1999). Holm et al. (1995) found residues of different sulfonamides at high concentrations in groundwater samples collected down gradient of a landfill in Grindsted, Denmark.

4.4.4 Antiepileptic Drugs

Treatment of seizures by antiepileptic drugs began in 1850, and since then, a variety of medications have been applied. The main groups of antiepileptic drugs include sodium channel blockers, calcium current inhibitors, gamma-aminobutyric acid (GABA) enhancers, glutamate blockers, carbonic anhydrase inhibitors, hormones, and drugs with unknown mechanisms of action. One of the widespread antiepileptic drugs, carbamazepine, has been detected frequently in municipal sewage and surface water samples (Heberer et al. 2001a; Ahrer et al. 2001). Various field studies have shown that carbamazepine (Heberer et al. 2001b) and primidone (Heberer et al. 2001b) are not attenuated during riverbank infiltration. Both compounds have been detected in shallow wells and water supply wells of a transect built to study the behavior of drugs during riverbank filtration (Heberer et al. 2001b). This also explains why carbamazepine has been detected in a number of groundwater samples at a maximum concentration up to 1.1 µg/L (Seiler et al. 1999; Sacher et al. 2001; Ternes 2001) and in drinking water at a concentration of 30 ng/L (Ternes 2001).

4.4.5 Beta-Blockers

Beta-blockers are medications that reduce the workload of the heart and lower blood pressure. They are commonly prescribed to relieve angina (a type of chest pain, pressure, or discomfort) or treat heart failure. They also are prescribed for people who have high blood pressure (hypertension). Several beta-blockers (metoprolol, propranolol, betaxolol, bisoprolol, and nadolol) have been detected in municipal sewage effluents up to the µg/L level (Ternes 1998) and in groundwater samples (Sacher et al. 2001).

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