INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

HAZARDOUS CHEMICALS IN HUMAN AND ENVIRONMENTAL HEALTH

a resource book for school, college and university students

Produced under the joint sponsorship of the United Nations Environment Programme, the International Labour Organisation and the World Health Organization, and within the framework of the Inter-Organization Programme for the Sound Management of Chemicals
The International Programme on Chemical Safety (IPCS), established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organisation (ILO), and the World Health Organization (WHO). The overall objectives of the IPCS are to establish the scientific basis for assessment of the risk to human health and the environment from exposure to chemicals, through international peer review processes, as a prerequisite for the promotion of chemical safety, and to provide technical assistance in strengthening national capacities for the sound management of chemicals.

The Inter-Organization Programme for the Sound Management of Chemicals (IOMC) was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization, the United Nations Institute for Training and Research, and the Organisation for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

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PREFACE

Chemicals have become an indispensable part of our life, sustaining many of our activities, preventing and controlling many diseases and increasing agricultural productivity. The benefits are incalculable, but, on the other hand, chemicals may endanger our health and poison our environment.

The nature, number and quantities of chemicals used in countries vary widely according to factors such as the national economy, its industries and agriculture. Thousands of chemicals are synthesized each year to determine if they offer advantages over their predecessors and are viable commercially. It has been estimated that approximately 100,000 chemical substances are at present in commerce, and about 2000 new ones come onto the market every year. The chemical scene is thus constantly changing as new chemicals and formulations supersede older ones, and the quantities produced and used vary with their effectiveness and demand.

Many have potentially toxic effects on health and the environment. There are risks from exposure during production, storage, handling, transport, use and disposal of chemicals, as well as from accidental leakage or illegal dumping.

Released inappropriately into the environment, chemicals may appear as pollutants in the air we breathe, the water we drink and the food we eat. They may affect our rivers, lakes and forests, may harm wildlife, change climate and ecosystems.

We are all exposed to toxic chemicals. Whether they harm us depends on the quantity, duration and frequency of exposure, and the toxicity as well as on the sensitivity of the individual. The amount may be minute, but some chemicals accumulate in the body over long periods. Some chemicals cause harm many years after the exposure. Although exposure duration may be short, exposure may occur frequently and to excessive concentrations. Children, the aged, pregnant women, and those weakened by disease may be more susceptible than the healthy adult.

The growth of chemical industries, in developing as well as developed countries, is predicted to go on increasing for the next century. Chemical safety, that is the prevention and management of chemical hazards, is essential if the growth is to be beneficial and not catastrophic for humans and the environment.

At the United Nations Conference on Environment and Development (UNCED) held in Rio de Janeiro, Brazil in June 1992, representatives of more than 150 countries adopted at the highest political level Agenda 21 — an action plan to guide national and international activities for the years to come. A specific chapter of Agenda 21 is devoted to the “Environmentally sound management of toxic chemicals including prevention of illegal international traffic in toxic and dangerous products”. UNCED recognized that many countries lack the scientific knowledge of judging the impact of toxic chemicals on human health and the environment. As a result, and all too often, toxic chemicals are being produced, transported, used and disposed of, without taking the necessary precautions to prevent chemical contamination and grave damage to human health and the environment.
This book is written for the young men and women who will work in industry, agriculture, government and other public or private sectors, so that they carefully consider the potential detrimental effects on health and the environment of hazardous chemicals and take appropriate actions at the local, national or international level for their environmentally sound management. It is hoped that they will leave for their children a better environmental legacy than the one we left for them.

In order to facilitate the use of this text by young men and women as students and as the future stewards of environmental quality and public health, several features have been incorporated. All chapters are introduced with a brief note of the specific learning objectives of the chapter, highlighted for easy reference. Technical terms and important phrases are typeset in bold the first time that they appear in the text and are defined in the glossary at the end of the text. Extensive use has been made of highlighted margin notes, which elaborate the most important concepts that are presented and discussed in the text. Finally, every chapter concludes with a highlighted review, summarizing the critical issues discussed in the preceding chapter.
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ABBREVIATIONS

ADI acceptable daily intake
AQG Air Quality Guidelines
CFC chlorofluorocarbon
CNS central nervous system
DNA deoxyribonucleic acid
FAO Food and Agriculture Organization of the United Nations
GV guideline value
HEIE health and environmental impact assessment
IARC International Agency for Research on Cancer
IPM integrated pest management
JECFA Joint FAO/WHO Expert Committee on Food Additives
IMPR Joint FAO/WHO Meeting on Pesticide Residues
LOAEL lowest-observed-adverse-effect level
NOAEL no-observed-adverse-effect level
PAH polycyclic aromatic hydrocarbons
PCB polychlorinated biphenyl
PVC polyvinyl chloride
TDI tolerable daily intake
WHO World Health Organization
1. SOURCES OF CHEMICALS IN THE ENVIRONMENT

This chapter will show:

- that chemicals in the environment are both natural and made by humans, and both have effects on human and environmental systems
- that all substances, whether natural or made by humans, have the potential to cause adverse health and environmental effects
- that naturally occurring chemicals can be just as toxic and dangerous as man-made chemicals
- how and why we are exposed to these chemicals and how to prevent exposure
- how man-made pollutants can have damaging effects on the environment
- that accidental discharges of many chemicals can have far-reaching effects, and that use must be carefully controlled
1.1 Naturally occurring chemicals in the environment

Chemical substances are everywhere in the environment, and just like plants or water, chemicals occur naturally in the environment. All matter is composed of chemicals, including our food, drinks, clothing, medicines, plants and even ourselves. Although it is often thought that if a chemical is present "naturally" in the environment it is harmless, this is sometimes not the case. In fact, many natural chemicals, or derivatives of those chemicals, can be just as toxic to humans and the environment as man-made (synthetic) chemicals like pesticides, therapeutic drugs, and the solvents we use in industry. Nature is capable of producing a vast array of toxic chemicals. In addition, the natural environment provides a number of hazards to humans, such as radiation, bacteria, fungi, viruses, plants and certain gases.

To illustrate this point, examples of naturally occurring hazardous chemicals that have resulted in adverse health effects in human populations are described below and include fluoride, arsenic, natural food contaminants such as mycotoxins, and toxins produced by bacteria found in food. Although this list is certainly not complete, several case studies will help illustrate why sometimes natural chemicals can be just as dangerous as synthetic chemicals.

1.1.1 Sources of toxicants

Since chemicals are found everywhere, there are many sources of toxic chemicals such as air, water, food, chemicals in the workplace, drugs, pesticides, solvents, natural hydrocarbons and combustion products, cosmetics, naturally occurring toxins e.g., mycotoxins, microbial toxins, plant toxins and animal toxins. People are also concerned about other environmental pollutants such as asbestos, carbon monoxide, tobacco smoke, lead, mercury, microwaves, electromagnetic fields, ozone, acid rain and volatile organic compounds, to name but a few.

1.1.2 Naturally occurring elements in the environment

1.1.2.1 Fluoride

Fluorides occur naturally in (i) water, (ii) soil, (iii) air, and (iv) food.

(i) The fluoride content of water in lakes, rivers or wells is usually below 0.5 mg/litre, although concentrations as high as 95 mg/litre have been recorded in Tanzania. Waters with high fluoride content are usually found at the foot of high mountains and in areas
with geological deposits of marine origin. Typical examples are the geographical belts from Syria through Jordan, Egypt, Libya, Algeria, Morocco and the Rift Valley through Sudan and Kenya. Another belt is the one stretching from Turkey through Iraq, Iran and Afghanistan to India, northern Thailand and China. The highest natural fluoride concentration ever found in water was recorded in Lake Nakuru in the Rift Valley in Kenya (2800 mg/litre).

Drinking-water is usually the principal source of exposure to natural fluoride, and presents an interesting case. It has been shown that exposure to fluoride from drinking-water at levels of 0.5–1.0 mg/litre is beneficial to health in that it reduces the prevalence of dental cavities. However, excessive exposure to naturally occurring fluoride in drinking-water can cause dental fluorosis. Dental fluorosis is characterized by dull, spotted and/or pitted patches in the enamel which may be stained yellow to dark brown. Long-term exposure to unusually high natural fluoride levels in drinking-water, in excess of about 10 mg/litre, has resulted in crippling skeletal fluorosis in China, India and South Africa. This condition is frequently complicated by factors such as calcium deficiency or malnutrition.

(ii) The main fluoride-containing minerals are fluorspar, cryolite and apatite. Volcanic rocks, as well as salt deposits of marine origin, also contain significant amounts of fluoride. Phosphate rock can naturally contain up to 4% fluoride, some of which is released into the atmosphere.

(iii) Fluoride can be found in air, originating from the dusts of fluoride-containing soils and from gases emitted in areas of volcanic activity. Although not a natural source, fluoride emissions from industries producing phosphate fertilizers and brickworks also contribute to high concentrations of fluoride in the air, which can result in additional human exposure to fluorides.

(iv) Certain plants, such as taro, yams and cassava, which constitute the staple diet in many tropical areas, particularly in South America and in the Pacific, have been found to contain relatively high fluoride levels. Tea leaves, also, may contain rather high levels of fluoride. Fish products, in particular canned fish such as sardines, the bones of which are also eaten, have a fluoride content of up to 40 mg/kg.

1.1.2.2 Arsenic

As with most chemicals, human exposure to arsenic occurs from natural, industrial and agricultural sources. Arsenic is widely distributed in the earth’s crust, where it occurs in over 150 minerals. It is found in the ores used for extraction of various metals such as gold, lead, copper, tin and zinc. Arsenic is released into the atmosphere as a by-product of the primary smelting of nonferrous ores, from pesticide manufacturing processes, and from
the glass-melting furnaces used in the manufacture of glass. Because arsenic compounds are sometimes used as pesticides, dust and gases emitted from cotton gins and tobacco contain arsenic. The greatest occupational exposure to arsenic occurs in the smelting of nonferrous metals in which arsenic-containing ores are commonly used. It has been estimated that 1.5 million workers worldwide are potentially exposed to inorganic arsenic compounds produced in this way.

Arsenic occurs widely in natural waters. Natural sources of arsenic in fresh water include the erosion of surface and volcanic rocks. Waters of hot springs have been found to contain up to 14 mg/litre of arsenic. Arsenic in water can also be added through industrial discharges.

Marine organisms are exposed only to the low levels of arsenic found in the sea. Nevertheless, they contain the highest arsenic concentrations (0.01–200 mg/kg) of all animals. Crustacea, such as prawns, mussels and scallops, generally have the highest arsenic concentrations. Arsenic levels in various fish species range from 0.2 to 70 mg/kg. However, arsenic present in aquatic organisms is mostly in the form of arseno-organic compounds which, unlike the inorganic forms of arsenic, are not toxic to humans.

Drinking-water is an important source of exposure to arsenic. Concentrations of arsenic are generally highest in groundwater. The World Health Organization has recommended a health-based provisional guideline value for arsenic in drinking-water of 0.01 mg/litre. Some examples of concentrations found in wells and surface waters include the following:

a) In water wells

- Taiwan up to 1.8 mg/litre
- Hungary > 0.1 mg/litre
- India > 0.05 mg/litre
- Mexico > 0.4 mg/litre
- USA > 0.1 mg/litre

b) In surface waters

- Chile 0.8 mg/litre
- Argentina >0.3 mg/litre

It is of interest to note that many countries have drinking-water levels of arsenic that exceed the WHO guideline value by up to 200 times.

Numerous reports indicate that chronic exposure to arsenic in drinking-water can be harmful to health. These include hyperpigmentation, keratosis (horny growth), and skin cancer. A high prevalence of a peripheral vascular disorder (blackfoot
disease) has been found in an area of Taiwan where high levels of arsenic occur naturally in drinking-water. Peripheral vascular effects have also been reported in a population in Chile exposed to arsenic in drinking-water. In addition, in certain parts of the world (e.g., Reichenstein, Silesia, Cordoba, Argentina, and a small area of the southwest coast of Taiwan), the high levels of arsenic found in drinking-water have been associated with a high rate of skin cancer cases. The International Agency for Research on Cancer (IARC) has classified arsenic as a "human carcinogen" (see Chapter 5).

In summary, most of the exposure to arsenic occurs from its natural presence in drinking-water, which does not necessarily mean it is safe. Harmful health effects have been well documented. Other naturally occurring elements and their potential effects on human health are listed in Table 1.

<table>
<thead>
<tr>
<th>Metal</th>
<th>Effects</th>
<th>Source of exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cadmium (Cd)</td>
<td>Kidney toxicity</td>
<td>Occupational exposure by inhalation to cadmium fumes and contamination of food</td>
</tr>
<tr>
<td>Chromium (Cr)</td>
<td>Dermatitis</td>
<td>Occupational exposure Wearing jewellery containing chromium</td>
</tr>
<tr>
<td>Lead (Pb)</td>
<td>Interferes with haemoglobin production; can cause kidney disfunction, mental retardation (children are particularly sensitive)</td>
<td>Occupational exposure Children's contact with soil and dirt, inhalation of motor fuels containing lead, and ingestion of lead-based paint</td>
</tr>
</tbody>
</table>

### 1.2 Natural food contaminants

Natural components (toxicants) are found in foods of plant and animal origin. Toxicants include compounds naturally occurring and present in foods regardless of their source. Toxicants are manufactured by plants, fungi and bacteria. Because plants cannot run away from their predators, their best defence is to produce foul-tasting or foul-smelling compounds and toxins. Some naturally occurring toxicants found in plants and animals include the following:

a) *In plants*

- alkaloids
- allergens
- cyanogens
- enzyme inhibitors
- glucosinolates
- toxic amino acids, proteins and peptides, lipids and saponins
b) In foods of animal origin

- marine toxins (shellfish poisons like saxitoxin, tetrodotoxin)

1.3 Bacterial toxins as food contaminants

Foodborne intoxication and foodborne infection are two major causes of disease worldwide. Foodborne intoxication occurs when pre-formed microbial toxins in the food are consumed, while foodborne infection results from the presence in food of bacteria that can cause disease either by multiplying in the intestines or by producing toxins in the intestinal tract following multiplication and growth. An example of foodborne infection is Salmonella, and an example of foodborne intoxication is botulism.

1.3.1 Clostridium botulinum

Microorganisms such as Clostridium botulinum are also considered natural food contaminants, and may also cause foodborne illness and disease. Clostridium botulinum, the most dreaded foodborne microorganism, is an anaerobic, spore-forming bacterium that produces a potent neurotoxin. The spores are heat-resistant and can survive in foods that are incorrectly or minimally processed. Foodborne botulism is a severe type of food poisoning caused by the ingestion of foods containing the potent neurotoxin formed during growth of the organism. The toxin itself can be destroyed if heated at 80 °C for 10 minutes or longer. The incidence of the disease is low, but the disease is of considerable concern because of its high mortality rate if not treated immediately and properly. Most of the outbreaks that are reported are associated with inadequately processed, home-canned foods, but occasionally commercially produced foods have been involved in outbreaks. Sausages, meat products, canned vegetables and seafood products are the most frequent vehicles for human botulism transmission.

Clostridium botulinum and its spores are widely distributed in nature. They occur in both cultivated and forest soils, bottom sediments of streams, lakes and coastal waters, in the intestinal tracts of fish and mammals, and in the gills and viscera of crabs and other shellfish.

1.3.2 Human foodborne botulism

Foodborne botulism is a disease caused by potent protein neurotoxins produced by Clostridium botulinum. Characteristic symptoms include abdominal pain, vomiting, motor disturbances and visual difficulties.
The onset of symptoms in foodborne botulism is usually 18 to 36 hours after ingestion (eating and drinking) of the food containing the toxin, although cases have varied from 4 hours to 8 days. Early signs of intoxication consist of exhaustion, weakness and dizziness, usually followed by double vision and progressive difficulty in speaking and swallowing. Difficulty in breathing, weakness of other muscles, abdominal cramps and constipation may also be common symptoms. Botulinum toxin causes flaccid paralysis (weakness of the limbs) by blocking motor nerve terminals at the myoneural junction. The flaccid paralysis progresses symmetrically downward, usually starting with the eyes and face, to the throat, chest and extremities. When the diaphragm and chest muscles become fully involved, respiration is inhibited and death from asphyxia results. Recommended treatment for foodborne botulism includes early administration of botulinal antitoxin and intensive supportive care (including mechanical breathing assistance).

1.4 Mycotoxins as natural food contaminants

The mycotoxins of greatest interest are those found in human food or in the feed of domestic animals. Mycotoxins include the ergot alkaloids (Figure 1) produced by *Claviceps* sp., the tricothecenes produced by several genera of fungi, primarily *Fusarium* sp., and aflatoxins (Figure 2) and related compounds produced by *Aspergillus* sp. Mycotoxins are examples of natural foodborne contaminants, which have worldwide implications and are the cause of many deaths.

1.4.1 Aflatoxins

1.4.1.1 Sources of aflatoxins

Aflatoxins are toxic substances produced by certain fungi that grow on plants and seeds. Aflatoxins are also found to contaminate grain, maize and peanuts. The major aflatoxin-producing fungi are *Aspergillus flavus* and *Aspergillus parasiticus*. Four major aflatoxins (B₁, B₂, G₁ and G₂) occur in plant products contaminated with fungi. Aflatoxin B₁, the most toxic of the aflatoxins, is usually found in the greatest concentration in the food supply, and most of the available toxicological data relate to this compound. The aflatoxin-producing *Aspergillus* species, and consequently dietary aflatoxin contamination, are ubiquitous in areas of the world with hot humid climates, including sub-Saharan Africa and South-East Asia. The amount of aflatoxins produced depends on the growing conditions. Under stress conditions such as drought or insect infestation, aflatoxin contamination is likely to be high. Storage conditions can also lead to aflatoxin contamination after crops have
been harvested. Usually, hot humid conditions lead to mould growth on the stored food and to high levels of aflatoxins.

1.4.1.2 Exposure to aflatoxins

Since countries in colder climatic areas import foods from areas where aflatoxin levels are high, aflatoxins are of worldwide concern. Exposure to aflatoxins can be acute or chronic. Generally, consumers from importing countries are subject to acute exposures. If aflatoxin-contaminated dietary staples such as maize and rice are continuously consumed, exposure is likely to be chronic.

High levels of dietary staple foods containing aflatoxins have been found in groundnut and cereal grains in Africa, South-East Asia and southern China. Contamination of raw commodities grown in the USA has also occurred periodically. High levels of aflatoxins are found in many products including maize, rice, cereal grains, peanuts and other products.

In general, data on the occurrence of and exposure to aflatoxins are available predominantly from importing countries, where strict regulations concerning contamination levels ensure relatively low exposure levels. In order to meet the requirements of prospective importers and to avoid having the food rejected and thus suffering economic losses, some producing countries keep substandard food supply for their own population, exporting only high quality products. Exposure of the population in countries practising such policies is likely to be very high.

1.4.1.3 Effects of aflatoxins

Aflatoxin B₁ is a well-known potent hepato-carcinogen and has been shown to cause cancer in many experimental animal studies. In epidemiological studies, a strong association was found between aflatoxin ingestion and the occurrence of liver cancer in humans. The International Agency for Research on Cancer (IARC) concluded that there is sufficient evidence to classify naturally occurring mixtures of aflatoxins and aflatoxin B₁ as human carcinogens (see chapter 5).

1.4.1.4 Preventing human exposure to aflatoxins

Aflatoxin contamination can be controlled by minimizing mould growth. To do this, several pre-harvest control measures, harvest precautions and storage practices are the most important methods available to reduce mould growth and aflatoxin production (Table 2). In addition to harvesting and storage precautions, the screening of crops prior to their processing and sale has been shown to be an important way of minimizing human exposure to aflatoxins.
1.5 Industrial sources of chemicals

Industry plays a major role in many peoples lives. Industry is economically important to countries and employs millions of workers throughout the world. Although well regulated in some countries, industry has been the source of many contaminants and chemicals. It is important to remember that industry is not just buildings and factories, but also includes industrialized agriculture, ships and other vessels at sea, refineries and oil drilling platforms in the ocean, and the trucks used to transport the goods and raw materials produced by the factories. Therefore, industry is all around us, and plays an important role in our daily lives. Major industrial activities have the potential for generating air emissions, wastewater effluents and solid wastes, all of which may contain a variety of chemical pollutants.

