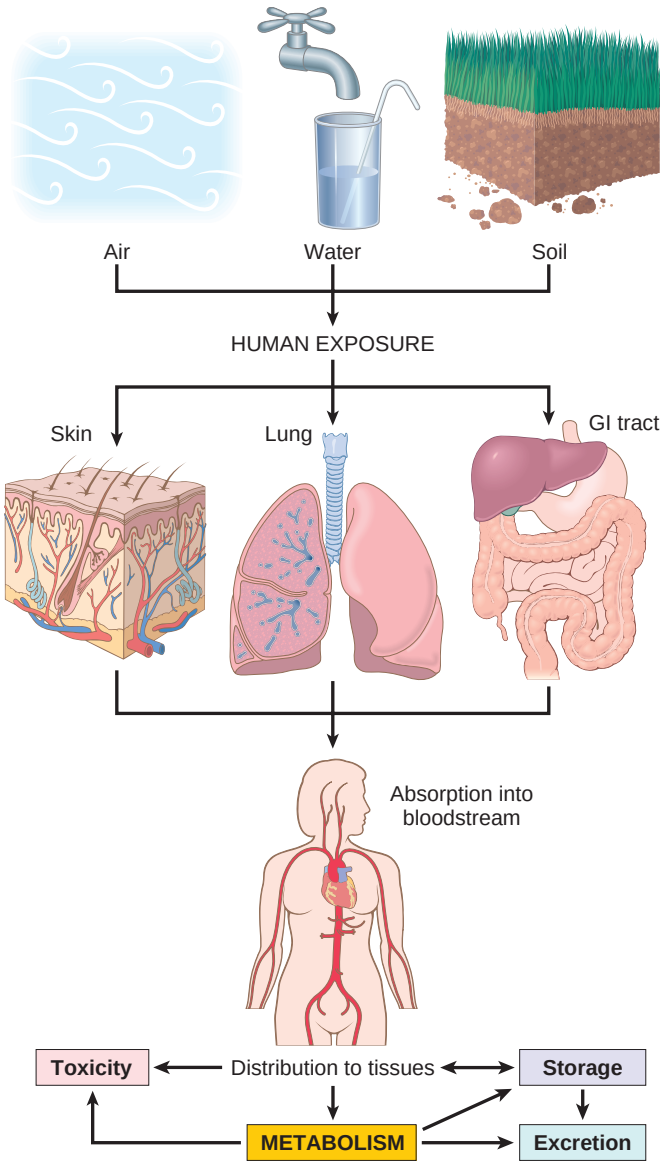

Figure 9-3 Human exposure to pollutants. Pollutants in the air, water, and soil are absorbed through the lungs, gastrointestinal tract, and skin. In the body they may act at the site of absorption but are generally transported through the bloodstream to various organs where they may be stored or metabolized. Xenobiotics may be metabolized to water-soluble compounds that are excreted, or to toxic metabolites, a process referred to as activation.

that activate xenobiotics to generate toxic compounds (Figs. 9-3 and 9-4), occur in two phases. In *phase I* reactions, chemicals undergo hydrolysis, oxidation, or reduction. Products of phase I reactions are often metabolized into water-soluble compounds through *phase II* reactions, which include glucuronidation, sulfation, methylation, and conjugation with glutathione. Water-soluble compounds are readily excreted. Enzymes that catalyze the biotransformation of xenobiotics and drugs are known as *drug-metabolizing enzymes*.

- The most important catalyst of phase I reactions is the *cytochrome P-450 enzyme system* (*abbreviated as CYP*) located primarily in the endoplasmic reticulum of the liver but also present in skin, lungs, and gastrointestinal mucosa, and other organs. CYPs are a large family of heme-containing enzymes, each with preferred substrate specificities. **The P-450 system catalyzes reactions that either detoxify xenobiotics or, less commonly, convert xenobiotics into active compounds that cause cellular injury.** Both types of reactions may produce, as a byproduct, *reactive oxygen species (ROS)*, which can cause cellular damage (Chapter 2). Examples of metabolic activation of chemicals through CYPs are the production of the toxic trichloromethyl free radical from carbon tetrachloride in the liver, and the generation of a DNA-binding metabolite from benzo[*a*]pyrene, a carcinogen present in cigarette smoke. CYPs participate in the metabolism of a large number of common therapeutic drugs such as acetaminophen, barbiturates, warfarin, and anticonvulsants, and also in alcohol metabolism (discussed later).

There is great variation in the activity of CYPs among individuals. The variation may be a consequence of genetic polymorphisms in specific CYPs, but more commonly it is due to exposure to drugs or chemicals that induce or diminish CYP activity. Known CYP inducers include environmental chemicals, drugs, smoking, alcohol, and hormones. In contrast, fasting or starvation can decrease CYP activity.

Inducers of CYP do so by binding to nuclear receptors, which then heterodimerize with the retinoic X receptor (RXR) to form a transcriptional activation complex that associates with promoter elements located in the 5′-flanking region of CYP genes. Nuclear receptors participating in CYP induction responses include the aryl hydrocarbon receptor, the peroxisome proliferator-activated receptors *(PPAR)*, and two orphan nuclear receptors, constitutive androstane receptor (CAR), and pregnane X receptor (PXR).

This brief overview of the general mechanisms of toxicity provides the background for the discussion of environmental diseases presented in this chapter.

Environmental Pollution

Air Pollution

Air pollution is a significant cause of morbidity and mortality worldwide, particularly among at-risk individuals with preexisting pulmonary or cardiac disease. Air is precious to life, but can also carry many potential causes of disease. Airborne microorganisms have long been major causes of morbidity and mortality, especially in developing countries. More widespread are airborne chemical and particulate pollutants, especially in industrialized nations. Here, we consider these hazards in outdoor and indoor air.

Outdoor Air Pollution

The ambient air in industrialized nations is contaminated with an unsavory mixture of gaseous and particulate pollutants, more heavily in cities and in proximity to heavy industry. In the United States, the Environmental Protection Agency monitors and sets allowable upper limits for six pollutants: sulfur dioxide, carbon monoxide, ozone, nitrogen dioxide, lead, and particulate matter. Collectively, these agents produce the well-known *smog* (smoke and fog) that sometimes stifles large cities such as Beijing, Los