temperature increase stems from questions about the degree to which positive-feedback loops will exacerbate factors driving the process. Examples of such self-reinforcing loops are increases in surface heat absorption due to loss of reflective ice and snow; increases in water vapor due to greater evaporation from warming rivers, lakes, and oceans; large releases of CO_2 and methane from organic matter in thawing Arctic "permafrost" and submarine methane hydrates; and decreased sequestration of CO_2 in oceans due to reduced growth of organisms, such as diatoms, that serve as carbon sinks. Increased heat energy in the oceans and atmosphere is also projected to increase the variability and severity of weather events, such as floods, droughts, and storms. An additional worrisome effect of increased atmospheric CO_2 concentrations is increasing acidity of the oceans, which may disrupt marine ecosystems and fisheries.

The health impacts of climate change will depend on its extent and rapidity, the nature and severity of the ensuing consequences, and humankind's ability to mitigate the damage. Even in the best case scenario, however, climate change is expected to have a serious negative impact on human health by increasing the incidence of a number of diseases, including the following:

- *Cardiovascular, cerebrovascular, and respiratory diseases*, all of which will be worsened by heat waves and air pollution
- *Gastroenteritis, cholera, and other foodborne and waterborne infectious diseases*, caused by contamination as a consequence of floods and disruption of clean water supplies and sewage treatment, after heavy rains and other environmental disasters
- *Vector-borne infectious diseases, such as malaria and dengue fever*, due to changes in vector number and geographic distribution related to increased temperatures, crop failures, and more extreme weather variation (e.g., more frequent and severe El Niño events)
- *Malnutrition*, caused by changes in local climate that disrupt crop production. Such changes are anticipated to be most severe in tropical locations, in which average temperatures may already be near or above crop tolerance levels; it is estimated that by 2080, agricultural productivity may decline by 10% to 25% in some developing countries as a consequence of climate change.

Beyond these disease-specific effects, it is estimated that melting of glacial ice, particularly in Greenland, combined with the thermal expansion of warming oceans, will raise sea levels by at least 1 to 2 feet by 2100. Of greater worry, temperatures in the vicinity of the western Antarctic ice sheet rose 2.4°C between 1958 and 2010, one of the greatest increases in temperature seen at any location on earth during this period. Complete melting of the western Antarctic ice shelf, which is certain to occur in coming centuries if current trends continue, will raise oceans levels by an additional 5 meters—approximately 16.5 feet. Approximately 10% of the world's population—roughly 600 million people—live in low-lying areas that are at risk for flooding even if the rise in ocean levels is at the low end of these estimates. The resulting displacement of people will disrupt lives and commerce, creating conditions ripe for political unrest, war, and poverty, the "vectors" of malnutrition, sickness, and death.

Both developed and developing countries will suffer the consequences of climate change, but the burden will be greatest in developing countries, which to date have been least culpable for increases in greenhouse gases to date. This equation is changing rapidly, however, owing to the growth of the economies of India and China, which has recently surpassed the United States to become the largest producer of CO_2 in the world. The urgent challenge is to develop new renewable energy resources that stem the production of greenhouse gases.

Toxicity of Chemical and Physical Agents

***Toxicology* is defined as the science of poisons. It studies the distribution, effects, and mechanisms of action of toxic agents.** More broadly, it also includes the study of the effects of physical agents such as radiation and heat. Approximately 4 billion pounds of toxic chemicals, including 72 million pounds of recognized carcinogens, are released per year in the United States. Of about 100,000 chemicals in commercial use in the United States, only a very small proportion has been tested experimentally for health effects. Several agencies in the United States set permissible levels of exposure to known environmental hazards (e.g., the maximum level of carbon monoxide in air that is noninjurious or the tolerable levels of radiation that are harmless or "safe"). Factors such as the complex interaction between various pollutants, and the age, genetic predisposition, and the different tissue sensitivities of exposed persons, create wide variations in individual sensitivity to toxic agents, limiting the value of establishing rigid "safe levels" for entire populations. Nevertheless, such cut-offs are useful for comparative studies of the effects of harmful agents between specific populations, and for estimating risk of disease in heavily exposed individuals.

We now consider some basic principles relevant to the effects of toxic chemicals and drugs.

- The *definition of a poison* is not straightforward. It is basically a quantitative concept strictly dependent on *dosage*. The quote from Paracelsus in the sixteenth century that "all substances are poisons; the right dosage differentiates a poison from a remedy" is even more valid today, given the proliferation of pharmaceutical drugs with potentially harmful effects.
- *Xenobiotics* are exogenous chemicals in the environment in air, water, food, and soil that may be absorbed into the body through inhalation, ingestion, and skin contact (Fig. 9-3).
- Chemicals may be excreted in urine or feces; eliminated in expired air; or may accumulate in bone, fat, brain, or other tissues.
- Chemicals may act at the site of entry or at other sites following transport through the blood.
- *Most solvents and drugs are lipophilic*, which facilitates their transport in the blood by lipoproteins and their penetration through the plasma membrane into cells.
- Most solvents, drugs, and xenobiotics are metabolized to form inactive water-soluble products *(detoxification)*, or are *activated to form toxic metabolites*. The reactions that metabolize xenobiotics into nontoxic products, or