If proper industrial procedures and precautions are followed, the general population is normally protected from exposure to the chemicals produced by industry. However, whether by accident or fault, chemical discharges sometimes occur. An example of an industrial substance contaminating the environment is the environmental discharge of inorganic mercury and subsequent human exposure to methylmercury. Heavy exposure to chemicals is more likely to be seen in workers operating the industrial facilities. This is known as occupational exposure. It is not surprising to find in some cases a high incidence of chemical-related diseases in the occupational setting. A few examples are given to highlight some important occupational hazards and associated cancers (Table 3), while major industrial activities and their potential sources of environmental pollution are listed in Table 4.
Table 3. Occupational hazards and associated cancers

<table>
<thead>
<tr>
<th>Agent (hazard)</th>
<th>Tumour site</th>
<th>Occupation</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-rays</td>
<td>Bone marrow</td>
<td>Medical and industrial personnel</td>
</tr>
<tr>
<td>Uranium</td>
<td>Bone marrow, skin, lungs</td>
<td>Medical and industrial chemists</td>
</tr>
<tr>
<td>Ultraviolet radiation</td>
<td>Skin</td>
<td>Outdoor occupations</td>
</tr>
<tr>
<td>Polycyclic hydrocarbons (soot, tar, oil)</td>
<td>Lung, skin, liver, bladder</td>
<td>Oil workers, gas workers</td>
</tr>
<tr>
<td>Vinyl chloride</td>
<td>Liver, brain</td>
<td>Plastics manufacturers</td>
</tr>
<tr>
<td>Arsenic</td>
<td>Skin, lung, liver</td>
<td>Miners and smelters, oil refiners</td>
</tr>
<tr>
<td>Cadmium</td>
<td>Lung, kidney, prostate</td>
<td>Battery workers, smelters</td>
</tr>
<tr>
<td>Nickel compounds</td>
<td>Lung and nasal sinuses</td>
<td>Smelters and process workers</td>
</tr>
<tr>
<td>Asbestos</td>
<td>Lung</td>
<td>Miners, millers, demolition workers</td>
</tr>
<tr>
<td>Wood and leather particles</td>
<td>Nasal cavities</td>
<td>Wood and shoe workers</td>
</tr>
</tbody>
</table>

Table 4. Major industrial activities and potential sources of pollution

<table>
<thead>
<tr>
<th>Industry</th>
<th>Air emissions</th>
<th>Waste-water</th>
<th>Solid wastes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agriculture and livestock production</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coal Mining</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slaughtering, meat production</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manufacture of dairy products</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manufacture of soft drinks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tanneries and leather finishing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manufacture of paper and products</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Petroleum refineries</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manufacture of cement/lime/plaster</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iron and steel industries</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electricity, light and power</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restaurants and hotels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical health services</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmaceutical</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 An asterisk in the column indicates a major source of pollution from the relevant industry.

1.5.1 Minamata and the environmental toxicity of mercury

Metallic mercury is used in the chlorine-alkali industry for electrolytic production of chlorine and sodium hydroxide. It is used to manufacture scientific and electrical apparatus, as a catalyst in chemical processing reactions, and to produce thermometers. The shiny silver substance you see in thermometers is a relatively common element in the environment. Scientists estimate that each year, the earth naturally releases 30,000 tonnes of mercury. Water discharge from industry is another source. Metallic mercury is a worldwide contaminant, but most mercury poisoning, however, has been due to methylmercury, particularly as a result of eating contaminated fish. The environmental toxicity of mercury is a good example of three important properties of a substance. These
In the 1950's, Minamata City, situated on a bay in the Yatsushiro Sea on the south island of Japan, was the home of Shin Nihon Chisso Co., a manufacturer of polyvinyl chloride for which mercury was used as a catalyst. From the 1930s to the 1960s, this company dumped thousands of tonnes of elemental mercury into Minamata Bay in Japan. The mercury was then methylated by bacteria. The methylmercury, a highly toxic form of mercury, eventually contaminated fish in the bay which were consumed by the residents of the region. A range of severe effects in victims then developed including death, deafness, tunnel vision, slurred speech and birth defects in children of mothers who had been exposed. The sequence of events is illustrated in Table 5.

are toxicity, volume of use (as an industrial substance, the release of which was poorly regulated and controlled) and mobility. In the case of mobility, an important new principle is illustrated, that of biological transformation.

1.5.1.1 Symptoms of methylmercury poisoning

The symptoms of the disease that developed in Minamata were probably first noticed in cats and then in humans. Human symptoms included degeneration of the nervous system with loss of vision, hearing, speech and motor-control. Other symptoms included tingling sensations, muscle weakness, unsteady gait, tunnel vision, slurred speech, hearing loss and abnormal behaviour. Approximately 40% of those affected were fatal cases. Neurotoxicity was the greatest concern for developing fetuses exposed during pregnancy. In many cases, infants born of mothers who had consumed methylmercury, particularly during the second trimester of pregnancy, showed damage even though the mothers themselves were only slightly affected. In children, several endpoints, including late walking, late talking, seizures, nervous system dysfunction and delayed mental development, were observed. Similar symptoms were also noted in cats, which showed tremors and unusual behaviour.

1.5.1.2 Treatment of poisoning

The reason that mercury is a problem is that it has a particular affinity for both brain and nervous tissue, and so, exposure and uptake cause damage at these locations. Chelation therapy (a chelate is a chemical with a particular “affinity” for a metal) is necessary, because the chelate has a stronger “pull” for mercury than the brain or nervous tissue. Therefore, if poisoning is immediately detected, treatment can be successful.

Table 5. Sequence of investigation in the Minamata Bay disaster

<table>
<thead>
<tr>
<th>Date</th>
<th>Impact/Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1930s–1950s</td>
<td>Factory wastes directed into Minamata Bay</td>
</tr>
<tr>
<td>1951</td>
<td>First cases appeared but not recognized</td>
</tr>
<tr>
<td>1952</td>
<td>A few cases each year, but mercury use increased</td>
</tr>
<tr>
<td>1956</td>
<td>Sick children reported to hospital, 40 cases identified, University team became involved</td>
</tr>
<tr>
<td>1957–1958</td>
<td>Fishing banned but cases continued and spread to greater distances from the Bay</td>
</tr>
<tr>
<td>1959</td>
<td>Mercury suspected as cause, but not the inorganic form</td>
</tr>
<tr>
<td>1960–1963</td>
<td>111 cases confirmed, 41 dead, methylmercury identified as cause</td>
</tr>
<tr>
<td>1966</td>
<td>Population with exposure, but without symptoms, identified</td>
</tr>
<tr>
<td>1970</td>
<td>Factory regulated, release of mercury decreases</td>
</tr>
<tr>
<td>1973–1975</td>
<td>1603 cases confirmed, 226 deaths</td>
</tr>
</tbody>
</table>
1.5.2 Textile manufacturing industry

Cloth and carpets have been made for thousands of years, and relics of ancient fabrics have been found throughout the world. Yarn was manufactured as long ago as 8000 BC, and it is believed that grass and tree materials were the first substances used to make yarn-like strands of cloth. The mechanical production of textiles began in England at the end of the eighteenth century, as part of the industrial revolution. Since that time, the industrial production of textiles has spread rapidly to all parts of the world. In fact, the textile industry is one of the largest employers worldwide. During the last 20 years, much of the basic textile industry has shifted to many African and Asian countries. The textile industry includes the spinning, weaving, knitting and finishing of all types of natural and artificial (synthetic) fibres. The machines vary from the old-fashioned hand-looms used in cottage industry to very expensive and intricate machines used in modern factories.

During fabrication, workers can be exposed to a variety of bleaching, scouring and dyeing agents. Toxic substances are not usually employed in the spinning and weaving of natural fibres. However, exposure to fibre dust is of concern. Raw cotton may also be contaminated with desiccants, defoliants and bacteria; while raw wool may be contaminated by pesticides applied previously to sheep as dips and medicated treatments. Effects on the health of the general population arise from dust-laden air, wastewater and volatile organic emissions.

1.5.2.1 Sources, exposure and effects

Toxic chemicals are used in the manufacture of synthetic fibres. Toxic dangers also exist in the dyeing and finishing sections of the textile industry. In dyeing and printing, workers are frequently exposed to dyes, a variety of acids such as formic, sulfuric and acetic acids, fluorescent brighteners, organic solvents and fixatives. Workers in the finishing operations are frequently exposed to crease-resistant agents, to flame retardants, and to a number of toxic solvents used for degreasing and spotting. Care must be taken in the use of these substances to prevent contact with the skin and suitable measures taken to ensure there is no escape of the material or its vapour into the atmosphere. Skin diseases of the dermatitis type are common in bleaching, dyeing and finishing, in the preparation of flax and in the use of solvents for making synthetic fibres. Certain dyestuff intermediates can produce bladder cancer. Chrome eczema or chrome poisoning is a hazard from the use of potassium or sodium dichromate in the textile industry.

Occupational health effects include byssinosis, chronic bronchitis, dermatitis, cancer of the bladder among dyers, and cancer of the bladder and of the nasal cavity among weavers and
other textile workers. They are summarized in Table 6. In its overall evaluation, the International Agency for Research on Cancer concluded that working in the textile manufacturing industry entails exposures that are "possibly carcinogenic to humans".

Table 6. Diseases and symptoms of textile workers exposed to chemicals

<table>
<thead>
<tr>
<th>Technical term of disease</th>
<th>Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bysinnosis</td>
<td>acute: tightness of the chest, wheezing, coughing</td>
</tr>
<tr>
<td></td>
<td>chronic: after years of exposure causes permanent shortness of breath (dyspnoea)</td>
</tr>
<tr>
<td>Chronic bronchitis</td>
<td>attacks of coughing</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>inflammation of the skin</td>
</tr>
<tr>
<td>Bladder/nasal cancer</td>
<td>bleeding, discomfort and pain</td>
</tr>
</tbody>
</table>

The wide range of substances to which workers in the textile manufacturing industry may be exposed to are listed in Table 7. These exposures may occur simultaneously with physical hazards, including noise, vibration and heat. Very few data are available on the chemicals used, exposure levels and the numbers of workers involved in specific processes in affected countries. The exposure levels and chemicals used in any one country could be quite different from those used elsewhere. In many processes, there is possibility for the use of non-toxic solvents, which have little, if any, human and environmental health effects.

It has been general practice to discharge dust-laden air, removed from textile mills, to the atmosphere. In modern mills, recirculation and filtration are now employed, but this may not be the case in some countries. Volatile organic emissions (from oils added during spinning and from solvents) are largely uncontrolled and are used in texturizing, heat-setting, finishing, dyeing and printing operations.

1.5.3 Asbestos and other fibres

Asbestos is used extensively in roofing felt and insulation, asbestos cements, brake linings, electrical appliances, and fire-proofing and coating materials. Asbestos is a general name for a group of naturally occurring silicates that will separate into flexible fibres. Exposure may take place from both natural sources and industrial applications. There are two types of fibres, namely chrysotile and crocidolite. Chrysotile (3MgO,2SiO₂,2H₂O) is the most important commercially and represents about 90% of the total asbestos used. Crocidolite (blue asbestos) is composed of short, rod-like fibres, which are more dangerous than chrysotile fibres.
Table 7. Substances found in textile manufacturing

<table>
<thead>
<tr>
<th>Material</th>
<th>Principal use or source of emission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetic acid</td>
<td>Control of dye pH</td>
</tr>
<tr>
<td>Biphenyl</td>
<td>Dye carrier</td>
</tr>
<tr>
<td>Cotton dust</td>
<td>Blending, spinning, weaving</td>
</tr>
<tr>
<td>Cyclic ethylene urea</td>
<td>Crease resistance</td>
</tr>
<tr>
<td>Decabromodiphenyl oxide</td>
<td>Flame retardant</td>
</tr>
<tr>
<td>Diammonium phosphate</td>
<td>Control of pH</td>
</tr>
<tr>
<td>Dichloromethane</td>
<td>Fabric scouring</td>
</tr>
<tr>
<td>Dimethylformamide</td>
<td>Fabric finishing</td>
</tr>
<tr>
<td>1,3-Diphenyl-2-pyrazoline</td>
<td>Fluorescent brightener</td>
</tr>
<tr>
<td>Formaldehyde resins</td>
<td>Crease resistance</td>
</tr>
<tr>
<td>Formic acid</td>
<td>Control of dye pH</td>
</tr>
<tr>
<td>Hydrogen peroxide</td>
<td>Fabric bleaching</td>
</tr>
<tr>
<td>Hypochlorites</td>
<td>Fabric bleaching, singeing</td>
</tr>
<tr>
<td>Monochlorobenzene</td>
<td>Fabric printing</td>
</tr>
<tr>
<td>Mordant dyes</td>
<td>Dyeing</td>
</tr>
<tr>
<td>Phenol</td>
<td>Printing</td>
</tr>
<tr>
<td>Polyvinyl alcohol</td>
<td>Fabric preparation, mercerizing</td>
</tr>
<tr>
<td>Sodium acetate</td>
<td>Dyeing of polyester</td>
</tr>
<tr>
<td>Sodium bichromate</td>
<td>Chrome-dyeing process</td>
</tr>
<tr>
<td>Sodium hydroxide</td>
<td>Fabric bleaching, mercerizing</td>
</tr>
<tr>
<td>Sodium perborate</td>
<td>Antisoiling agent</td>
</tr>
<tr>
<td>Spinning oils</td>
<td>Lubricants</td>
</tr>
<tr>
<td>Starch</td>
<td>Sizing agent</td>
</tr>
<tr>
<td>Sulfur dyes</td>
<td>Dyeing</td>
</tr>
<tr>
<td>Sulfuric acid</td>
<td>Carbonizing process, desizing</td>
</tr>
<tr>
<td>Tetrachloroethylene</td>
<td>Fabric scouring, dye carrier</td>
</tr>
<tr>
<td>Tetrasodium pyrophosphate</td>
<td>Control of dye pH</td>
</tr>
<tr>
<td>Trichloroethylene</td>
<td>Dye carrier, scouring</td>
</tr>
<tr>
<td>Tris(2,3-dibromopropyl) phosphate</td>
<td>Flame retardant</td>
</tr>
<tr>
<td>Vat dyes</td>
<td>Dyeing</td>
</tr>
</tbody>
</table>

Inhalation of asbestos fibres deep into the lungs causes physical damage, and is linked to mesothelioma, a form of lung cancer. Asbestosis, a respiratory disease, is characterized by lung fibrosis and calcification, and can lead to cancer. Inhalation of asbestos should therefore be avoided, and properly trained personnel should be consulted for its removal from applications such as insulation and roofing.

1.5.4 Petroleum

Petroleum oil was used for many centuries in Egypt, China, Iraq and Iran for heating, lighting, road making and building. Today, the world petroleum refining industry produces more than 2500 products including naphthas, distillates, residual fuels, asphalts, liquefied petroleum gas, petrol, kerosene/paraffin, aviation fuels, and diesel fuels, a variety of other fuel oils and lubricating oils.
Crude oil is a mixture of thousands of different hydrocarbons with a wide range of boiling points. In addition, crude oil compounds contain various amounts of sulfur, nitrogen, oxygen, salt, trace metals and water. Petroleum refineries produce a wide variety of air and water pollutants and hazardous solid wastes. The specific mix of pollutants varies with the activities and processes involved. Frequently emitted pollutants include all the distillation products of refining (fuels, solvents, oils, waxes, greases, asphalt) and, specifically, hydrogen sulfide, polycyclic aromatic hydrocarbons (PAHs), carbon monoxide, carbon dioxide and benzene (Figure 4). Because these facilities are usually sited in large industrial zones, often involving multiple petrochemical facilities, significant contamination of air and water is usually associated with their presence. Residents of adjoining communities are potentially at risk from the inhalation of polluted air and the ingestion of polluted water. Large volumes of hazardous wastes are generated and must be appropriately disposed of, or they may adversely affect health through the contamination of soil and groundwater.

Residents living downwind of refineries have been shown to be at greater risk of developing respiratory symptoms (coughing and wheezing). An elevated risk of brain cancer has been suggested by a study conducted in the USA on people living near a petrochemical plant, and the fact of living near to a petroleum plant in Louisiana for more than 10 years has been reported to increase the risk of lung cancer.

A wide range of potential occupational health hazards is also present in petroleum refineries. Exposure results from skin contact and the inhalation of gases and vapours, mainly hydrocarbons, which are either naturally present in crude oil and emitted during its refining or are formed and emitted during processing. Gaseous sulfur compounds such as hydrogen sulfide, sulfur dioxide and mercaptans are emitted during removal and treatment of sulfur. Exposure to dusts and fumes results mostly from maintenance operations such as abrasive blasting, the use of catalysts and the handling of viscous or solid products such as bitumen and coke. The main substances to which workers may be exposed while working in petroleum refineries are "probably carcinogenic to humans".

1.5.5 Solvents

Organic solvents and their vapours are commonly encountered in our modern environment. Industries use large quantities in the manufacturing process of many different end products. We may also be exposed through materials such as gasoline (petrol)
Table 8. Main substances to which workers may be exposed in petroleum refineries

<table>
<thead>
<tr>
<th>Material</th>
<th>Principal uses or sources of emission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alumina</td>
<td>Catalyst</td>
</tr>
<tr>
<td>Aluminum chloride</td>
<td>Catalyst</td>
</tr>
<tr>
<td>Amines, aliphatic</td>
<td>Hydro-desulfurization</td>
</tr>
<tr>
<td>Amines, aromatic</td>
<td>Catalytic cracking, antioxidant</td>
</tr>
<tr>
<td>Ammonia</td>
<td>Distillation, catalytic cracking</td>
</tr>
<tr>
<td>Arsenic compounds</td>
<td>Crude oil, gas scrubbing</td>
</tr>
<tr>
<td>Asbestos</td>
<td>Insulation, seals</td>
</tr>
<tr>
<td>Bitumen fumes</td>
<td>Tanker loading, cleaning</td>
</tr>
<tr>
<td>tert-Butyl alcohol</td>
<td>Unleaded gasoline blending</td>
</tr>
<tr>
<td>Chromium and its compounds</td>
<td>Catalyst, welding</td>
</tr>
<tr>
<td>Cobalt and its compounds</td>
<td>Catalyst</td>
</tr>
<tr>
<td>Coke</td>
<td>Coking units</td>
</tr>
<tr>
<td>Copper and its compounds</td>
<td>Desulfurization, catalyst</td>
</tr>
<tr>
<td>Crude oil</td>
<td>Distillation and processing unit</td>
</tr>
<tr>
<td>Hydrocarbons, aromatic</td>
<td>Most process units</td>
</tr>
<tr>
<td>Hydrogen chloride</td>
<td>Isomerization</td>
</tr>
<tr>
<td>Hydrogen fluoride</td>
<td>Catalyst</td>
</tr>
<tr>
<td>Hydrogen sulfide</td>
<td>Distillation, cracking</td>
</tr>
<tr>
<td>Ketones</td>
<td>Solvent</td>
</tr>
<tr>
<td>Lead and its compounds</td>
<td>Desulfurization</td>
</tr>
<tr>
<td>Mineral oils</td>
<td>Oil and grease units</td>
</tr>
<tr>
<td>Nickel and its compounds</td>
<td>Catalyst, welding, combustion products</td>
</tr>
<tr>
<td>Nitrogen oxides</td>
<td>flares, furnaces</td>
</tr>
<tr>
<td>Palladium</td>
<td>Catalyst</td>
</tr>
<tr>
<td>Phenol</td>
<td>Crude distillation, wastewaters</td>
</tr>
<tr>
<td>Pitch</td>
<td>Bitumen department, loading operations</td>
</tr>
<tr>
<td>Phosphoric acid</td>
<td>Catalyst</td>
</tr>
<tr>
<td>Platinum</td>
<td>Catalyst</td>
</tr>
<tr>
<td>Polynuclear aromatic hydrocarbons (PAHs)</td>
<td>Distillation, coking, bitumen processing coking, wastewater treatment</td>
</tr>
<tr>
<td>Petroleum solvents</td>
<td>Petroleum solvent manufacturing</td>
</tr>
<tr>
<td>Sulfuric acid</td>
<td>Catalyst</td>
</tr>
<tr>
<td>Tetraethyllead</td>
<td>Gasoline blending</td>
</tr>
<tr>
<td>Vanadium compounds</td>
<td>Residual fuel oils, flue cleaning</td>
</tr>
</tbody>
</table>

Vapours, aerosol sprays and paint removers. A good example of a solvent is benzene. Benzene, an excellent solvent for rubber latex, was used in large quantities throughout the nineteenth century in the rubber industry. In the 1930s, many cases of benzene toxicity occurred in the printing industry where benzene was used as an ink solvent. In fact, benzene is still used today as a solvent, with estimates reaching as high as 42 million m³ used per year. Chronic exposure to benzene may cause severe bone marrow damage and aplastic anaemia. Benzene exposure has also been associated with cases of leukaemia. It is important to remember that many solvents are dangerous and that proper personal protective equipment must be worn when handling any solvent. Expert advice should always be sought when selecting the appropriate equipment.
1.6 Agricultural sources of chemicals

Many chemicals are used in agriculture, including nitrogen and phosphorus fertilizers, pesticides, (soil and seed treatments), plant growth regulators, disinfectants and veterinary drugs (including the administration of antibiotics to animals and the use of antibiotics in fish farming). Of these, pesticides are the chemicals that cause the most health and environmental concerns. Pesticides are substances that control or kill pests. Pests are organisms perceived by humans to interfere with their own activities; they may interfere directly with our health, with the production and protection of our food, or with our enjoyment. Pesticides are poisons, but they have a special purpose: to protect humans and their crops from other organisms, namely the pests. Therefore, if pesticides must be used, they should be chosen for their selectively, destroying target organisms, while leaving non-target organisms unharmed. In reality, most pesticides are not so selective, and can have lasting effects on biological systems if used incorrectly.

1.6.1 Uses of pesticides

Arthropod-borne diseases were major problems to humans long before the development of the first pesticides. Malaria and other vector-borne diseases kill millions of people every year (Figure 6). Pesticides, improved sanitation and health education are all used as vector control methods in public health programs throughout the world. Many of the chemicals used have caused serious environmental problems, and are now considered environmental pollutants. On the other hand, they have probably saved millions of lives throughout history.

Pesticides are also used in agriculture, horticulture, forestry and livestock production. By far, the largest source of contamination by pesticides has resulted from their use in agriculture and public health. Pesticides are widely misused, most seriously in countries where legislation, monitoring and enforcement are inadequate. Some pesticides, like DDT (Figure 5), have been banned or restricted in many countries, but are still widely available in others. Additionally, most pesticide preparations include carrier substances, in addition to the active ingredients, as well as solvents and compounds that improve absorption. These “inert ingredients” frequently comprise a large part of a commercial pesticide product, and their adverse effects may exceed those of the active ingredients. Pesticides may also contain impurities, such as dioxins in certain phenoxyacid herbicides, which may be more toxic than the pesticide itself.
Figure 6. Worldwide distribution of malaria
1.6.2 Contamination of air, soil and water due to pesticides

Air can become contaminated with pesticides during spraying operations. The evaporation of droplets during the spraying of emulsified pesticide formulations may result in the formation of tiny particles that can be carried great distances in air currents. This has been confirmed, for example, by studies showing the presence of pesticides in urban smog. It is also common practice in many countries to treat houses with pesticides to control disease vectors. The pesticide evaporates in the house and may be inhaled by the inhabitants. Further amounts may be taken in through the skin by contact with treated surfaces, or ingested by consuming contaminated food.

Soil may be deliberately treated with pesticides to control insects or nematodes. In addition, a large proportion of the pesticide sprayed on crops or used as a herbicide misses its target and falls on to the soil surface. Some pesticides, notably organochlorines, are known to persist in soil for years. Water may be polluted by the dumping of excess pesticides left over after spraying operations, accidental spillage of pesticide formulations or by the application of pesticides to rivers or ponds for aquatic weed control. Dumping of pesticides into water bodies may lead to contamination of drinking-water.

1.6.3 Exposure of humans to pesticides

In some countries, there is little control or advice on the timing of the applications; often pesticides are applied only days or hours before the crops are harvested. Such crops may contain residues that lead to high exposures if the crops are consumed soon after harvest. In some countries, this is a major problem because many vegetables are grown on small plots close to towns and the treated crops go straight to the market, often with little washing. Sometimes they may even be treated with pesticides in the marketplace to control flies.

Apart from direct contamination caused by the spraying of food crops, there are various other ways in which foods can be contaminated. For example, meat may contain high levels of pesticides because they become concentrated in certain tissues, following cattle dipping or vector treatment. Fish caught in pesticide-treated rice paddies may also contain significant levels of pesticide residues. Treatment with pesticides to prevent losses of food during storage or bulk transport also creates a hazard. The losses caused by arthropod pests and rodents can be extremely heavy, and it is common practice to treat food and grain with pesticides, sometimes indiscriminately, to avoid such losses. Foods treated in this way may contain high concentrations of pesticide. In times of food shortage, there have been many instances of
pesticide-treated seed grains being eaten by people or domestic animals, either accidentally or intentionally and producing mass poisoning.

Many countries have legislation relating to food contamination, and imported and local foods are regularly analysed. In some countries where pest problems are much greater, there is little legislation, and spraying close to harvest time is common.

Acute poisoning from pesticides is a widespread problem, with an estimated global number of cases of 1–3 million/year. Mortality rates vary from 1 to 9% of cases presented for treatment, and depends on the availability of antidotes and the quality of medical services. Intentional poisonings (mainly attempted or successful suicides) make up a large proportion of the poisonings by pesticides in certain countries. Pesticides are easily available in many households, and may become the “method of choice” for an individual with suicidal intentions.

The majority of cases of unintentional pesticide poisoning occur largely among farm workers and their families. Exposure occurs primarily during mixing or using pesticides, spraying using aircraft or re-entering a previously treated area. Acute occupational exposure may also occur during the manufacture, formulation, packaging and transport of pesticides. Acute effects associated with high occupational exposure to pesticides include chemical burns of the eye, skin damage, neurological effects and liver effects. Chronic exposures are suspected of leading to reproductive problems and an increased risk of developing cancer, delayed neurological and psychological effects, and effects on immune function.

Many cases of pesticide poisoning occur in children who gain access to opened pesticide packs kept in the home. Episodes of mass poisoning following the consumption of food contaminated with pesticide have also occurred and resulted in numerous deaths. In some cases, the food was contaminated with pesticides during transport or storage, while in other cases, seeds have been consumed that had been treated with fungicides and were intended for planting.

1.7 Urban sources of chemical contamination

It has been known for thousands of years that human activity and urbanization may lead to air pollution (Figure 7). In fact, air pollution no doubt began as soon as humans started to use wood fires for heating and cooking. Many cities throughout the world are now faced with major air pollution problems caused by both urbanization and industrialization. Today, many sources contribute to the air pollution problems of cities around the world. The main contributors to air pollution and their relative importance vary
greatly from city to city. Industries within cities are sometimes the main contributor, while congested streets, poorly maintained motor vehicle engines, and (often) high levels of lead additives in petrol (gasoline) also contribute to the air pollution problems. Frequently, thermal power stations burning high sulfur coal or oil are major contributors. In some cities, the use of wood or coal as the main household fuel is a major contributor and a cause of respiratory problems in the young and the elderly.

1.7.1 Natural sources of air pollution

Many different pollutants and chemicals are formed and emitted from the earth’s crust by natural processes. For example, an erupting volcano emits particulate matter as well as gaseous pollutants such as sulfur dioxide, hydrogen sulfide and methane. Forest fires also contribute to air pollution by emitting smoke, soot, unburned hydrocarbons, carbon monoxide, nitrogen oxides and ash. Particulate from sea spray, bacterial spores, pollen and dust from soil are also natural contributors of air pollution. Plants and trees are also a source of hydrocarbons; the blue haze over forested mountain areas is mainly from the atmospheric reactions of the volatile organic compounds produced by the vegetation.

In January 1986, over 96 asthma attacks were recorded in Barcelona, Spain; 10% of these required advanced life support and 2% died. Following extensive epidemiological analysis, the cause was found to be the dust from a shipment of soybeans unloaded in Barcelona harbour.

Figure 7. An example of urban air pollution
1.7.2 Fossil fuels as a source of air pollution

The combustion of fossil fuels for domestic heating, power generation, transportation and in industrial processes, summarized in Table 9, contributes to the principal sources of anthropogenic air pollutant emissions in the atmosphere in urban areas. Traditionally, the most common air pollutants in urban environments include sulfur oxides (SO$_x$), especially sulfur dioxide (SO$_2$), the nitrogen oxides (NO and NO$_2$, collectively termed NO$_x$), carbon monoxide (CO), ozone (O$_3$), suspended particulate matter (SPM) and lead (Pb).

Table 9. Human activities and the by-products of fossil fuel combustion

<table>
<thead>
<tr>
<th>Activity</th>
<th>Air pollutants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Power plants used to generate electricity</td>
<td>SO$_x$, NO$_x$ (NO and NO$_2$)</td>
</tr>
<tr>
<td>(e.g., coal-burning power plants)</td>
<td>Primary particulate: fly ash, soot</td>
</tr>
<tr>
<td></td>
<td>Secondary particulate: sulfate (SO$_4^{2-}$) and nitrate (NO$_3^-$) aerosols</td>
</tr>
<tr>
<td>Oil combustion</td>
<td>SO$_x$</td>
</tr>
<tr>
<td></td>
<td>Soot</td>
</tr>
<tr>
<td>Burning of domestic solid fuels (coal and wood)</td>
<td>SO$_x$</td>
</tr>
<tr>
<td></td>
<td>Soot (e.g., smog)</td>
</tr>
<tr>
<td></td>
<td>Fly ash</td>
</tr>
<tr>
<td>Diesel fuel combustion</td>
<td>SO$_x$ and soot</td>
</tr>
<tr>
<td></td>
<td>NO$_x$</td>
</tr>
<tr>
<td>Petrol (gasoline) fuelled vehicles</td>
<td>NO$_x$, CO, Pb (if leaded fuel is used), hydrocarbons</td>
</tr>
<tr>
<td>Cigarette smoking and barbeques</td>
<td>Polycyclic aromatic hydrocarbons and others</td>
</tr>
</tbody>
</table>

1.7.3 Ozone as a source of air pollution

Although ozone depletion is of concern in the upper atmosphere, at ground level the reverse problem (excessive ozone levels) can occur under conditions of urban air pollution. Ozone, a photochemical oxidant, is formed in the lower atmosphere in the presence of NO$_x$, hydrocarbons and volatile organic compounds (VOCs). Atmospheric temperatures above 18 °C, together with plenty of sunlight to catalyse the reactions, are also required. The VOCs may be emitted from a variety of synthetic sources including road traffic, production and use of organic chemicals (e.g., solvents), transport and use of crude oil, use of natural gas and, to a lesser extent, from waste disposal sites and wastewater treatment plants. Cities in warm sunny locations with high traffic densities tend to be especially prone to the net formation of O$_3$ and other photochemical oxidants from precursor emissions. High concentrations of ozone at ground level are toxic to plants (phytotoxic) and cause respiratory problems in the elderly and asthmatics.
1.7.4 Variations in air pollution

The relative contributions of mobile and stationary sources to air pollution emissions differ markedly between cities and are dependent on the level of motorization, vehicle density and type of industry present. Cities in Latin America, for example, tend to have higher vehicle densities than in other developing regions and therefore are likely to experience a higher contribution of nitrogen oxides from motor vehicles to the total urban pollution load. Motor vehicle contributions are proportionately less in cities with a lower level of motorization and in cities located in temperate regions that are dependent on coal or biomass fuels for space heating and other domestic purposes (e.g., some cities in China and in parts of eastern Europe). It is also worth noting that in some countries vehicles tend to be old and poorly maintained, a factor that increases the significance of motor vehicles as a pollutant source.

In addition to the more common or “traditional” air pollutants, a large number of toxic and carcinogenic chemicals are increasingly being detected in urban air, albeit at low concentrations. Examples include metals (e.g., beryllium, cadmium and mercury), trace organics (e.g., benzene, polychlorinated dibenzo-dioxins and dibenzo-furans, formaldehyde, vinyl chloride and PAHs) and fibres (e.g., asbestos). Such chemicals are emitted from a wide range of sources including waste incinerators, sewage treatment plants, industrial and manufacturing processes, solvent use (e.g., in dry cleaning establishments), building materials and motor vehicles.

1.7.5 Liquid and solid wastes

In many cities of the world, domestic and industrial wastewater goes directly into major water bodies without treatment. Hazardous chemicals used in the home and industry sometimes find their way into the aquatic environment, causing damage to the ecosystem and contaminating drinking-water supplies. For example, the city of Bucharest, Romania, (population of 2 million) has no wastewater treatment plant. All wastewater is dumped in the river Danube.

Hazardous chemical wastes from industrial sources are often dumped onto poorly prepared and managed landfill sites with little or no separation of toxic wastes. This frequently results in contamination of drinking-water, soil and air. Disposal of liquid wastes such as dyes is also a particular problem in some countries.

1.8 Accidental releases of toxic chemicals

Accidents at production facilities or during the transport of hazardous materials have also contributed to air, water and ground
pollution, and to adverse human health effects. Accidents such as explosions, fires and collisions of transport vehicles can lead to the release of many potentially dangerous chemical agents into the environment. Once this occurs, workers and the general population are subject to exposure. The frequency of occurrence and severity of such episodes is alarming.

Most chemical accidents occur because of carelessness, but unskilled engineers, poorly trained operators or lack of communication may also contribute to produce deadly results. To avoid accidents, it is important that industries provide proper training for personnel involved in hazardous industrial processes. Table 10 highlights some of the major accidents that have occurred.

Table 10. Accidents that have affected the environment and human life

<table>
<thead>
<tr>
<th>Year</th>
<th>Location</th>
<th>Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>1974</td>
<td>Chemical plant explosion and release of cyclohexane</td>
<td>Flixborough, England</td>
</tr>
<tr>
<td>1976</td>
<td>Release of 2,3,7,8-tetrachloro-dibenzo-p-dioxin</td>
<td>Seveso, Italy</td>
</tr>
<tr>
<td>1979</td>
<td>Train derailment and release of chlorine gas</td>
<td>Mississauga, Canada</td>
</tr>
<tr>
<td>1984</td>
<td>Explosion/liquid petroleum</td>
<td>Mexico City, Mexico</td>
</tr>
<tr>
<td>1984</td>
<td>Chemical leak of isocyanate</td>
<td>Bhopal, India</td>
</tr>
<tr>
<td>1986</td>
<td>Fire at a pesticide factory</td>
<td>Basel, Switzerland</td>
</tr>
<tr>
<td>1986</td>
<td>Nuclear power plant explosion</td>
<td>Chernobyl, Ukraine</td>
</tr>
</tbody>
</table>

1 These figures are only estimates.
Review

After reading this chapter, you should be aware that:

- Chemicals occur both naturally and are synthetic. Chemicals that occur naturally can be just as toxic as synthetic chemicals. Nature is very good at making a vast array of toxic chemicals.

- The sources of chemicals to which we can be exposed are wide and varied. Chemicals are found in the air we breathe, the water we drink and the food we consume. We are also exposed to drugs, pesticides, solvents, naturally occurring hydrocarbons, combustion products, microbial toxins, plant toxins and animal toxins, to name but a few.

- Foodborne toxicants can be deadly if a large enough dose of the compound is ingested.
2. ROUTES OF EXPOSURE

This chapter will show:

- The oral routes of exposure
- The nasal routes of exposure
- The effect of multiple types of exposure
- The effects of chemical mixtures
2.1 Introduction

Chemicals can cause damage to humans and other living organisms in a number of different ways and many of these will be discussed in Chapter 3. Before a chemical can be harmful however, there must be a route of exposure. The route of exposure is the pathway by which a chemical enters the body. If you do not come into contact with a chemical, no matter how toxic the chemical is, it cannot be harmful. There are different routes of exposure and the type of exposure can affect the toxicity of the chemical. There are three principal routes of exposure: penetration through the skin (dermal absorption), absorption through the lungs (inhalation), and absorption from the digestive tract (ingestion). The most common forms of occupational exposure are inhalation and dermal, whereas accidental and suicidal poisonings occur most frequently by oral exposure.

Various pathways through which hazardous chemicals from the environment can reach the general population are shown in Figure 9.

2.2 Dermal route of exposure

The skin is one of the most common routes of exposure to substances but, fortunately, it is an effective barrier against many chemicals. If a chemical cannot penetrate the skin, it cannot exert a toxic effect by the dermal route. If a chemical can penetrate the skin, its toxicity depends on the degree of absorption that takes place. The greater the absorption, the greater the potential for a chemical to exert a toxic effect. Chemicals are absorbed much more readily through damaged or abraded skin than through intact skin. A chemical must cross a large number of cell layers in the skin before it can reach the circulation. Once a chemical penetrates the skin, it enters the blood stream and is carried to all parts of the body. The ability of a chemical to penetrate the skin depends on whether or not the chemical is fat-soluble. Chemicals that can dissolve in fat are much more likely to penetrate the skin than chemicals that are water-soluble.

Skin irritation and skin allergy are the most common conditions resulting from dermal exposure in the workplace in the chemical industry. Of particular concern is dermal exposure of workers to pesticides during mixing and application of these materials. Some pesticide formulations are especially hazardous if they are both toxic and contain fat-soluble solvents, such as kerosene, xylene and other petroleum products that make it easier for the pesticide to penetrate the skin. Recognized skin effects of pesticides are given in Table 11.
Figure 9. Pathways by which environmental chemicals can reach the general public.
Table 11. Recognized skin effects of pesticides

<table>
<thead>
<tr>
<th>Pesticide</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>paraquat, captafol, 2,4-D, mancozeb</td>
<td>contact dermatitis</td>
</tr>
<tr>
<td>benomyl, DDT, lindane, zineb, malathion</td>
<td>skin sensitization, allergic reaction, rash</td>
</tr>
<tr>
<td>hexachlorobenzene, benomyl, zineb</td>
<td>photoallergic reactions</td>
</tr>
<tr>
<td>organochlorine pesticides</td>
<td>chloracne</td>
</tr>
<tr>
<td>hexachlorobenzene</td>
<td>deep scarring, loss of hair, skin atrophy</td>
</tr>
</tbody>
</table>

Irritation is a skin condition that can be produced by prolonged contact with certain chemicals. After a time the skin dries out, becomes tender, reddens and cracks. This condition is caused by solvents, acids, alkalis, detergents and coolants. Once contact with the chemical that caused the condition has stopped, the skin can heal. Generally speaking, the healing process takes many months. During this period the skin is even more susceptible to damage than usual and therefore must be protected.

Allergic contact dermatitis is a delayed type of skin disease caused by high sensitivity to a chemical. Very small quantities of the chemical, which normally would not cause any irritation, produce damage to the skin due to increased sensitivity. Symptoms are rash, swelling, itching and possibly blistering of the skin. The symptoms normally disappear once contact with the substance stops but will reappear if the skin is exposed again. Allergic contact dermatitis is caused by repeated contact with substances such as chromium (present in cement, leather, rust-proofing agents, etc.), cobalt (present in detergents, colour pigments), and nickel (nickel-plated objects such as earrings, keys, coins, tools). Rubber and certain types of plastics and adhesives can produce these effects. For more information on allergies, see section 3.6.

Contact of chemicals with the eyes may cause skin damage ranging from mild temporary discomfort to permanent damage. Examples of substances causing eye irritation are acids, alkalis and solvents.

Although skin irritation commonly occurs after dermal exposure to certain chemicals, the effects of most concern are the systemic effects. After a chemical has been absorbed through the skin and has entered the systemic circulation, it can travel throughout the body and damage organs and body systems (see chapter 3).

2.3 Inhalation route of exposure

The lung is another common route of exposure but, unlike the skin, lung tissue is not a very protective barrier against chemical exposure. The main function of the lung is the exchange of oxygen.
from air to blood and carbon dioxide from blood to air. Consequently, the lung tissue is very thin and allows the passage not only of oxygen, but also of many other chemicals directly into the blood. In addition to systemic damage, chemicals that pass through the lung surface may also injure the lung tissue and interfere with its vital role of oxygen supply.

If a chemical cannot become airborne, it cannot enter the lungs and, thus, cannot be toxic by the inhalation route. Chemicals can become airborne in two ways, either as tiny particles (i.e., dust) or as gases and vapours. Most of the traditional air pollutants (sulfur dioxide, nitrogen oxides, carbon monoxide, ozone, suspended particulate matter and lead) directly affect the respiratory (lung) and cardiovascular (heart and blood vessels) systems. Decreased lung function and increased mortality have been associated with elevated levels of sulfur dioxide and suspended particulate matter. Nitrogen dioxide and ozone also affect the respiratory system; acute exposure can cause inflammation and a decrease in lung function. Carbon monoxide binds to haemoglobin (found in the red blood cells that transport oxygen throughout the body) and is able to displace oxygen in the blood, which in turn can lead to damage to the heart and nervous system. Lead inhibits haemoglobin synthesis in red blood cells, impairs liver and kidney function and causes nerve damage.

The human health effects of exposure to air pollutants vary with the amount and length of exposure but also with the health status of the people exposed. Certain people are at greater risk of damage from inhalation exposure. For example, the young and the elderly, those already suffering from respiratory and cardiopulmonary disease, and people exercising are at a higher risk.

The release of pollutants in indoor air from fossil fuel or wood fires can also pose serious health risks, especially from smoke inhalation. Fossil fuels include coal and oil products and have resulted in high exposure to airborne pollutants such as sulfur dioxide, oxides of nitrogen and carbon monoxide.

Biomass fuels include burning wood, sawdust and vegetable matter containing grass, leaves and agricultural waste. Nearly half of the world’s population relies mainly or exclusively on biomass fuel for daily energy needs. It is usually burnt in open fires or in a simple clay or metal stove. The combination of open fires or inefficient stoves, absence of chimneys and poor ventilation leads to substantial exposure by inhalation to indoor air pollutants with adverse effects on human health. The principal adverse effects on health are respiratory, but in poorly ventilated homes, especially when biomass fuels such as charcoal or coal are used to heat rooms, carbon monoxide poisoning is a serious hazard.

In industry, inhalation of chemicals in the form of gases, vapours or particles and absorption through the lungs is the most important route of exposure. A variety of chemicals, too numerous
to mention, can become airborne in the workplace. The health risks from occupational exposure to airborne contaminants is often higher in small workshops, which are usually not covered by national regulatory systems. For instance, the recycling and repair of lead-acid batteries in small enterprises have led to heavy exposure of workers to airborne lead. The use of mercury by gold miners to separate pure gold from impurities by subjecting the mixture to high temperatures has resulted in serious mercury poisoning. In order to decrease the risk of inhalation exposure, it is necessary to have very good ventilation and wear a respirator fitted with the correct type of filter.

2.4 Ingestion as route of exposure

Ingestion is the principal pathway for entry of compounds that are present in food and drink. Chemicals that are ingested enter the body by absorption from the gastrointestinal tract. If they are not absorbed, they cannot cause systemic damage. Absorption of chemicals can occur anywhere along the digestive tract, from the mouth to the rectum, but the major site for absorption is the small intestine because of its physiological function in absorbing nutrients (Figure 10).

2.4.1 Food

Ingestion of food contaminated with high levels of hazardous chemicals has resulted in severe health damage.

Organomercury compounds have been the cause of several major poisoning epidemics in the general population due either to the consumption of contaminated fish or to eating bread prepared from cereals treated with alkylmercury fungicide. Methylmercury — the most toxic form of mercury — has been shown to have serious effects on the nervous system, which, in severe cases, may be irreversible.

2.4.2 Water

Thousands of organic and inorganic chemicals have been identified in drinking-water around the world, many in extremely low concentrations. There are few chemical constituents of water that can lead to acute health problems except through massive accidental contamination of a supply. Moreover, experience shows that, in such incidents, the water usually becomes undrinkable owing to unacceptable taste, odour or appearance. The problems associated with chemical constituents of drinking-water arise primarily from their ability to cause adverse health effects after prolonged periods of exposure; of particular concern are contaminants that have cumulative toxic properties, such as metals, and substances that are carcinogenic.
Figure 10. The gastrointestinal system
Long-term exposure to arsenic in well water in Taiwan has resulted in 370 cases of "Blackfoot" disease and 428 cases of skin cancer. Blackfoot disease is a local term for a vascular disorder that results in gangrene of the extremities, especially of the feet. The affected people were chronically exposed to low levels of arsenic over a lifetime, frequently for as long as 50 to 60 years. As a consequence of the cumulative exposure to arsenic from ingestion of drinking-water, the major symptoms increased in frequency with age. Thus blackfoot disease and skin cancer in particular, appeared mainly in adolescents and adults, but not in children.

Arsenic contamination of groundwater, the main sources of drinking-water, has been detected in six districts of West Bengal, India and in several villages in Bangladesh that border India. Levels up to 70 times higher than the national drinking-water standard of 0.05 mg/litre have been measured in both countries. The contamination is due to the natural soil composition of the region. While the true extent of the problem is not yet known, it has been estimated that some 30 million people may be at high risk from arsenic exposure. Meanwhile, evidence of chronic arsenic toxicity in the population is accumulating and includes incidence of abnormal black-brown pigmentation of skin, thickening of palm and sole, gangrene of the lower extremities and skin cancer. In West Bengal alone, 200,000 people have been reported to be suffering from arsenical skin lesions. Priority areas for solving the problem include development of alternative safe drinking-water sources, appropriate water treatment technology for arsenic removal, treatment of patients and development of public awareness.

Acute intoxications due to the ingestion of well water containing high nitrate levels have been reported. The toxic effects of nitrate in humans depends on the conversion of nitrate to the toxic compound nitrite. This conversion occurs more frequently in infants under the age of 3 months. For this reason infants are considered as a special risk group. The major biological effect of nitrite in humans is its involvement in the conversion of normal blood haemoglobin, which transports oxygen in the blood, to methaemoglobin, which is unable to transport blood oxygen to the tissues and organs.

### 2.5 Multi-media exposure

In actual practice, it is rare to be exposed to a chemical solely by the dermal, inhalation or oral route. For example, exposure to lead may occur from food, drinking-water, air and the domestic environment.

There are few chemicals that are equally toxic by all three routes of exposure. The organophosphate pesticide parathion is an exception. It is easily absorbed through the skin, lung or digestive tract and, as such, is equally toxic by all three routes. The majority
of chemicals are not equally toxic by all three routes. Vitamin D, if administered in a high enough dose, is highly toxic by oral exposure but is not toxic by dermal exposure.

There are two reasons why toxicity varies with the route of exposure. One relates to the amount of chemical absorbed into the body and the other to the pathway that the chemical follows once it has entered the circulation. The most toxic route of exposure is the route that permits the greatest amount of absorption. Inhalation offers the greatest amount of chemical absorption, followed by ingestion and dermal absorption.

The pathway the chemical follows once it passes into the blood circulation is very important in determining the toxicity of the chemical. Chemicals absorbed through the skin or lungs are sent directly to all other organs of the body before going to the liver. However, the majority of chemicals absorbed through the digestive tract pass through the liver before being transported to the rest of the body. This is important because the liver is the primary organ that detoxifies chemicals through a process called biotransformation. Foreign chemicals can be processed by the liver, which generally makes them less toxic. Occasionally, the liver may convert a chemical into a more toxic compound. Thus, assuming equal absorption by all three exposure routes, a chemical that is detoxified by the liver would be less toxic if it entered the body by ingestion rather than through inhalation or dermal exposure.

2.6 Exposure to chemical mixtures

When humans are exposed to two or more chemicals, the chemicals may interact with each other, altering their toxicity. Chemical interactions can occur in a variety of ways such as altering the absorption, biotransformation or excretion of one or both of the interacting toxicants. There are four types of effects chemicals can have on each other. Two or more chemicals given simultaneously can produce a response that is independent, additive, synergistic or antagonistic. These terms are defined below and illustrated in Figure 11.

- **independent** — when the chemicals produce different effects or have different modes of action, they do not interfere with each other.
- **additive** — when the combined effect produced by two or more chemicals is equal to the sum of the effects of each agent given alone. For example, the effects of organophosphate pesticides are usually additive. Numerically, it could be represented by the equation $3 + 3 = 6$.
- **synergistic** — when chemicals act synergistically, the toxic effect observed is greater than the sum effect of the chemicals given alone. The effect is more than additive. For instance,
asbestos fibres and cigarette smoking act together to increase the risk of lung cancer by a factor of forty, taking it well beyond the risk associated with independent exposure to either of these agents. This would be illustrated by $3 \times 3 = 9$.

- **antagonistic** — the opposite of synergism.

An antagonistic effect is the result of a chemical counteracting the adverse effect of another; in other words, exposure to two or more chemicals has less effect than the sum of their independent effects. The effect is less than additive. For example, $3 - 2 = 1$. Antagonistic effects are often very desirable in toxicology and are the bases of many antidotes. For example, dimercaprol binds with various elements such as arsenic, mercury and lead, and the toxic effect will be less than expected.

One mechanism that can cause synergistic or antagonistic effects of chemicals is if one chemical interferes with the **biotransformation** of the other chemical. If biotransformation converts a chemical to a more toxic form, inhibition of this process by another chemical will prevent that conversion and the toxic effect will be less than expected (antagonism). Conversely, if biotransformation produces a less toxic compound, inhibition of biotransformation by another chemical will prevent detoxification and the resulting toxic effect will be greater than normal (synergism).

Little information is available that could help in predicting the likely effects of the potential interactions of hazardous chemicals. Other areas where knowledge is insufficient are the possible effects of low-level, continuous exposure to mixtures of chemicals and the effects of multiple stresses including chemicals, physical factors such as heat and noise, and pre-existing disease or conditions such as malnutrition.
After reading this chapter, you should be aware that:

- There are three principal routes of exposure: penetration through the skin (dermal), absorption through the lungs (inhalation), and absorption from the digestive tract (ingestion). The most common forms of occupational exposure are inhalation and dermal.

- There are two reasons why toxicity varies with the route of exposure. One relates to the amount of chemical absorbed into the body and the other to the pathway that the chemical follows once it has entered the bloodstream.

- The most toxic route of exposure is the route that permits the greatest amount of absorption. Inhalation offers the greatest amount of chemical absorption followed by ingestion and then dermal absorption.

- There are four types of effects chemicals can have on each other. Two or more chemicals given simultaneously can produce a response that is independent, additive, synergistic or antagonistic.
  - Independent — when the chemicals produce different effects or have different modes of action, they do not interfere with each other.
  - Additive — when the combined effect produced by two or more chemicals is equal to the sum of the effects of each agent given alone.
  - Synergistic — when chemicals act synergistically, the toxic effect observed is greater than the sum effect of the chemicals given alone.
  - Antagonistic — the opposite of synergism. An antagonistic effect is the result of a chemical counteracting the adverse effect of another; in other words, exposure to two or more chemicals has less effect than the sum of their independent effects.
3. ADVERSE EFFECTS OF CHEMICALS ON HUMANS

This chapter will show:

- The most common adverse effects associated with exposure to toxic chemicals
- The difference between acute and chronic exposure
- The difference between local and systemic effects
- The detoxification process of chemicals in the body
- The physiology of body systems and the effects of toxic chemicals on those systems
3.1 Introduction

Humans are exposed to an array of chemicals whether as medicines, industrial or environmental chemicals, or naturally occurring substances. All substances have the potential to cause harmful effects, which are referred to as toxic or adverse effects. It is mainly the dose that determines whether the substance will be toxic. For instance, at a high enough dose, even an innocuous substance such as sugar can be lethal. Conversely, at low enough doses, no substance will be toxic (with the exception of non-threshold chemicals discussed in chapter 5). Even substances that are essential to our bodies, such as iron, can be toxic at high doses. Without enough iron, we would develop anaemia, but too much iron causes liver abnormalities. An adverse effect can be defined as an abnormal, undesirable or harmful change following exposure to a potentially toxic chemical. The different types of possible adverse effects are too numerous to mention, but the severity of the effect can range from a skin rash to blindness to cancer with a multitude of possibilities in between. Specific body organs can be targeted by certain chemicals or a number of body parts can be affected simultaneously. The resulting adverse effect depends not only on the chemical to which one is exposed but also on the type of exposure and level of exposure.

There are three types of exposure; acute, subchronic and chronic. Acute exposure to chemicals is defined as exposure to a chemical for less than 24 hours. It usually refers to a single dose of a chemical. Long-term exposure, known as chronic exposure refers to repeated or continuous exposure to a chemical for an extended period of time. Chronic exposure can produce completely different adverse effects than acute exposure. Subchronic exposure is greater than acute but less than chronic. The adjectives acute and chronic can also be used to describe adverse effects. Some chemicals cause an acute adverse effect that occurs shortly after exposure, while others produce chronic effects, such as cancer, which may not be seen until 10 to 20 years after the exposure. The level of exposure can vary from minute quantities to very high doses. Exposure may be due to a single substance or to multiple chemicals.

Several terms can describe the adverse effects, or toxicity, of chemicals. In a general sense, the toxicity of a chemical could be defined as the capacity to cause a harmful effect in a living organism. A highly toxic substance will damage an organism if administered in very small amounts (e.g., botulinum toxin); a substance of low toxicity will not produce an adverse effect unless the amount is very large (e.g., sodium chloride, commonly known as salt). Thus, toxicity cannot be defined without reference to the quantity (dose) of a chemical to which we are exposed, the way in which this quantity reaches us (e.g., inhalation, ingestion, dermal) and the duration of exposure (e.g., single dose, repeated doses), the
type and severity of adverse effects, and the time needed to produce these effects.

Chemicals can enter our body three different ways as described in the previous chapter. Whether a substance enters the body by ingestion, inhalation or by absorption through the skin, different chemicals will cause different adverse effects. If the effect of a chemical is limited to the area of contact, it is known as a local effect. However, if the substance is absorbed into the blood circulation it will be transported to various organs throughout the body causing a systemic effect.

Not all chemicals that are absorbed into the body will necessarily cause adverse effects. The body is equipped with several mechanisms for protecting itself against harmful substances. Some substances may be directly excreted from the body, without having any effect on the organism. Substances absorbed into the body that are lipophilic (not soluble in water, soluble in fat) are more difficult to excrete. These substances can undergo a process of detoxification in the liver called biotransformation which will alter the substance, forming metabolites. These metabolites are similar to the original substance but they are more water soluble and therefore easier to excrete. Generally, they are much less toxic to us than the original substance. Occasionally, some metabolites are actually more toxic than the original substance.

If a chemical does produce an adverse effect, the damage may be reversible or it may be irreversible. Reversible effects are characterized by the fact that the change from normal structure or function induced by a chemical will return to within normal limits following cessation of exposure. Damage associated with irreversible effects persists or may progress, even after exposure has stopped. For example, exposure to solvents may cause contact dermatitis, headache or nausea, these symptoms disappearing after cessation of exposure. These changes/injuries are reversible. Certain effects of toxic chemicals are irreversible, including certain neurological diseases, the production of cancer, liver cirrhosis, or emphysema in the lungs.

This chapter will discuss the adverse effects specific chemicals elicit on some of the essential body systems as well as the role of carcinogens.

### 3.2 Effects on the respiratory system

Inhalation is a very important route of exposure to toxic chemicals, especially in the workplace. Chemicals that enter the lung can either exert a direct effect on the cells of the lung, or can be absorbed into the systemic circulation. It is necessary to distinguish between "inhalation toxicology" which is simply the
route of exposure and "respiratory toxicology" which is the response of the lung to toxic chemicals. Inhalation exposure differs from ingestion because chemicals absorbed into the blood system from the lungs pass to the heart and are then distributed to other organs without passing through the detoxification process of the liver. This contrasts with ingestion where chemicals absorbed into the blood are transported directly to the liver where they can be metabolically transformed into less toxic compounds.

3.2.1 How the respiratory system works

The primary purpose of the respiratory system is the exchange of oxygen and carbon dioxide between the alveoli, which are tiny air sacs in the lungs, and the blood system.

The respiratory system consists of the nose, larynx, trachea, bronchi, lungs and pleura (Figure 13). Air enters through the nose or mouth and passes through the larynx into the trachea, which divides into the left and the right bronchi, which in turn lead to the lungs. The lungs expand and contract with movement of the rib cage and diaphragm.

On entering the lungs the bronchi branch out like a tree. The finest branches are called bronchioles. At the end of the bronchioles are multiple tiny air sacs, the alveoli, in which the air and other gaseous exchanges take place with the blood that flows through the alveolar walls.

The oxygen in the air we inhale is absorbed by the red blood cells in the blood vessels which lie in the alveolar wall, from where it is transported, by way of the heart, to all parts of the body Figure 12.

Used blood, the venous blood, which has a high carbon dioxide content but low oxygen content, returns through the pulmonary vessels, passes through the thin walls of the alveoli and removes the carbon dioxide through the air we exhale.

The lung is in direct constant contact with the external environment and is exposed to many infectious organisms as well as an increasing number of potentially hazardous particles and gases. The lung has defense mechanisms that, under most circumstances, successfully protect the lungs from adverse effects. Primarily, the lung is protected from hazardous substances by their removal from the respiratory system before they are able to cause any damage.

All the respiratory passages, from the nose to the terminal bronchioles, are kept moist by a layer of mucus that coats the entire surface. In addition to keeping the surfaces moist, the mucus also traps small particles from the air and keeps most of these from ever reaching the alveoli. The mucus is then removed from the respiratory tract by cilia, which are tiny hair-like structures that line the surface of the respiratory passages. The cilia beat continuously, slowly moving the mucus out of the lungs. The
mucus and its entrapped particles are then either swallowed or coughed to the exterior. This is known as mucociliary clearance.

The respiratory system is also protected by the immune system which will be discussed in more detail in section 3.6.

### 3.2.2 How chemicals affect the respiratory system

Chemicals absorbed by inhalation have specific properties. They are either: (a) gases such as carbon dioxide; (b) vapours, i.e., the gaseous phase of a material that is ordinarily a solid or liquid such as mercury; or (c) aerosols, i.e., small particles suspended in the air. Gases and vapours may be inhaled directly into the lungs or they may be absorbed onto the surface of aerosols and then inhaled. For example, many elements (zinc, arsenic) that are released during coal combustion are concentrated on the surface of aerosols.

If the gases or vapours are water soluble (i.e., will dissolve in water), they may dissolve in the mucus that covers the respiratory tract causing local irritation and they may not reach the lower airways and alveoli (e.g., sulfur dioxide). For aerosols, particle size is the critical factor determining how far down the respiratory tract the particles will go and, therefore, what part of the respiratory system they will affect.

When we inhale, the particles that make up aerosols are deposited all along the respiratory tract. Where the particles are deposited affects the severity of tissue damage, the amount of absorption of the toxicants into systemic circulation, and the ability of the lungs to remove the particles. The smaller the particles, the farther they can pass into the respiratory tract. Aerosols of 5–30 micrometres (μm) are mainly deposited in the upper respiratory tract (nose and throat). The depth of penetration increases as aerosol size decreases, and aerosols in the 1–5 μm range are, for the most part, deposited in the lower respiratory tracts (trachea, bronchi and bronchioles). Deposited particles are cleared by the mucociliary clearance described in section 3.2.1. Particles cleared in this way are swallowed and may be absorbed from the gastrointestinal tract. Aerosols of 1 μm and smaller gain access to the alveoli. Aerosols in the alveoli may be absorbed into the blood system or cleared by immune cells (macrophages) which ingest the particles. Transport of particles through the respiratory tract is illustrated in Figure 14.

The respiratory system can respond in a number of ways to the hazardous gases and particles that are not removed by mucociliary clearance or immune cells. Changes observed in the lung as a result of the inhalation of hazardous gaseous or particulate materials depend upon the concentration of the inhaled material, the duration of exposure, and the nature of the chemical. A list of inhalation and respiratory toxicants is given in Table 12. Acute changes in the
Table 12. Some toxicants found in air and their effects on human health

<table>
<thead>
<tr>
<th>Substance</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>nitric oxide</td>
<td>eye irritation, reduced athletic performance</td>
</tr>
<tr>
<td>aldehydes</td>
<td>eye irritation</td>
</tr>
<tr>
<td>lead</td>
<td>effects on the central nervous system</td>
</tr>
<tr>
<td>suspended particulates</td>
<td>irritation of bronchi</td>
</tr>
<tr>
<td>sulfur dioxide and sulfuric acid</td>
<td>irritation of bronchi, bronchospasm, susceptibility to respiratory infection</td>
</tr>
<tr>
<td>polycyclic aromatic hydrocarbons</td>
<td>lung cancer</td>
</tr>
<tr>
<td>nitrogen dioxide</td>
<td>asthma attacks</td>
</tr>
<tr>
<td>ozone</td>
<td>asthma attacks</td>
</tr>
<tr>
<td>carbon monoxide</td>
<td>reduction in oxygen-carrying capacity of blood</td>
</tr>
</tbody>
</table>

Lung include bronchoconstriction, airway oedema, and impairment of defence mechanisms such as mucociliary clearance. Bronchoconstriction is the narrowing of the airways causing wheezing. Acute exposure to sulfur dioxide for as little as 3 minutes can produce bronchoconstriction. Oedema is a general term for accumulation of fluid, causing swelling. Pulmonary oedema or airway oedema is the filling of the alveoli and surrounding tissue with large amounts of fluid. This can be caused by harmful substances such as chlorine or sulfur dioxide. Both of these gases can damage the blood vessels (capillaries) in the lungs causing fluid to leak out and fill the alveoli. A severe case of pulmonary oedema can be fatal.

Impaired mucociliary clearance will allow hazardous substances to remain in the lung for prolonged periods, and this prolonged exposure will increase the risk of adverse effects. Impairment of this defence mechanism is one of the many toxic actions of cigarette smoke. Ozone and sulfuric acid cause a similar effect.

Despite the defences of the lung, chronic injury can occur when defences and repair processes simply cannot prevent or repair the damage from acute exposure to high concentrations of a toxic substance or from repeated chronic exposure to low levels of the substance. Types of chronic damage include cancer, fibrosis, and diseases such as emphysema and chronic bronchitis.

3.2.3 Respiratory diseases caused by chemicals

Although the topic of cancer is covered more thoroughly in section 3.7, it is necessary to discuss the chemicals involved in the development of lung cancer. In industrialized countries, lung cancer is one of the leading causes of all cancer deaths. Most lung cancer deaths occur in people between the ages of 40 and 70.
Smoking is the number one risk factor in lung cancer and 80% of lung cancers occur in smokers. Exposure to certain chemicals in the workplace is also clearly associated with the development of lung cancer. Increases in the incidence of lung cancer have occurred in workers exposed to some forms of nickel, chromium and asbestos.

Asbestos is widely used in the construction industry. Important uses include asbestos cement sheets and pipes, insulation materials, taping compounds and floor and ceiling tiles. Contamination of the air inside buildings, especially schools, has been a major concern in many countries. Some countries have banned the use of asbestos in buildings and/or ordered the demolition of such buildings.

Respiratory system disease from exposure to asbestos includes asbestosis, lung cancer and mesothelioma. Other cancers linked to asbestos exposure include those of the larynx, pharynx, oesophagus, stomach, colon-rectum, and possibly the pancreas.

Asbestosis is a slowly developing fibrosis of the lung caused by the inhalation of high concentrations of asbestos dust or long exposure. Its severity depends both on the length of time since onset of exposure and on the intensity of the latter. Advanced asbestosis is often associated with lung cancer, especially among smokers.

Mesothelioma is a rare type of cancer of the pleura. An increased incidence of mesothelioma has been related to the inhalation of asbestos fibres in the occupational environment. Although there are few initial symptoms, mesothelioma is incurable when diagnosed. The amount of time between first exposure to asbestos and the clinical signs of tumours ranges from 20 to 50 years for mesothelioma. Increased incidence rates of mesothelioma have been seen in non-occupationally exposed people living in the same household as asbestos workers or in the vicinity of strong asbestos emission sources. Even if asbestos is no longer used for insulation purposes, it is still a concern because of the long amount of time between exposure and effects and because of the hazard from buildings already insulated with asbestos.

Emphysema is clearly associated with heavy cigarette smoking and often occurs in combination with chronic bronchitis. Emphysema is a common disease characterized by the destruction of alveolar walls. These changes usually progress slowly over many years causing wheezing, coughing and a decreased ability for gas exchange, which reduces the ability of the lungs to oxygenate the blood and to remove carbon dioxide.

Chronic bronchitis is caused by excessive production of mucus in the bronchi and bronchioles. Chronic irritation by inhaled substances such as those that form air pollution can cause bronchitis. Some examples of normal and damaged lung tissue are shown in Figure 15.
3.3 Effects on the liver

The liver (Figure 16) has many different functions. It is involved in digestion, metabolism and synthesis of nutrients needed by the body, and it plays a very important role in the detoxification of drugs and chemicals. This is not surprising since the primary role of the liver is to receive and process chemicals absorbed from the gastrointestinal tract before they are distributed to other tissues. After nutrients (and chemicals) have been absorbed into the blood from the digestive tract, the nutrient-rich blood passes directly to the liver. The cells of the liver remove amino acids (building blocks of protein), fats, glucose and toxicants from the blood so that they can be processed. The liver is the primary site for fat metabolism and it stores glycogen, which can be converted into energy when it is needed. It makes bile, cholesterol and proteins such as albumin and clotting proteins.

Figure 16. The Liver

The hepatocyte (liver cell), the main structural component of the liver, might be likened to a factory (it makes chemical compounds); a warehouse (it stores glycogen, iron, and certain vitamins); a waste disposal plant (it excretes bile, urea, and various detoxification products); and a power plant (it produces considerable heat during breakdown of complex molecules).

Unlike many organs of the body, the liver is protected from permanent damage in two ways. The liver can still function normally even after a large portion of it has been damaged. Second, the liver has the ability to regenerate itself rapidly and easily. However, this does not mean the that the liver cannot be permanently damaged by chemicals.
Liver damage may be caused by many chemical substances (hepatotoxicants) and is characterized in two ways: accumulation of fat or death of liver cells (Table 13). Accumulation of fat in the liver (steatosis) is a common sign of liver toxicity and can be due to toxic chemicals, including alcohol. However, provided there is no cell death, steatosis does not affect liver function. Hepatic necrosis (death of liver cells) may result from exposure to a number of chemical agents, including aflatoxins, carbon tetrachloride, chloroform, and tannic acid. In cirrhosis, a well-known liver condition, large number of liver cells are destroyed and replaced by permanent scar tissue. Cirrhosis can be caused by chronic alcohol abuse, viral hepatitis, or chemical agents that attack liver cells. Liver tumours, which can be benign or malignant, have been associated with exposure to arsenic, polychlorinated biphenyls (PCBs), thorium and, notoriously, vinyl chloride. If too many hepatocytes are killed, the liver will not be able to replace them. This will ultimately lead to liver failure and consequently, death.

Table 13. Examples of acute hepatotoxic chemicals

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Produces necrosis</th>
<th>Produces steatosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>allyl alcohol</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>allyl formate</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>aflatoxin</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>beryllium</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>bromobenzene</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>bromotrichloromethane</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>carbon tetrachloride</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>cerium</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>chloroform</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>cycloheximide</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>dimethylaminoazobenzene</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>dimethylnitrosamine</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>ethanol</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>ethionine</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>galactosamine</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>mithramycin</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>phosphorus</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>puromycin</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>pyrrolizidine alkaloids</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>tannic acid</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>tetrachloroethylene</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>thiocetaimide</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>trichloroethylene</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>urethane</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>
A large number of studies have shown that vinyl chloride causes a rare type of liver cancer, angiosarcoma. However, the overwhelming majority of cancers of the liver are due to transfer of cancer cells from other parts of the body (metastasis), most commonly, breast, lung and colon cancer; these in turn may be due to chemical insults. For more information on cancer, see section 3.7.

3.4 Effects on the kidney

The kidneys are two purplish-brown, bean-shaped organs situated at the back of the abdominal cavity, one on each side of the spinal column. The kidney is a complex organ. In addition to the formation of urine to rid the body of wastes, the kidney plays a significant role in the regulation of volume and composition of body fluids. For water and virtually all electrolytes (calcium, potassium, sodium) in the body, the balance between intake and output is maintained by the kidneys. The kidney is also a major site of formation of hormones, the formation of ammonia and glucose, and the activation of vitamin D. A toxicological insult to the kidney could affect any or all of these functions. However, the effect usually reported following exposure to a toxic chemical is decreased elimination of waste.

The functional unit of the kidney (Figure 17) is the **nephron**. Each kidney contains over one million nephrons. The kidney cannot regenerate new nephrons. Each nephron has three major components: (a) a large blood supply; (b) a glomerulus (with glomerular capillaries) through which large amounts of fluid and dissolved substances are removed from the blood; and (c) a long tubule in which this filtered fluid is converted into urine. The kidney receives approximately 21% of circulating blood via the renal artery, which progresses into smaller blood vessels called glomerular capillaries. The glomerular capillaries are found in the glomeruli where large amounts of fluid and small molecules are selectively removed from the blood. The tubules reabsorb most of the fluid and substances that were removed by the glomerulus back into the blood system because they are needed by the body. However, unwanted substances and excess fluid are formed into urine in the tubules and removed from the body. Furthermore, the tubule secretes material (waste) into the urine for removal from the body. In this way the nephrons are very selective in what and how much they remove from the blood. If there is an excess of water in the body, the kidney will produce very dilute urine, whereas, if the body is trying to conserve water, the kidneys will produce a low volume of urine that is very concentrated. The ureter carries the urine from the kidney to the bladder, where it is stored until emptied.
Toxicants that affect the kidney (nephrotoxicants) can act in one of four ways:
(a) decrease blood flow to the kidney, which decreases glomerular filtration rate and ultimately the formation of urine; a decrease in blood flow would also damage kidney tissue;
(b) affect the glomerulus directly and hinder its selective ability to filter the blood;
(c) affect the reabsorptive or secretory function of the tubule;
(d) block the tubule, preventing urine flow.
Decreasing the number of functional nephrons would cause major decreases in renal excretion of water and solutes. Loosing more than 70% of nephrons leads to electrolyte and fluid retention, and ultimately death.

The kidney is unusually susceptible to the toxic effects of chemicals due to its unique features. As water and electrolytes are reabsorbed into the blood system at the tubule, the urine and therefore any potential toxicants in the urine are concentrated. Thus, a non-toxic dose of a chemical in the blood could become toxic in the kidney due to concentration with the urine. The kidney is also highly susceptible because of the high blood flow it receives. Any drug or chemical in the blood system will be delivered in relatively large amounts to the kidney.

Most metals are potent nephrotoxicants. Kidney damage is probably due to a combination of decreased blood flow resulting in decreased urine production and tissue damage, and the toxicity of the metals on the tubules, resulting in tubule blockage. One such nephrotoxic metal is mercury. An acute dose of mercury salt will damage the tubules and can lead to kidney failure within 24 to 48 hours after exposure. Other elements that can damage the kidney include cadmium, chromium, arsenic, gold, lead and iron.

Both acute and chronic nephrotoxicity have been reported after exposure to halogenated hydrocarbons, organic solvents, and pesticides (e.g., trichloroethylene, methyl parathion).

Certain individuals, owing to hereditary or environmental factors, can be unusually susceptible to toxic substances that affect the kidney. For example, some individuals are unusually susceptible to copper nephrotoxicity because of their inability to maintain normal copper concentrations in the body (Wilson’s disease). People with kidney damage from diabetes or the natural decline in kidney function associated with ageing, exhibit cadmium nephrotoxicity at doses of cadmium that would not normally affect people. Other factors can cause some individuals to be more sensitive to the effects of these substances; these include nutritional status, alcohol drinking, smoking, genetic background and medications.

3.5 Effects on the nervous system

The nervous system is divided into two parts, the central nervous system and the peripheral nervous system. The central nervous system (CNS) consists of the brain and spinal cord (Figure 18) which primarily interpret incoming sensory information and issue instructions based on past experience. The peripheral nervous system (PNS) consists of nervous system structures outside the CNS, which carry impulses to and from the brain and spinal cord. The nerves serve as communication lines.
They link all parts of the body by carrying impulses from the sensory receptors to the CNS and commands from the CNS to the appropriate glands or muscles.

The nervous system receives millions of bits of information from the different sensory organs and then integrates all these to determine the response to be made by the body. Input to the nervous system is provided by the sensory receptors that detect such sensory stimuli as touch, sound, light, pain, cold, warmth and so on. This sensory experience can cause an immediate reaction or its memory can be stored in the brain and then can help determine the bodily reactions at some future date. Ultimately, the nervous system regulates the various bodily activities by controlling the muscles throughout the body. This is called the motor response. This includes skeletal muscle, which is responsible for movement, and the smooth muscle of internal organs such as the intestine. Another function of the nervous system is to control the secretion of chemicals from glands.

The major function of the central nervous system is to process the incoming sensory information in such a way that the appropriate motor responses occur. After the important sensory information has been selected, it is then channelled into the proper region of the central nervous system to cause the desired response. Thus, if a person places a hand on a hot stove, the desired response is to lift the hand.

### 3.5.1 How the nervous system works

The functional unit of the nervous system is the **neuron** (Figure 19). Neurons are highly specialized cells that conduct or transmit messages (nerve impulses) from one part of the body to another. Neurons have fibres extending out from the body of the cell called **axons**. Messages are passed along the axon to the presynaptic terminal, which releases chemicals called **neurotransmitters**. These pass across the synaptic cleft to cause a response in the body (soma) of the next neuron or muscle fibre. Most axons are covered with a fatty material called myelin. Myelin protects and insulates the fibres and increases the rate of transmission of the nerve impulses. This process continues from one neuron to the next neuron or muscle cell, successfully passing the message from one area to another.

Unlike most cells of the body, neurons cannot reproduce. Therefore, if a neuron is destroyed it will not be replaced, making the nervous system particularly vulnerable if damaged by a toxic chemicals. To counteract its inability to replace damaged cells, the nervous system decreases its exposure to chemicals by the **blood-brain barrier**. Although the nervous system, like all parts of the body, needs a blood supply to survive, there is a protective barrier between the nervous system and the rest of the body that restricts the entry of some substances. The brain, spinal chord and peripheral nerves are completely covered with a continuous lining
of specialized cells that allow necessary nutrients to pass through but limit the entry of toxicants. Even with the blood-brain barrier, some toxicants can damage the nervous system. It should be noted that the blood-brain barrier is not completely developed at birth. Thus newborn babies and, especially, fetuses and premature babies are more susceptible to neurotoxicants. For example, fetuses are particularly susceptible to alcohol (ethanol). If a pregnant woman drinks too much alcohol, it can cause a disease called “fetal alcohol syndrome”.

3.5.2 How chemicals affect the nervous system

Neurotoxicity is the capacity of chemical, biological, or physical agents to cause adverse effects on the nervous system. A list of compounds that are neurotoxic can be found in Table 14.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Compound</th>
</tr>
</thead>
<tbody>
<tr>
<td>aluminum</td>
<td>kanamycin</td>
</tr>
<tr>
<td>azide</td>
<td>lead</td>
</tr>
<tr>
<td>bismuth</td>
<td>manganese</td>
</tr>
<tr>
<td>carbon monoxide</td>
<td>methanol</td>
</tr>
<tr>
<td>carbon tetrachloride</td>
<td>methylbromide</td>
</tr>
<tr>
<td>cyanide</td>
<td>methyImercury</td>
</tr>
<tr>
<td>dichlorodiphenylchloroethane</td>
<td>thallium</td>
</tr>
<tr>
<td>hydrogen sulfide</td>
<td>trimethyltin</td>
</tr>
<tr>
<td>kainate</td>
<td></td>
</tr>
</tbody>
</table>

Moreover, in addition to toxicants acting directly on the nervous system, the nervous system is greatly affected by any changes in blood circulation. All cells require oxygen but for the nervous system a constant supply is essential. Any decrease in blood flow can be reflected in adverse effects on the nervous system before other systems would be affected.

Certain toxicants are specific for neurons (neurotoxicants), or a certain part of a neuron, resulting in their injury or death (necrosis), and the loss of a neuron is irreversible. Neurotoxicants can act on the axon, protective myelin, or the transmission of the nerve impulse (Figure 20). Ultimately, destroyed neurons result in a break in the communication between the nervous system and the rest of the body. The amount of function lost from damage to the nervous system depends on the number of neurons permanently damaged and where they are located. Some neurons may be slightly but not permanently damaged and, in time, may return to normal function. Permanent damage can result in loss of sensation and paralysis. It can also result in effects such as disorientation where a person cannot distinguish left from right or up from down. Because the nervous system controls many functions of the body, almost any function such as speech, sight, memory, muscle strength and coordination can be inhibited by neurotoxicants.
The neuronal toxicity of organic mercury, such as methylmercury, was tragically seen in the poisonings in Japan and Iraq. The residents of Minamata Bay in Japan whose diet was mostly fish from the bay were exposed to large doses of methylmercury when industrial waste that contained high amounts of mercury was dumped into the bay. Even more people were injured by methylmercury in Iraq. More than 400 people died and 6000 people were hospitalized after eating grain that had been coated with methylmercury. Another example of mercury poisoning occurred in London. In the 19th century, mercury was used in the production of top hats to prevent fungus from growing in the hats. Repeated exposure to mercury caused the workers to develop tremors and brain damage and led to the term “as mad as a hatter”. Exposure of adults to mercury results in initial loss of coordination, followed by tremors, hearing problems, muscle weakness and even mental disturbances.

Another neurotoxicant, carbon disulfide (CS₂) destroys axons. This chemical has been used for a variety of industrial purposes, particularly vulcan rubber and viscose rayon production. Since its discovery in 1776, there have been numerous examples of CS₂-induced neurotoxicity. Many cases of human CS₂ poisoning consisted of various neurological and behavioural effects. Initially, sensory and motor symptoms develop but there can also be personality changes, irritability, memory deficits, insomnia (sleeplessness), bad dreams and constant fatigue.

That the metal lead is toxic to the nervous system has been known for centuries. By destroying myelin, lead slows the transmission of impulses between neurons and can eventually stop them. People can be exposed to lead occupationally, if they work at a lead smelting plant, or at home through lead pipes and lead-based paints. Children are particularly susceptible to lead poisoning. Extremely low doses of lead, which will not cause the typical effects of lead poisoning, may nevertheless affect the intelligence of children.

Organophosphates form a class of insecticides widely used today that are neurotoxic to humans. These insecticides act at the synapse where neurotransmitters are secreted. Normally, after a neurotransmitter has been secreted by the axon, it crosses the synapse, stimulates the next nerve and is then destroyed. Organophosphates inhibit the destruction of the neurotransmitter such that the neurons are constantly being stimulated and the message is repeatedly transmitted from one neuron to the next. Depending on where the effected neurons are located, organophosphates can cause change in heart rate, tremors, muscle weakness or paralysis, restlessness, mental confusion, loss of memory, convulsions and coma. Current organophosphates available as insecticides are much less toxic than their predecessors, which have been used in chemical warfare.
3.6 Immunotoxicity

The immune system is a highly evolved defence system that protects our bodies from invading organisms, tumour cells and environmental agents. Our bodies are exposed to many bacteria, viruses, fungi and parasites, which are capable of causing serious diseases such as pneumonia, malaria and typhoid fever. Fortunately, our bodies have various systems, including the immune system, that combat these invaders. Environmental chemicals or drugs that can affect the immune system are called immunotoxicants. Immunotoxicants can have three different effects on the immune system: they can suppress the immune system; they can make it hypersensitive, which causes allergies; or they can cause the immune system to attack its own body (autoimmunity).

Our blood is composed of three different types of cells: red blood cells, which transport oxygen to different parts of the body; white blood cells (also called leukocytes), which are a major component of our immune system; and thrombocytes, which are responsible for blood clotting. There are many different types of white blood cells but this chapter will discuss the three most important types; neutrophils, macrophages and lymphocytes. All three of these white blood cells have different mechanisms for protecting the body.

The neutrophils and macrophages protect the body against invading organisms such as bacteria, viruses or other foreign particles by ingesting them. They can also ingest damaged or dead tissue that is in the body. The process of ingesting the organisms is called phagocytosis, and neutrophils and macrophages are therefore classified as phagocytes. In addition to phagocytosis, after a macrophage or neutrophil has ingested a bacteria it will digest it. Obviously, phagocytes must be selective concerning the material that is phagocytized, or otherwise some of the normal cells and structures of the body would be ingested. Foreign cells and particles (antigens) are not recognized as “self”, making them more likely to be ingested.

Once inside the body, bacteria are labelled with an antibody, making them especially susceptible to phagocytosis. A neutrophil can usually phagocytize 5 to 20 bacteria before the neutrophil itself becomes inactivated and dies. Macrophages are much more powerful and can phagocytize as many as 100 bacteria. They also have the ability to ingest much larger particles, such as malarial parasites and damaged body tissue, whereas neutrophils are incapable of phagocytizing particles much larger than bacteria.

There are two types of lymphocytes, T and B. B lymphocytes produce compounds called antibodies. Each toxin or organism has a specific chemical compound attached to it that is different from all other compounds. These compounds are called antigens. Each antibody is specific for a particular antigen. Once an antigen has
been recognized, B lymphocytes will produce a specific antibody that will bind to that antigen. Antibodies have two roles, they can act directly on the invading organism, inactivating it, or they can enhance another part of the immune system. For example, antibodies activate phagocytosis, causing neutrophils and macrophages to engulf the bacteria to which the antibody is attached.

Lymphocytes, macrophages and neutrophils are transported by the blood to areas where they are needed.

The function of the immune system is to recognize and eliminate agents that are harmful to the host. When the immune system is functioning properly, the foreign agents are eliminated quickly and efficiently. If the immune system is inhibited in any way (immunosuppression), it will result in increased susceptibility to infection from bacteria, parasites and viruses and an increase in cancer. Organisms that our body would normally be able to ward off will be able to infect tissues causing potentially deadly diseases. Because the immune system is so diverse, immunosuppression could occur in many ways. Chemical agents may inhibit phagocytosis or they could affect lymphocytes and their production of antibodies. Numerous chemicals such as metals (lead, mercury) and pesticides have been identified that can suppress the immune system. These include polychlorinated biphenyls, which have been used for over half a century in plasticizers and transformers, and polycyclic aromatic hydrocarbons, which are formed during the combustion of fossil fuels. These chemicals have been shown to suppress immune responses, resulting in reductions in antibody-producing cells. A list of immunosuppressive chemicals and materials is given in Table 15.

Table 15. Examples of immunotoxic chemicals

<table>
<thead>
<tr>
<th>Immunosuppression</th>
<th>lead</th>
<th>dibenzodioxins</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mercury</td>
<td>polycyclic aromatic hydrocarbons</td>
</tr>
<tr>
<td></td>
<td>ethanol</td>
<td>urethane</td>
</tr>
<tr>
<td></td>
<td>benzene</td>
<td>pesticides (carbamates, organochlorines, organophosphates)</td>
</tr>
<tr>
<td></td>
<td>polybrominated biphenyls</td>
<td></td>
</tr>
<tr>
<td></td>
<td>polybrominated biphenyls</td>
<td></td>
</tr>
<tr>
<td>Allergies</td>
<td>formaldehyde</td>
<td>nickel</td>
</tr>
<tr>
<td></td>
<td>phthalic anhydrides</td>
<td>chromium</td>
</tr>
<tr>
<td></td>
<td>pesticides</td>
<td>gold</td>
</tr>
<tr>
<td></td>
<td>ethylenediamine</td>
<td>mercury</td>
</tr>
<tr>
<td></td>
<td>food additives (azodyes, BHT, BHA)</td>
<td>beryllium</td>
</tr>
<tr>
<td></td>
<td>antimicrobials (EDTA, mercurials)</td>
<td>resins and plasticizers (toluene disocyanate, trimellitic anhydride)</td>
</tr>
<tr>
<td></td>
<td>platinum compounds</td>
<td></td>
</tr>
<tr>
<td>Autoimmunity</td>
<td>diethyln</td>
<td>perchloroethylene</td>
</tr>
<tr>
<td></td>
<td>trichloroethylene</td>
<td>epoxy resins</td>
</tr>
<tr>
<td></td>
<td>quartz</td>
<td>hydrazine</td>
</tr>
</tbody>
</table>
Occasionally, the immune system responds adversely to environmental agents, resulting in an **allergic reaction**. Allergies can cause many different effects including hayfever, asthma, rheumatoid arthritis, and contact dermatitis (skin allergy). The cause of allergies is referred to as a hypersensitivity response that occurs following exposure to some occupational and environmental agents. Antigens that cause allergic responses are called allergens. Instead of initiating the production of typical antibodies, allergens stimulate B lymphocytes to produce “sensitizing antibodies” called reagins. When the reagin binds to the allergen, it causes an allergic reaction. A number of industrial chemicals and drugs can induce allergic responses. The most common types of allergic responses from occupational or consumer exposure are asthma and contact dermatitis.

Asthma is characterized by contraction of the muscles in the bronchioles of the lung, which makes breathing extremely difficult. Finishes such as formaldehyde are used in the textile industry to improve the wrinkle resistance and durability of fabrics. When formaldehyde was first used in the textile industry, many workers developed asthma due to the free formaldehyde. Fabrics are now allowed to “off-gas” the free formaldehyde or are washed prior to being used. Metals such as platinum and certain pesticides have also been shown to induce asthma in people exposed to them.

Allergic contact dermatitis can occur within days of exposure but, typically, it develops after several years of continuous low-level exposure to a substance. It results in a rash, swelling, itching and possibly blistering of the skin. A variety of substances may cause allergic contact dermatitis including cosmetics, certain metals and many chemicals. For example, beryllium, which was previously used to coat fluorescent lamps, led to skin hypersensitization when shards of broken lamps became embedded under the skin. Cosmetics contain antimicrobial chemicals that can cause contact dermatitis in some people. These chemicals include phenolics, organic mercurials, ammonium compounds and formaldehyde. Some individuals exposed to nickel in costume jewellery have developed contact hypersensitivity to it. The mechanism of nickel dermatitis includes diffusion of nickel through the skin and binding of nickel directly with lymphocytes, activating them. Contact dermatitis has also been described in people coming into contact with silver, copper and its salts.

As previously discussed, the immune system has ways of distinguishing host cells and substances from foreign cells and substances, which prevent the immune system from attacking its own body. When the immune system loses the ability to distinguish between the body’s own cells and foreign cells, it will attack and kill host cells, resulting in serious tissue damage. This condition is called **autoimmunity**. Although not as common as immunosuppression or allergies, occupational exposure to certain chemicals has been associated with autoimmune responses. These
include the pesticides aldrin and dieldrin, vinyl chloride, and metals such as gold and mercury. In most cases, if the exposure stops, so will the autoimmunity. This is also the case with allergies.

The immune system reacts differently to toxic substances when compared with the responses of other organ systems. The toxic response to a substance is usually dose-related, such that a high enough dose of a chemical will cause an adverse effect in most of the general population. Allergic reactions and autoimmunity, on the other hand, are usually not dose-related. Frequently only a small fraction of the population will be affected regardless of the amount of dose received. Additionally, the effects of chemicals on the immune system are related to the consequences of activating or inactivating of the immune system, rather than a direct toxic effect.

### 3.7 Reproductive toxicity of chemicals

*Reproductive toxicity* includes adverse effects on sexual function and fertility in males and females as well as any effect interfering with normal development both before and after birth (also called developmental toxicity). The physiology of the reproductive system is different for men and women but, in both cases, the reproductive system is controlled by chemicals called **hormones**. A hormone is a chemical substance that is secreted by glands in the body and exerts control on other cells of the body. The central nervous system (CNS) controls the secretion of hormones. In males, hormones control the development of the reproductive organs and the formation of sperm (spermatogenesis). In females, hormones control the development of reproductive organs, the female reproductive cycle, preparation of the uterus for pregnancy, and lactation. Hormones also play an essential role in pregnancy and development of the fetus.

Under normal conditions, in humans it is estimated that one in five couples cannot have children (are sterile), over one third of early embryos die, and about 15% of pregnancies abort spontaneously. Among the babies that are born, approximately 3% have developmental defects. Not surprisingly, chemicals (or drugs) can further interfere with a number of biological processes of the reproductive system in both males and females.

There are three main targets for reproductive toxicants. They can act directly on the CNS altering secretion of hormones (e.g., synthetic steroids). The gonads (ovary and testis) are also targets for a host of drugs and chemicals, particularly cancer chemotherapeutic drugs. Reproductive toxicants can inhibit or alter spermatogenesis. The outcome of such toxic effects includes sterility, decreased fertility, increased fetus death, increased infant

**Recent studies in the USA have consistently found an association between exposure to certain hazardous substances found at waste sites and birth defects among nearby residents. Proximity to these waste sites seems to be associated with a small to moderate increased risk of nervous system birth defects, cleft lip and palate, heart defects and limb reductions.**
death and increased birth defects. Chemicals that cause an increase in birth defects are called teratogens.

Adverse effects on the developing organism may result from exposure prior to conception (either parent), during pregnancy, or from birth to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism. The major manifestations of developmental toxicity include: (a) death of the developing organism; (b) structural abnormality; (c) altered growth; and (d) functional deficiency. Exposure to chemicals during pregnancy may result in defective development. The developing fetus is particularly sensitive to toxic chemicals during certain periods, generally related to the development of particular organ systems or types of cells. In humans, a critical phase for the induction of structural malformations usually occurs 20–70 days after conception.

The impact of chemicals (or drugs) on the reproductive system was tragically demonstrated by the thalidomide incidence in the 1960s. Thalidomide was administered to pregnant women as an antinausea drug. It has no adverse effects on adults but it is a teratogen and interferes with limb development in the fetus. Consequently, children whose mothers consumed thalidomide while pregnant were born with severely underdeveloped or missing legs and/or arms.

For certain chemicals, epidemiological studies, occupational exposure data, or data from animal studies indicate an association between exposure and adverse reproductive effects (Table 16).

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Adverse effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aldrin</td>
<td>spontaneous abortion, premature labour</td>
</tr>
<tr>
<td>Arsenic</td>
<td>spontaneous abortion, decreased birth weight</td>
</tr>
<tr>
<td>Benzene</td>
<td>spontaneous abortion, low birth weight, menstrual disorders</td>
</tr>
<tr>
<td>Cadmium</td>
<td>low birth weight</td>
</tr>
<tr>
<td>Carbon disulfide</td>
<td>menstrual disorders, spontaneous abortion, adverse effects on sperm</td>
</tr>
<tr>
<td>Chlorinated compounds</td>
<td>eye, ear and oral cleft defects, CNS disorders, perinatal deaths, childhood leukaemia</td>
</tr>
<tr>
<td>1,2-Dibromo-3-chloropropane</td>
<td>adverse effects on sperm, sterility</td>
</tr>
<tr>
<td>Dichloroethylene</td>
<td>congenital heart disease</td>
</tr>
<tr>
<td>Dieldrin</td>
<td>premature labour, spontaneous abortion</td>
</tr>
<tr>
<td>Hexachlorocyclohexane</td>
<td>hormonal imbalances, premature labour, spontaneous abortion</td>
</tr>
<tr>
<td>Lead</td>
<td>still birth, low birth weight, spontaneous abortion, neurobehavioural deficits, mental retardation, delayed development, brain damage</td>
</tr>
<tr>
<td>Mercury</td>
<td>menstrual disturbances, spontaneous abortion, blindness, deafness, mental retardation, delayed development, brain damage</td>
</tr>
<tr>
<td>Polycyclic aromatic hydrocarbons</td>
<td>decreased fertility</td>
</tr>
<tr>
<td>Polychlorinated biphenyls</td>
<td>preterm delivery, low birth weight, reduced head circumference, growth deficiencies, neurobehavioural effects</td>
</tr>
<tr>
<td>Trichloroethylene</td>
<td>congenital heart disease</td>
</tr>
</tbody>
</table>

Table 16. Environmental toxicants and adverse reproductive outcomes
Several epidemiological studies indicate that inorganic arsenic can cause developmental effects in humans, the developing fetus is especially sensitive to methylmercury, and exposure of pregnant women to lead has been shown to interfere with the mental development of their children. The list of adverse reproductive effects is growing longer, and there are more and more indications that pregnant women, fetuses, nursing infants and very young children are high-risk groups that are more susceptible to the adverse effects of chemicals than the general population.

The infant and young child have different structural and functional characteristics from those of the older child and adult. These represent stages in normal growth and development, and may affect their vulnerability when exposed to chemicals. Generally speaking, chemicals, both organic and inorganic, are absorbed more readily by infants than by adults. Organic compounds undergo biotransformation less readily in the infant, and the kidneys are immature and less able than those of the adult to excrete chemicals. Thus, a similar dose of a chemical per unit body weight is likely to accumulate to a greater extent in the body of an infant than in that of an older child or adult and consequently will be more likely to exert toxic effects.

All these characteristics points to the special need to protect these sensitive segments of the population from the health risks due to exposure to chemicals.

3.8 Cancer-causing chemicals

Cancer is one of the three leading causes of death in most countries. Under normal conditions, the body's cells reproduce in an orderly manner, so that worn out tissues are replaced, injuries are repaired, and growth of the body proceeds. However, under some conditions, certain cells undergo a poorly understood transformation that changes the cells. This transformation occurs due to damage to the cell's DNA (deoxyribonucleic acid), the material of inheritance found in the nucleus of the cell. Cells can often repair damage done to the DNA, or the immune system may recognize that a cell has been damaged and then kill the cell so that it does not persist to cause cancer. If neither of these events occurs, the damaged cell may continue to divide and grow, producing more damaged copies of itself. A cell that has sustained damage once to its DNA, especially cells which first lose the ability to repair themselves, will often continue to accumulate more damage. If the damage does not kill the cells it will cause the cells to look and act differently from normal healthy cells.

A healthy cell has particular features that identify it from all other types of cells because each cell type performs special functions in the body. For example a bone-forming cell is very different from a muscle cell. They appear to be different because they do different jobs. Cancer cells will often lose their special
features when they become damaged. The cells can no longer perform their special functions. Healthy cells will reproduce at a set rate but cancer cells will reproduce at abnormal rates, causing uncontrolled cell growth. This new growth or tumour resulting from the accumulation of rapidly reproducing cells within an area is referred to as a “neoplasm”.

Generally, tumours that are entirely confined to one location or organ without invading the surrounding tissues are called “benign” tumours and are not life-threatening. In contrast, some tumours spread to other areas of the body and invade other organs and tissue causing the destruction of normal cells. These tumours are called “malignant” tumours and are life-threatening. Cancer is the common term used for all malignant tumours. A malignant tumour will cause blood vessels to grow towards it so that can get the nutrients from the bloodstream it needs for its quick growth. This is called angiogenesis.

Once these blood vessels are formed around the tumour, individual tumour cells or clumps of cells will be shed from the primary tumour and leave the area through the new blood vessels. This process is called metastasis. Cells leave the original tumour and spread to other parts of the body, forming secondary tumours. The disease will eventually be fatal because the body’s normal functioning becomes clogged with the secondary tumours. Tumours also consume a great deal of the bodies resources and the individual becomes weakened, which contributes to the loss of health in the cancer patient.

It is now generally accepted that cancer in humans involves three distinct phases:

(a) *Initiation* is a relatively rapid and apparently irreversible process that results in permanently altered cells. These cells have lost the controls that regulate normal growth. The permanent alteration of cells is thought to involve damage to the cell’s DNA.

(b) *Promotion*: under appropriate conditions, initiated cells are able to develop into tumours (neoplasms).

(c) *Progression* involves transition from a benign tumour to a malignant tumour that invades tissue and metastasizes.

Certain chemicals (carcinogens) may cause cancer in humans, but cancer may also be caused by viruses and radiation (ionizing radiation, X-rays, ultraviolet light). There is no single mode of action by which all carcinogens produce cancer. Nevertheless, the ultimate effect of carcinogens is the same, they lead to the development of a tumour. Approximately 35 specific chemicals or processes have been judged by The International Agency for Research on Cancer (IARC) to have caused cancer in humans. Most of these are industrial chemicals or drugs and the majority are mutagens (can damage DNA). Such agents, however, do not account for most human cancer. Many studies implicate lifestyle choices, particularly use of tobacco products, diet and alcohol consumption, as contributors to the majority of cancers. A listing of known and suspected carcinogenic agents is given in Table 17.
Table 17. Some chemicals considered to be carcinogenic to humans by the International Agency for Research on Cancer

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Chemical</th>
<th>Chemical</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-aminonaphthalene</td>
<td>benzidine</td>
<td>soot</td>
</tr>
<tr>
<td>4-aminobiphenyl</td>
<td>chromium compounds</td>
<td>sulfur mustard</td>
</tr>
<tr>
<td>5-azacytidine</td>
<td>coal tars</td>
<td>tobacco smoke</td>
</tr>
<tr>
<td>aflatoxins</td>
<td>mineral oils</td>
<td>treosulphan</td>
</tr>
<tr>
<td>alcohol</td>
<td>nickel compounds</td>
<td>triethylenethiophosphoramide</td>
</tr>
<tr>
<td>arsenic</td>
<td>nitrogen mustard</td>
<td>vinyl chloride</td>
</tr>
<tr>
<td>benzene</td>
<td>shale oils</td>
<td></td>
</tr>
</tbody>
</table>

A typical confirmed human carcinogen is vinyl chloride. This is used for the production of polyvinyl chloride (PVC), which in turn is mainly used in the production of plastic pipes. PVC pipes are widely used in plumbing. Vinyl chloride has been associated with tumours of the liver, brain, lung and lymphatic system. In 1974, more than 40 years after the introduction of vinyl chloride into industry, an association of exposure to this chemical with human cancer was reported. Three cases of liver cancer were reported in men who were employed in the manufacture of PVC resins in a single plant in the USA. By reviewing medical records the association between exposure to vinyl chloride and tumours of the liver was confirmed. Once a chemical is recognized as a human carcinogen, many countries set strict limits for its use in the workplace and its release into the environment.

Aluminum production is another case where IARC has concluded that an agent is carcinogenic to humans. There is an increased risk of lung cancer among people that work in aluminum production. In Canada, an increased risk of bladder cancer was found to be associated with work in aluminum production. To decrease the risk of cancer, companies introduced the use of a different processing method, improved the ventilation, required protective masks, and initiated an urine monitoring programme for the early detection of bladder cancer.

Many carcinogens come from natural sources. A variety of different types of carcinogens is produced by plants. The best known of these, accounting for at least 30% of all cancers in the USA, are agents found in the tobacco plant. Tobacco contains certain carcinogens such as nitrosonornicotine. Tobacco smoke is a complex chemical mixture and contains many different types of carcinogens, including polycyclic aromatic hydrocarbons (PAHs).
Review

After reading this chapter, you should be aware that:

- If the dose is high enough, most chemicals will produce adverse effects. An adverse effect can be defined as an abnormal, undesirable or harmful change following exposure to a potentially toxic chemical.

- Acute exposure to chemicals is defined as exposure to a chemical for less than 24 hours. It usually refers to a single dose of a chemical. Long-term exposure, also known as chronic exposure, refers to repeated or continuous exposure to a chemical for more than 3 months. Chronic exposure can produce completely different adverse effects from acute exposure.

- If the effect of a chemical is limited to the area of contact, it is known as a local effect. However, if the substance is absorbed into the circulation, it will be transported to various organs throughout the body causing a systemic effect.

- Substances absorbed into the body that are lipophilic (soluble in fat, not soluble in water) are difficult to excrete. In order to remove them from the body and, therefore, protect the body from potentially toxic chemicals, these substances undergo a process of detoxification in the liver called biotransformation, which will chemically alter the substance. The chemical is changed by the liver and the products are called metabolites. Metabolites are often more water soluble than the original substance and therefore easier to excrete. Generally, these metabolites are much less toxic to us than the original substance. Occasionally, some metabolites are actually more toxic than the original substance.

- Carcinogens, a special type of toxicants, have complex multistage effects producing cancers years after the initial exposure.

- Specific systems, including the respiratory system, liver, kidney, nervous system, immune system and reproductive system, are affected in specific ways by toxicants and carcinogens.
This chapter will show:

- the relationship of hazard and exposure in estimating risk and the importance of reducing exposure in order to reduce risk
- that all substances may be poisons and that only the right dose differentiates a poison from a safe substance or remedy
- the concept of a "no-observed-adverse-effect-level" (NOAEL)
- the concept of a "tolerable daily intake" (TDI)
- the concept of an "acceptable daily intake" (ADI)
- the difference between a "TDI" and an "ADI"
- the international convention for determining if a chemical is likely to cause cancer in humans
- the potential sources and routes of exposure in humans to toxicants and why guideline values for toxicants may not be protective of the entire population
Assessing the risks to human health that a chemical may cause is a prerequisite to planning for its safe and beneficial use.

Risk is a mathematical concept and refers to the likelihood of undesirable effects resulting from exposure to a pollutant. Risk may be expressed either in absolute terms or in relative terms. The absolute risk is the excess risk due to exposure. The relative risk is the comparison between the risk in the exposed population and the risk in the unexposed population. Safety, the opposite of risk, is a term that has been used often but is difficult to define. One definition is that safety is the practical certainty that adverse effects will not result when a substance is used in the quantity and in the manner proposed for its use.

Risk assessment is the process by which the nature and magnitude of the risk is determined. In order to estimate the “quantity of risk”, one requires the establishment of a “dose–effect relationship” in individuals and a “dose–response relationship” in populations. The dose–effect relationship provides information on how the risk increases as a function of increasing exposure.

Every chemical is toxic under certain conditions of exposure. An important corollary is that for every chemical there should be some exposure condition that is safe as regards human health and the environment, with the possible exception of chemicals that may cause cancer or cause permanent changes in the genetic material of the cell, which are unsafe at any level. The main purpose of risk assessment is to determine the level of exposure to a chemical that is considered to be without appreciable risk for human health and defined ecosystems.

Risk assessment is a scientific process that evaluates the probability (likelihood) and nature of adverse effects which may occur from exposure to a chemical. Risk management considers the results of this scientific assessment with technical, social, legal and financial factors in order to develop national chemical pollution prevention and control programmes. These programmes recognize the importance of chemicals in modern society, as well as their potential hazard, and seek to minimize exposure and reduce overall risk.

Risk assessment is resource-intensive. It requires, among other things, toxicity testing on experimental animals, exposure analysis, and epidemiological studies in exposed populations. Before embarking on a full risk assessment of a particular chemical, there must be at least an indication that the chemical is “hazardous”, i.e., is likely to cause an adverse effect under the conditions in which it is produced or used. In other words, there should at least be an indication that exposure to the chemical may be significant, and that adverse effects may occur from such exposure. Even if a chemical is inherently hazardous, if there is no exposure there will be no risk.

Within the large group of chemicals that may be considered as hazardous to human health, priorities must be established for
assessing the risks of such chemicals. Not all chemicals that are potentially hazardous are of equal importance in all countries. Because there are generally insufficient resources available to deal with all chemicals that are produced or used in a country, priorities must be established so that very limited resources are not unnecessarily diverted to risk assessment of substances of relatively minor importance.

Essential criteria for establishing priority in the selection of chemicals for risk assessment are: (a) indication or suspicion of hazard to human health and/or the environment, and type and severity of potential adverse effects; (b) likelihood that the extent of production and use may create opportunity for exposure; (c) potential for persistence in the environment; (d) potential for bioaccumulation, and (e) type and size of populations (both human and other species) likely to be exposed. A chemical of greatest priority for risk assessment would rate highly with respect to all or most of these criteria.

4.1 Methods used for assessing human health risks resulting from exposure

There are two main sources of information on health effects resulting from exposure to chemicals. The first consists of studies on human populations. The second, and the one used most often, consists of toxicity studies using laboratory animals.

Human data on the toxicity of chemicals are obviously more relevant to risk assessment than those obtained from the exposure of experimental animals. However, experiments involving controlled exposure of humans to hazardous or potentially hazardous substances are limited by ethical considerations, and information obtained from humans in typical exposure situations (epidemiological studies) must be used. The value of epidemiological studies is often limited, owing to lack of quantitative information on the concentrations to which people are exposed or on exposure to other chemicals which may take place at the same time, thereby complicating interpretation of effects. Where such information on health effects in humans is not available, as in the case of all new synthetic chemicals that have not yet been used, data must be obtained from tests on experimental animals and other laboratory procedures. In many cases, such studies with laboratory animals are the basis for predicting the toxic effects of chemicals in humans.

Figure 21 depicts the relationship between dose and the magnitude of adverse effects obtained from studies, usually in experimental animals, for different types of chemicals. Most commonly, the term “dose” is used to specify the amount of chemical administered to, or taken by an organism, usually
4.1.1 Derivation of health-based tolerable levels of exposure for humans

4.1.1.1 Threshold chemicals

The objective of the safety evaluation of chemicals in food, air or water is to determine the tolerable daily intake (TDI). The TDI is an estimate of the daily intake of a chemical which can occur over a lifetime without appreciable health risk.

Since, in the majority of cases, there are inadequate data from humans to permit calculation of the TDI, results from animal studies must often be extrapolated to humans.

4.1.1.2 Safety (or uncertainty) factor

In calculating the tolerable daily intake for a chemical, a safety factor or uncertainty factor is often applied to the NOAEL from the most appropriate study for the assessment of human health risks. The safety factor utilized reflects the confidence in the database and the degree of concern for the toxic effect. This is especially true for carcinogenic effects. Where the inherent hazard of a chemical is so great that there is a need for a very high safety factor due to concern about the safety of the chemical, it may be prudent to recommend that the chemical should not be used where exposure of humans may occur.

No hard and fast rules can be made with regard to the magnitude of this safety factor, since many aspects have to be considered, such as differences in sensitivities to the toxic effects between different species, individual variations, incompleteness of available data, and several other factors. Consideration must be given to the fact that people of all ages throughout their whole life span, the sick and the healthy, as well as children, may be exposed to the chemical, and that there are wide variations in individual exposure patterns. All of these considerations affect the selection of safety or uncertainty factors. Some considerations in selecting safety factors are illustrated in section 4.1.3.1.

The safety factor usually has a value of 100 in the case of a NOAEL derived from animal studies involving daily exposure for a lifetime (in rats, “lifetime” exposure is typically 2 years). This factor is based on the assumption that humans are ten times as sensitive as the test animal used and that there is a ten-fold range of sensitivity within the human population. When no adverse effects are seen in long-term studies, a safety factor of 100 may be applied to the NOAEL derived from short-term studies where higher dose levels have been used and an effect has been noted (e.g., a 3-month study). However, there are times when a safety factor of 100 is considered insufficient. Thus, higher safety factors may be required when the data are incomplete, when the study in which the NOAEL was established was inadequate (e.g., too few
animals), when the effects are irreversible, and especially when reproductive and effects relating to cancer are suspected. Safety factors as high as 5000–10,000 have been used by some international organizations in their safety evaluation of chemicals. Safety factors are not used for chemicals that are known to cause cancer through alteration of the genetic material because no completely safe level of exposure can be determined. These chemicals require special evaluation to allow use.

When relevant human data are available, the factor for interspecies variability is not necessary and the intraspecies safety factor, usually ten, may be applied. However, relatively few parameters are studied in humans in the assessment of chemical safety, and data on cancer, reproductive and long-term effects are rarely available. Consequently, safety factors as low as ten are rarely utilized.

4.1.2 The nature of the tolerable daily intake (TDI)

TDIs are regarded as doses of chemicals that are tolerable on a daily basis throughout life; the levels chosen are such that exceeding them for short periods of time should cause no problem.

Although the TDI can be exceeded for short periods of time, it is not possible to make generalization on the duration of the time frame which may cause concern. The likelihood that detrimental effects will occur depends on factors that vary from chemical to chemical. The biological half-life of the chemical or how long it will take the body to get rid of the chemical, the nature of the toxicity, and the amount by which the exposure exceeds the TDI are all crucial.

The large safety factors generally involved in establishing a TDI also serve to provide assurance that exposure exceeding the TDI for short time periods is unlikely to result in any deleterious effects upon health. However, careful consideration must be given to chemicals that require only a single exposure to produce acute toxic effects.

The TDI is expressed in a range, from 0 to an upper limit, which is considered to be the zone of acceptability.

4.1.2.1 Non-threshold chemicals

It is generally considered that chemical carcinogens which produce cancer through interaction with the genetic material do not have a threshold. In other words, there is a probability of harm or risk at any level of exposure. Therefore, the development of a TDI is considered inappropriate, and mathematical models are used to estimate the risk at the very low exposure levels which may occur in day-to-day situations. On the other hand, there are carcinogens that are capable of producing tumours in animals or humans.
without interaction with the genetic material, but acting through an indirect mechanism. Many scientists believe that a threshold dose, i.e., a dose below which adverse effects are not expected, exists for these non-genotoxic carcinogens.

Carcinogenic chemicals, natural or man-made, are present in the environment. In order to investigate whether a chemical may cause cancer in humans, studies are usually conducted in laboratory rats and mice, involving daily exposure for most of their lifetime (2 years for rats and 18 months for mice). Studies are conducted in both rats and mice at very high dose levels, in order to test the chemical under exaggerated conditions of exposure. These high dose levels are never intended to mimic typical human exposure. Rather these high doses are intended to maximize the chance for cancer to develop if the chemical is capable of producing this effect. Mathematical models can then be used to estimate risk at dose levels or at exposure levels that are more typical of human exposure.

In order to make the distinction with respect to the underlying mechanism of carcinogenicity, each compound that is shown to be a carcinogen should be evaluated on a case-by-case basis, taking into account the evidence of genotoxicity, the number and kinds of species in which cancer was induced, and the relevance to humans of the tumours observed in experimental animals.

Certain compounds should not be used at all if they have caused cancer in experimental animals and if high levels of human exposure can be expected from the typical use of the chemical.

Animal studies to determine the potential of a chemical to cause cancer in humans are thought to be quite reliable. All known human carcinogens that have been studied adequately in experimental animals have been shown to cause cancer in one or more animal species. For several agents (aflatoxins, tobacco, coal-tars, vinyl chloride), cancer in experimental animals was established or highly suspected even before epidemiological studies confirmed the ability of these chemicals to cause cancer in humans. Although this evidence does not prove that all agents that cause cancer in experimental animals also cause cancer in humans, nevertheless, it is generally believed that "in the absence of adequate data on humans, it is prudent to regard agents or chemicals which induce cancer in experimental animals as if they presented a cancer risk to humans". Based on this principle, the International Agency for Research on Cancer (IARC) in its overall evaluation of the carcinogenicity of chemicals, has assigned chemicals to the following groups:

Group 1 — *The agent is carcinogenic to humans.* This category is used when there is sufficient evidence of carcinogenicity in humans (e.g., aflatoxins, arsenic and arsenic compounds, benzene, soot, tobacco smoke).

Group 2 A — *The agent is probably carcinogenic to humans.* This category is used when there is limited evidence of carcinogenicity
in humans and convincing evidence of carcinogenicity in experimental animals (e.g., acrylonitrile, benzo[a]pyrene, cadmium and cadmium compounds, formaldehyde, polychlorinated biphenyls, vinyl bromide).

Group 2 B — *The agent is possibly carcinogenic to humans.* This category is used when there is only limited evidence of carcinogenicity in humans and less than convincing evidence for carcinogenicity in experimental animals (e.g., acetaldehyde, carbon tetrachloride, DDT, hexachlorobenzene, saccharin, urethane).

Group 3 — *The agent is not classifiable as to its carcinogenicity.* This category is used most commonly when the evidence for carcinogenicity is inadequate in humans and inadequate or limited in experimental animals (e.g., acrylic fibres, aldrin, aniline, captan, cholesterol, dieldrin, maneb, pulp and paper manufacture, polyvinyl chloride, vinyl acetate, zineb).

Group 4 — *The agent is probably not carcinogenic to humans.* This category is used when a chemical has been thoroughly tested but is not believed to be capable of inducing cancer in either experimental animals or humans (e.g., caprolactam).

### 4.1.3. Case studies

#### 4.1.3.1 Health-based guideline values for chemicals in drinking-water

In 1993, WHO published the *Guidelines for drinking-water quality.* Some 120 priority chemicals were selected for evaluation in the *Guidelines,* and health-based levels of exposure from drinking-water (guideline values) were recommended for 95 of these. The selection of chemicals for evaluation was guided by three main criteria:

- the substance presented a potential hazard for human health;
- the substance was known to be present frequently and at relatively high concentrations in drinking-water;
- the substance was of international concern (i.e., of interest to several countries).

Guideline values were not recommended for certain substances because they were found not to be hazardous to health, because of inadequate health effects information, or because the concentration of the chemical normally found in drinking-water does not represent a hazard to human health. Contaminants evaluated included a wide range of chemicals used in industry and agriculture.

For chemicals exhibiting a threshold for toxic effects, the guideline values were derived by using the following methodology:

- Development of a tolerable daily intake (TDI) on the basis of interpretation of the available data on toxicity. The TDI is
developed by applying an uncertainty factor to the NOAEL or LOAEL.

- The assumption that a proportion of total daily exposure to the chemical, and hence the TDI, will come from intake of drinking-water. The relative allocation was based on information on the relative exposure via different routes (air, food and water).

This methodology is depicted in the following two equations:

\[
\frac{NOAEL}{UF} = TDI
\]

\[
\frac{TDI \times bw \times P}{C} = GV
\]

where:

- **NOAEL** = no-observed-adverse-effect level — the greatest dose of a chemical, found by experiment or observation, which causes no detectable adverse health effect. If a NOAEL was not available, the lowest-observed-adverse-effect level (LOAEL) was used with a corresponding increase in the uncertainty factor (UF). The LOAEL is the lowest dose of a substance which causes a detectable adverse health effect.

- **UF = uncertainty factor** — a value by which the NOAEL (or LOAEL) is divided to derive a tolerable daily intake (TDI). The value of the uncertainty factor depends on the nature of the toxic effect, the size and type of population to be protected and the quality of the toxicological information, and it is decided upon on a case-by-case basis. Uncertainty factors from 1 to 10,000 were used.

The basis of the UF is usually as follows:

<table>
<thead>
<tr>
<th>Source of uncertainty</th>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interspecies variation (animals to humans)</td>
<td>1–10</td>
</tr>
<tr>
<td>Intraspecies variation (variation insensitivity between members of the same species)</td>
<td>1–10</td>
</tr>
<tr>
<td>Adequacy of studies or database</td>
<td>1–10</td>
</tr>
<tr>
<td>Nature and severity of effect</td>
<td>1–10</td>
</tr>
</tbody>
</table>

If the available information suggests that an uncertainty factor higher than 10,000 is required, then the resulting TDI would be so imprecise as to lack meaning. Such a situation indicates an urgent
need for additional data and that a reliable estimate of risk cannot be made on the basis of the available information.

- **TDI** = *Tolerable daily intake* — an estimate of the amount of a contaminant substance in food and drinking-water, expressed on a body weight basis (mg or µg/kg of body weight), that can be ingested daily over a life-time without appreciable health risk.

- **bw** = *Body weight* (kg) — usually the body weight of an adult (60 kg). Where infants and children are especially at high risk, body weights of 5 kg or 10 kg were used.

- **P** = *Percentage* of the TDI allocated to drinking-water, expressed as a fraction. The allocation was based on information on relative exposure via different routes. Values ranging from 0.01 to 1 were used depending on the magnitude of exposure from food and air. When information on sources of exposure was limited, a default value of 10% of the TDI was used.

- **C** = *Daily drinking-water consumption* — 2 litres for adults, 1 litre for a 10 kg child and 0.75 litre for a 5 kg infant.

- **GV** = *Guideline value* in mg or µg per litre of drinking-water.

For non-threshold chemicals, such as those that may produce cancer through interaction with the genetic material (genotoxic carcinogen), a conservative mathematical model was generally adopted in the development of guideline values. Estimated risks were based on a 60-kg person drinking 2 litres of water per day for a lifetime of 70 years. The guideline value is the concentration in drinking-water that would not be expected to increase the excess lifetime cancer risk by more than one additional cancer per 100,000 of the population ingesting drinking-water containing the substance at the guideline value for 70 years. This excess lifetime cancer risk is an arbitrary value and it is up to an individual country to select its own acceptable excess cancer risk. Concentrations associated with estimated excess lifetime cancer risks of one in ten thousand and one in a million can be calculated by multiplying and dividing, respectively, the guideline value by 10.

It should be emphasized that guideline values for carcinogenic substances computed using mathematical models must be considered at best as a rough estimate of cancer risk. Uncertainties involved may produce errors of a hundred fold or more. However, the use of a conservative mathematical model tends to over-estimate risks at low doses typical of human exposure, giving higher estimates of cancer risk than will many other models; the actual risk might be zero. Moderate short-term exposure to levels exceeding the guideline value for carcinogens does not significantly affect the overall lifetime risk.
Examples of WHO recommended guideline values for chemical contaminants in drinking-water are given in Table 18.

Table 18. Guideline values (GV) for selected contaminants in drinking-water

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Guideline value (mg/litre)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic</td>
<td>0.01</td>
<td>For excess skin cancer risk of $6 \times 10^{-4}$ (provisional GV).</td>
</tr>
<tr>
<td>Cadmium</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Fluoride</td>
<td>1.5</td>
<td>Climatic conditions, volume of water consumed, and intake from other sources should be considered when setting national standards.</td>
</tr>
<tr>
<td>Lead</td>
<td>0.01</td>
<td>It is recognized that not all water will meet the guideline value immediately; meanwhile, all other recommended measures to reduce the total exposure to lead should be implemented.</td>
</tr>
<tr>
<td>Mercury (total)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Nitrate</td>
<td>50</td>
<td>As nitrate ion.</td>
</tr>
<tr>
<td>1,2-Dichloroethane</td>
<td>0.03</td>
<td>For an estimated excess cancer risk of $10^{-5}$.</td>
</tr>
<tr>
<td>DDT</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Chloroform</td>
<td>0.2</td>
<td></td>
</tr>
</tbody>
</table>

4.1.3.2 Health-based guideline values for chemicals in air

Various chemicals are emitted into the air from both natural and anthropogenic sources. The quantities may range from hundreds to millions of tonnes annually. Natural air pollution stems from various biotic and abiotic sources (e.g., plants, radiological decomposition, forest fires, volcanoes and other natural sources, emissions from land and water), leading to a natural background concentration that varies according to local sources or specific weather conditions. Man-made air pollution has existed at least since people learned to use fire, but it has increased rapidly since industrialization began. The increase in air pollution as a consequence of the expanding use of fossil energy sources and the growth in the manufacture and use of chemicals has been accompanied by mounting public awareness and concern about its detrimental effects on health and the environment.

The impact of air pollution is broad. In humans, chemicals that are inhaled into the lung and absorbed into the body can have direct consequences for health. However, public health can also be indirectly affected by the deposition of air pollutants in plants, animals and the other environmental media. This results in chemicals entering the food chain or being present in drinking-water and thereby represents additional potential sources of human exposure. Furthermore, the direct effects of air pollutants on plants, animals and soil can influence the structure and function of
ecosystems, including their natural self-regulating ability, thereby affecting the quality of life.

Air pollutants can cause several effects which require attention: irritation, odour annoyance, and short- and long-term health effects (including carcinogenic effects). *Air Quality Guidelines* (AQG) have been developed by the World Health Organization, and they provide a basis for protecting public health from adverse effects of air pollution. The guideline values given in the AQG indicate levels combined with exposure times at which no adverse effect is expected concerning non-carcinogenic endpoints. Alternatively, they provide an estimate of lifetime cancer risk arising from those substances that are proven human carcinogens or carcinogens with at least limited evidence of human carcinogenicity (see section 4.1.2.1). However, compliance with the guideline values does not guarantee that effects will not occur at levels below such values. For example, highly sensitive groups especially impaired by disease or other physiological limitations may be affected at or near the guideline concentrations normally considered to be safe for most of the population. Health effects at or below guideline values can also result from combined exposure to various chemicals or from exposure to the same chemical from various sources and routes (air, food, water).

The AQG deal with single chemicals. Chemicals, in mixtures, can have additive, synergistic or antagonistic effects; however, knowledge of these interactions is generally quite poor. With a few exceptions, such as the combined effect of sulfur dioxide and minute particles in air, there is insufficient information at present to establish guidelines for mixtures.

### 4.1.3.3 Procedures for establishing air quality guideline values

For compounds without carcinogenic effects, the starting point for the derivation of guideline values was to define the lowest concentration at which effects are observed in humans, animals and plants (lowest-observed-adverse effect level, LOAEL). In the case of irritant and sensory effects on humans, the no-observed-adverse-effect level (NOAEL) was determined. Considerable scientific judgement is used to determine the LOAEL or NOAEL.

The development of a toxic response is a complex function of the interaction between the amount of exposure and the frequency and duration of exposure. A chemical may cause acute, minor, reversible effects after brief exposure and irreversible or incapacitating effects after prolonged exposure. Generally, when short-term exposures lead to adverse effects, short-term averaging times are recommended. The use of a long-term average exposure under such conditions would be misleading, since the typical pattern of repeated high exposures is averaged over time and the risk manager may have difficulty in deciding on effective
strategies. In other cases, exposure–response knowledge is sufficient to recommend a long-term average. This frequently occurs for chemicals that accumulate in the body over time, thereby resulting in adverse effects. In such cases, repeated exposure even at lower levels can have more impact than the pattern of high intermittent exposure.

A similar situation occurs for effects on vegetation. Plants are generally damaged by short-term exposures to high concentration as well as by long-term exposures to low concentration. Therefore, both short- and long-term guidelines to protect plants are proposed (see section 5.3).

In the AQG, the risk associated with lifetime exposure to a certain concentration of a carcinogen in the air has generally been estimated by models that assume some risk at every exposure level.

The choice of the mathematical model selected depends on the current understanding of the mechanisms of cancer induction. No single mathematical procedure can be regarded as fully appropriate for estimating risks at dose levels typical of human exposure. Models which assume that every level of exposure carries some risk have been used at the international and national level more frequently than models which assume a safe or virtually safe threshold.

Calculations expressed in unit risk estimates provide the opportunity to compare the carcinogenic “potency” of different agents and can help to set priorities in pollution control according to the existing exposure situation. By using a unit risk estimate, any reference to the acceptability of risk is avoided. The decision on the acceptability of a risk should be made by national authorities in the framework of risk management.

Examples of air quality guideline values are given in Tables 19 and 20.

<table>
<thead>
<tr>
<th>Substance</th>
<th>Guideline value</th>
<th>Allowable duration of exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon monoxide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 mg/m³</td>
<td>15 minutes</td>
<td></td>
</tr>
<tr>
<td>60 mg/m³</td>
<td>30 minutes</td>
<td></td>
</tr>
<tr>
<td>30 mg/m³</td>
<td>1 hour</td>
<td></td>
</tr>
<tr>
<td>10 mg/m³</td>
<td>8 hours</td>
<td></td>
</tr>
<tr>
<td>Lead</td>
<td>0.5–1.0 µg/m³</td>
<td>1 year</td>
</tr>
<tr>
<td>Nitrogen dioxide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>400 µg/m³</td>
<td>1 hour</td>
<td></td>
</tr>
<tr>
<td>150 µg/m³</td>
<td>24 hours</td>
<td></td>
</tr>
<tr>
<td>Ozone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>150–200 µg/m³</td>
<td>1 hour</td>
<td></td>
</tr>
<tr>
<td>100–120 µg/m³</td>
<td>8 hours</td>
<td></td>
</tr>
<tr>
<td>Sulfur dioxide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>500 µg/m³</td>
<td>10 minutes</td>
<td></td>
</tr>
<tr>
<td>350 µg/m³</td>
<td>1 hour</td>
<td></td>
</tr>
</tbody>
</table>
4.1.4 Safety evaluation of chemicals in food

The World Health Organization has for some 40 years been involved in the safety evaluations of food additives and contaminants, veterinary drugs and pesticide residues in food. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) deals with the first three items, while the Joint FAO/WHO Meeting on Pesticide Residues (JMPR), as its title indicates, deals with pesticide residues in food. These two expert committees provide estimates of the maximum daily intake of a substance that will not result in adverse effects at any stage in the human life span. These estimates, termed Acceptable Daily Intakes (ADIs), are then used by national regulatory agencies and by the Codex Alimentarius Commission to establish safe levels of these substances in foodstuffs.

The data used by JECFA and JMPR in the assessment of the toxicity of chemicals in food generally comprise studies on animals, including acute studies, short-term studies in which the toxicant is administered in the diet (feeding studies), long-term feeding studies, and biochemical studies (including absorption, tissue distribution, excretion, metabolism, biological half-life, and effects on enzymes). In addition, studies on specific effects, e.g., carcinogenicity, reproduction, teratogenicity (birth defects) and, for some compounds, neurotoxicity are usually necessary. Human data are also considered whenever available.

The overall objective of the evaluation is to determine a no-observed-adverse-effect level (NOAEL), based upon consideration of the total toxicological data available. The NOAEL is then utilized in conjunction with an appropriate safety factor to determine the ADI.

The ADI is defined as an estimate of the amount of a substance in food or drinking-water, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk. The ADI concept is used for food additives, veterinary drugs and pesticides that have necessary technological or food production purposes. Trace contaminants such as lead, cadmium
or mercury have no intended function, so JECFA uses the term “tolerable” intake, which signifies permissibility rather than acceptability for the intake of contaminants unavoidably associated with the consumption of otherwise wholesome and nutritious food. In this convention, tolerable intakes are expressed on a weekly basis, because the contaminants given this designation may accumulate within the body over a period of time. On any particular day, consumption of food containing above-average levels of the contaminant may exceed the proportionate share of its weekly tolerable intake.

When a substance is identified with confidence as a human carcinogen, neither JECFA nor JMPR establish an ADI. JMPR has sometimes recommended that certain compounds should not be used where residues may occur in food, due to their carcinogenicity (e.g., hexachlorobenzene, captan). Similarly, when JECFA considered the low-level migration of carcinogenic contaminants from food packaging material to food, it did not consider it appropriate to establish an ADI for such materials. It recommended that human exposure to known carcinogenic migrants (e.g., vinyl chloride) from food-contact materials be restricted to the lowest levels technologically attainable.

Yearly evaluations of chemicals in food are performed by JECFA and JMPR. To date, JECFA has evaluated over 700 food additives, 60 veterinary drugs and more than 20 food contaminants, such as lead, cadmium, mercury, aflatoxins and styrene. JMPR has evaluated some 220 pesticides. Risk managers should be well aware of these evaluations to ensure that established maximum acceptable or tolerable intake levels are not being exceeded by the population due to the absence of appropriate regulatory or compliance measures or because of excessive levels of such substances in the food supply.
After reading this chapter you should be aware that:

- Both hazard and exposure are key components in estimating risk. Chemicals which pose only a small hazard but to which there is frequent and excessive exposure may pose as much risk as chemicals which have a high degree of hazard but to which only limited exposure occurs.

- Risk mitigation is often directly related to effective exposure reduction practices. For example, some agricultural chemicals necessary for food production purposes may be inherently hazardous, but their use may pose little or no risk to applicators if effective exposure reduction strategies are utilized.

- The no-observed-adverse-effect level (NOAEL) is the maximum concentration or dose of a chemical which causes no observed adverse effects in the test population.

- The lowest-observed-adverse-effect level (LOAEL) is the lowest dose which produces an adverse effect in a test population.

- The virtually safe dose (VSD) is that dose of an otherwise hazardous chemical which is so low that it is not considered to pose a risk to humans even with daily lifetime exposure.

- The tolerable daily intake (TDI) is an estimate of the daily intake of a chemical contaminant which can occur over a lifetime without appreciable health risk. The concept of a TDI generally applies to unavoidable and undesirable contaminants which have no useful purpose.
The acceptable daily intake (ADI) is an estimate of the daily dose of a substance that is anticipated to be without appreciable health risk to humans when taken daily over the course of a lifetime. The concept of the ADI generally applies to residues of chemicals which have been used in the production of food and the use of which contributes to residues in food production.

The ADI concept is used for food additives, veterinary drugs, and pesticides that have useful food production purposes. The term "tolerable" in the TDI concept is intended for trace contaminants which have no useful purpose. The term "tolerable" is intended to signify the possibility rather than acceptability.

In the absence of data in humans, the contrary, chemicals that can induce cancer in experimental animals should be regarded as if they could induce cancer in humans.

Exposure to chemical pollutants may occur in the air we breathe and as contaminants or residues in the water and food we eat. On any exposure is due to a combination of all three. Guideline values for chemical contaminants may not be adequate to protect the very young, the infirm, those with underlying disease, or the very old.
5. ENVIRONMENTAL EFFECTS OF CHEMICALS

This chapter will show:

- how chemicals affect aquatic, freshwater and terrestrial environments when exposure occurs

- how the release of chemicals into the environment can have global impacts. Chemicals can be transported throughout the atmosphere and are not bound by political borders.

- how chemicals cause problems like acid rain, ozone depletion and enhancement of the greenhouse effect

- how global warming is a concern to scientists and to people worldwide

- that methods are available to reduce emissions of harmful gases that cause acid rain and ozone depletion

- how an international treaty, the Montreal Protocol, was drawn up to avoid the predicted catastrophic effects of ozone depletion
Hazardous chemicals not only have adverse effects on human health but can also disrupt ecological systems that exist in rivers, lakes, oceans, seas, estuaries, wetlands, forests and soils. The discoveries of a growing hole in the stratospheric ozone layer, evidence of the enhanced greenhouse effect, which causes an increase in global temperatures, and acid rain, which damages lakes, streams and forests, have forced us to recognize that chemical contamination and pollution is not just a regional problem but a worldwide concern. Ecological systems across the globe can be affected.

5.1 Chemicals and the aquatic environment

The contaminants that pose the greatest threat to the aquatic environment are sewage, excess nutrients, synthetic organic compounds, litter, plastics, metals, oil/hydrocarbons and polycyclic aromatic hydrocarbons (PAHs). Many of the polluting substances originating from land-based sources, such as pesticides and metals, are of particular concern to the marine environment since they exhibit both toxicity and persistence and are known to bioaccumulate in the food chain.

5.2 Chemicals and freshwater ecosystems

Untreated sewage, discharges of toxic industrial chemicals, poorly selected sites of industrial plants and/or solid waste landfills, and poor agricultural practices in the use of fertilizers and pesticides may damage aquatic ecosystems and threaten freshwater resources.

Nutrient overloading of water bodies, primarily with nitrogen and phosphorus, causes eutrophication of lakes and reservoirs by promoting excessive plant growth (algal blooms). The algal blooms then deplete oxygen composition of water as they decompose. Adequate dissolved oxygen content (DOC) in water is universally critical to aquatic life.

Guidelines for the protection of aquatic life have been developed by several national authorities. As an example, the Canadian Water Quality Guidelines recommend safe concentrations of chemicals in water for the protection of freshwater aquatic life. In many cases, freshwater aquatic life is more susceptible than humans to the adverse effect of chemicals. Some examples of the Canadian guidelines are shown in Table 21.
Table 21. Canadian Water Quality Guidelines for freshwater aquatic life

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Guideline (µg/litre)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminium</td>
<td>5–100</td>
<td>depending on pH, calcium and dissolved oxygen concentration</td>
</tr>
<tr>
<td>Cadmium</td>
<td>0.2–1.8</td>
<td>depending on hardness of water</td>
</tr>
<tr>
<td>Chlorine</td>
<td>2</td>
<td>as total residual chlorine</td>
</tr>
<tr>
<td>Copper</td>
<td>2–4</td>
<td>depending on hardness of water</td>
</tr>
<tr>
<td>DDT</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Endrin</td>
<td>0.002</td>
<td></td>
</tr>
</tbody>
</table>

5.3 Effects on terrestrial ecosystems

Vegetation is recognized as a sink for atmospheric pollution. Most of the major urban air pollutants such as nitrogen oxides, ozone/photochemical oxidants and sulfur oxides are known to have adverse effects at low levels on plants, including food crops. Nitrogen dioxide is the most phytotoxic oxide of nitrogen. Foliar injury is often caused by mixtures of nitrogen dioxide with sulfur dioxide and/or ozone at threshold concentrations much lower than those for individual pollutants. The main consequence of pollutant mixtures is a reduction of plant growth. Among the terrestrial ecosystems that are considered most threatened by nitrogen compounds are coniferous forests, especially those at higher altitudes.

WHO has recommended that, in order to protect sensitive plants from direct effects of nitrogen dioxide (in the presence of levels of sulfur dioxide and ozone not higher than 30 µg/m³ and 60 µg/m³, respectively), the nitrogen dioxide concentration should not exceed 30 µg/m³ as a yearly average of 24-hour mean values. However, limiting the one-year average level of pollutants does not protect the environment effectively against peak values. Therefore peak concentrations should also be limited. Sensitive plants are protected against the adverse effects of nitrogen dioxide if the average concentration over 4 hours does not exceed 95 µg/m³ (in the presence of similar concentrations of sulfur dioxide).

5.4 Global environmental impacts of chemicals

As we have seen in the first chapter, air pollutants are found throughout our atmosphere. Atmospheric chemicals have far-reaching effects and are involved in the acidification of lakes, rivers and other water bodies, in ozone depletion, and other atmospheric reactions. The acidification of lakes and other water
bodies and the possible depletion of the ozone layer through atmospheric pollution are matters of great current concern.

5.4.1 Acid rain

"Acid rain" is rain that has a lower pH than normal. Normal rain has a pH of 5.6, due mainly to the dissolution of CO₂ in water. Rain becomes acidic when gaseous oxides of sulfur and nitrogen (SO₂ and NOₓ) dissolve in the rain, lowering the pH to < 4.0. SO₂ and NOₓ are more soluble in water than CO₂ and also form stronger acids.

Acid rain is a regional problem, but the effects are not restricted by borders. The acid gases can be produced in one country and then transported to another country by atmospheric circulation over large distances. Large, modern fossil-fuelled power stations are constructed away from cities, and use high chimneys (called "super-stacks", which are up to 500 metres in height) to disperse the pollutants produced by combustion. This lowers the exposure of nearby inhabitants, but favours the long-distance transport of the pollutants. Thus, acidic precipitation can occur far away from the emission point. The dramatic deterioration in the health of forests in many parts of Europe (e.g., the Black Forest in Germany) has been linked to the emission of air pollution and acid rain.

5.4.1.1 Sources of SO₂ and NOₓ

The major sources of SOₓ and NOₓ, the precursors of acid rain, are the following:

a) combustion of coal — coal naturally contains 2–3% sulfur (the actual amount depends on the type of coal). When coal is burned, the sulfur combines with oxygen to form SO₂.

b) smelting of sulfide ores (smelting is carried out to recover the metal from the ore).

c) combustion of fuels (petrol, oils).

Over 90% of the total global man-made emissions of sulfur dioxide originates from the northern hemisphere. In tropical regions natural emissions from soils, plants, the burning of biomass and volcanoes are believed to be the predominant sources of sulfur dioxide.

5.4.1.2 Reactions important in the formation of acid rain

Normal rain \[ \text{CO}_2 + \text{H}_2\text{O} \rightarrow \text{H}_2\text{CO}_3 \] (the acid normally found in rainwater)

Acid rain \[ \text{SO}_2 + \text{H}_2\text{O} \rightarrow \text{H}_2\text{SO}_3 \] (a weak acid)
\[ \text{SO}_2 + \frac{1}{2} \text{O}_2 \rightarrow \text{SO}_3 \]
\[ \text{SO}_3 + \text{H}_2\text{O} \rightarrow \text{H}_2\text{SO}_4 \] (a strong acid)
5.4.1.3 Effects of acid rain

- **Human health:** high levels of acid rain may cause respiratory distress.
- **Vegetation:** SO$_2$ is toxic to plants, causing cessation of growth at concentrations >0.1 ppm. Very few plants can tolerate acidic soils.
- **Buildings:** acid rain causes disintegration of buildings made of limestone and marble. Iron and steel structures corrode at accelerated rates when exposed to acid rain. Many historic buildings are now being damaged by the corrosive properties of acid rain, e.g., the Parthenon (Athens, Greece) and the Great Pyramids (Egypt).
- **Natural waters:** aquatic organisms may be sensitive to the effects of acid rain. Acidification of lakes is a problem in areas where granite is the underlying rock. Limestone lakes are naturally buffered against the effects of acid rain. The acid levels of lakes may also increase during the spring, when snow melts. Some regions in North America and Europe have lakes with such a low pH that they can no longer support fish and other aquatic life.
- **Increased metal concentrations in water:** metallic compounds are often formed when the metals from underlying rock form salts with sulfuric acid. These metals may be toxic to humans and animals.

5.4.1.4 Solutions to reduce acid rain

Because we depend on coal and other fossil fuels for energy, there is little that can be done to eliminate acid rain apart from the complete cessation of the use of these fuels. Hopefully, in the future, new technologies developed by scientists and engineers will solve this problem. Below are just some of the possible methods that are currently used to reduce the likelihood of acid rain.

- Reduction in emissions of SO$_2$ and NO$_x$. This can be done by using catalytic converters in automobile exhaust systems. Catalytic converters help turn the harmful exhaust gases into non-harmful products.
- Burning cleaner fossil fuels with reduced sulfur content (e.g., switch to natural gas).
- Conversion of SO$_x$ into usable or harmless substances (e.g., sulfuric acid).
- Chemical removal of SO$_x$ from effluent gas via scrubbing techniques. Scrubbing the gases means using a base to neutralize the acid gases. Usually calcium hydroxide is employed to do this.
- Removal of sulfur from coal before combustion using “oil filtration methods”.

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5.4.2 Stratospheric ozone depletion

Ozone (O₃) is continuously produced and destroyed in the stratosphere through complex photochemical reactions. In the absence of human interference, the balance between production and destruction results in a constant amount of stratospheric ozone. The ozone layer plays an extremely important role in absorbing the biologically damaging fraction of the ultraviolet light coming from the sun. This absorption shields the earth from a major portion of radiation which, if received in full, would be damaging to life. By the mid-1980s, evidence presented by scientists showed an “Antarctic ozone hole” which developed in late winter and had local depletions of stratospheric ozone of up to 50%. The consequences are discussed in the next section.

5.4.2.1 Effects of ozone depletion

The potential effects of increased levels of ultraviolet light reaching the Earth’s surface include health problems in the form of skin cancer, cataracts and depressed immunity to disease. It can also cause damage to marine food chains, crops and materials such as plastics and paints used outdoors. Ozone depletion has other far-reaching effects: the potential for increased global warming and air pollution, and even genetic mutations. Figure 23 shows how the increased ultraviolet light (wavelength 280–315 nm) and change in climate caused by depleted ozone will affect life on earth.

5.4.2.2 Causes of ozone depletion

The reduction in the ozone has been caused, in part, by the release of chlorofluorocarbons (CFCs), which were widely used as refrigerants, propellants, plastic foam blowers and cleaning agents for electronic circuitry. Other substances, including fire-fighting gases and solvents such as carbon tetrachloride (CCl₄), also contribute by interacting photochemically with ozone in the stratosphere. All are extremely stable substances, persistent in the lower atmosphere and can be found worldwide. Once released into the atmosphere they diffuse through the lower troposphere and into the upper stratosphere, where they interact chemically with ozone and destroy it.

5.4.3 The Montreal Protocol

Awareness of the ozone depletion problem was reflected in the signing in 1987 of the “Montreal Protocol on substances that deplete the ozone layer”. This international treaty set targets for CFC production to be cut back to 50% of 1986 levels (considered the baseline) by 1998. Further amendments have been made to strengthen the original terms of the Montreal Protocol, so that a complete phase-out of the most damaging “hard” CFCs such as
Figure 23. Ozone depletion effects
After reading this chapter you should be aware that:

- CFCs are chemicals not only have adverse effects on human health but also disrupt ecological systems that exist in rivers, oceans, farms, wetlands, forests and soils.

- Atmospheric can effect many environments including aquatic, groundwater and terrestrial ecosystems.

- Acid rain is caused by the combustion of coal and other substances containing substances. This problem effects vegetation, human health, forests and fresh waters, and causes many other environmental problems.

- Several methods are available for reducing emissions of acid rain, including the burning of cleaner fossil fuels, dilution of the pollutants in the atmosphere, and removal of sulfur from coal and other fuels. Each has its benefits and all have their associated costs. In the future, new technologies will help improve our efforts in reducing acid air emissions.

- Ozone depletion in the upper stratosphere is a worldwide problem, and one that requires cooperation by world leaders. The Montreal Protocol, which was an international treaty signed by many countries, was designed to reduce the release of CFCs, which are thought to be harmful to the ozone layer. Although the adverse consequences were not actually observed, politicians accepted scientists predictions of catastrophic effects.
6. ENVIRONMENTALLY SOUND MANAGEMENT OF TOXIC CHEMICALS

This chapter will show:

- the importance of the environmentally sound management of chemicals from manufacture to disposal

- the advantages of preventing pollution rather than treating it after it has occurred

- the definition and role of a health and environmental impact assessment (HEIA)

- the role of enforcement in achieving national standards of safety

- the intent of the FAO "Prior Informed Consent" procedure

- the role and responsibility of the FAO/WHO Joint Meeting on Pesticide Residues (JMPR)

- how to achieve the benefits of pesticide use while minimizing the risks to the environment and human health
Introduction

The environmentally sound management of toxic chemicals requires proper management of a chemical from when it is first manufactured to when it is disposed (often referred to as cradle-to-grave or life-cycle management). A chemical may pose serious risks through occupational exposure, air and water pollution, groundwater and food contamination, or generation of hazardous solid wastes.

Strategies for the environmentally sound management of toxic chemicals are as varied as the chemicals that enter the environment. However, certain broad strategic principles and actions are common. They generally apply to the safe manufacture, storage, transport, use and disposal of hazardous chemicals to prevent or reduce their adverse effects on human health and the environment.

6.1 Prevention

The strategy of choice in a national programme for the sound management of hazardous chemicals is first and foremost that of anticipating and preventing the release of toxic chemicals into the environment rather than relying on an “after-the-fact” approach of remediation and treatment.

Several pollution prevention strategies can be adopted to protect human health and prevent environmental degradation. These include:

- encouraging and promoting greater efficiency in the use of energy;
- using fuel low in sulfur content;
- recycling in industrial processes to reduce hazardous waste generation thereby reducing the cost of disposal;
- reducing wasteful packaging of products, which also reduces the cost of disposal of unnecessary packaging;
- developing alternative manufacturing technologies to minimize solid, liquid and gaseous wastes;
- minimizing the use of pesticides through good agriculture practices and integrated pest management;
- promoting cars with catalytic converters to reduce the quantity and toxicity of gaseous emissions;
- promoting adequate public transportation systems to reduce the use of individual cars;
- legislation and enforcement to provide meaningful incentives to achieve the above objectives and to prevent imports of hazardous chemicals that have been banned or severely restricted in exporting countries.

In order to predict reliably and to prevent potential adverse effects from hazardous chemicals, a health and environmental
impact assessment (HEIA) must be a prerequisite for any major industrial development project. The HEIA is a comprehensive study to evaluate, anticipate and prevent the ways in which a chemical production facility will affect the local community and environment. It concerns not only the media (air, water, soil) but also traffic patterns, further land utilization in the area, and aesthetic considerations in the community. The assessment should provide opportunities:

- to include health and environmental considerations in project plans;
- to identify the most appropriate location for a plant and its design characteristics;
- to choose a process to minimize wastes and, hence, reduce costs;
- to incorporate control measures to prevent pollution rather than to control it after the fact;
- to provide for emergency response where appropriate.

The HEIA must include a preliminary appraisal of the sources and levels of emissions from the proposed facility, an essential step towards the development of techniques to control environmental pollution and to protect workers. It is more cost-effective to foresee and plan for the effective control of the release of chemicals into the environment than to subsequently fit an operating plant to control such a release.

Examples of information required in an HEIA are: explosion and fire hazards of the products and raw materials used; rate and amount of expected release of hazardous chemicals in air, water and land; expected exposure of workers and the public to such chemicals; the range and magnitude of health and environmental risks; and the likelihood of failure of equipment, explosions and natural disasters at the selected site. Where air or water quality standards exist, it is important that measures be incorporated into the operation of the plant to ensure compliance with such standards. Regular monitoring should be carried out to ensure continuing compliance with appropriate standards.

6.2 Control technology

Controlling a particular chemical requires the selection of economically feasible technology that will reduce exposure (and hence risks) to acceptable levels. Strategies to reduce exposure to chemicals, and hence risks, must be cost-effective, and health and environmental quality objectives must be realistic if they are to be achieved.

It is fundamentally incorrect to believe that "the solution to pollution is dilution". The dilution effect might not result in a safe concentration of the contaminant and, as noted above, preventing
pollution is often more cost-efficient and effective when applied at the source to prevent release than when the pollutant has been dispersed in the environment. For instance, it is less costly and more technologically practical to remove a chemical from an industrial wastewater effluent, where it is in a concentrated phase, than to remove it from a drinking-water supply source where it has been diluted in the receiving waters.

There are many different technologies available to control emissions of hazardous chemicals from high-pollution industries such as iron and steel, chemicals, textile manufacture and energy production. For instance, sulfur and nitrogen compounds are amenable to "scrubbing" from smokestack gases, chromium can be removed from leather tannery wastewater by electrodeposition or by coagulation with chemical addition followed by sedimentation, and dust from iron foundries or cement manufacturing can be removed by fabric filters, electrostatic precipitators and wet collectors of various types. Each industry has available its own specific physical, biological and/or chemical treatment methods to control or prevent, at a reasonable cost, hazardous chemical emissions.

In addition to treatment methods, methods for taking emergency containment and clean-up action and for warning the surrounding community must be well developed in order to handle any accidents that do occur.

### 6.3 Regulations, Incentives and Standards

The primary aim of establishing regulations and standards is to protect public health and to eliminate or reduce to an acceptable level exposure to toxic chemicals. Regulations should be clear, simple to understand, and govern such matters as treatment requirements for industrial waste streams. They should prevent air and water pollution, setting standards for chemicals in air, food and water, and they should set exposure limits for workers and limits on the quantity of toxic chemicals that may be present in solid wastes to be discharged on land. However, standards and regulations achieve nothing unless they can be implemented and enforced. This requires facilities, technical knowledge and expertise, and the appropriate legislative framework.

The establishment of national standards must follow a very careful process in which the health risk is considered together with other factors, such as technical and economic feasibility. When establishing national standards, consideration must be given to the practical measures needed to institute certain types of control technology and to provision for adequate monitoring and enforcement.
All chemicals are not of equal concern and there are generally insufficient resources available to deal with all chemicals that may be present in the environment. It is thus necessary to establish priorities for regulations. Several criteria can be applied in determining the priority for chemical regulation. These include:

- severity and frequency of observed or suspected adverse health effects; of special importance are chemicals that cause irreversible damage such as cancer or reproductive and birth defects;
- extent of production and use;
- abundance and persistence in the environment; chemicals that are present frequently and at significant concentrations in the environment, as well as those that do not break down easily in the environment and accumulate in humans, or in air, water or food, deserve priority attention;
- population exposed; attention should be paid to exposure involving a large proportion of the general population and to exposure of highly sensitive groups such as pregnant women, newborn children, the infirm and the elderly.

Incentives such as the “Polluter Pays” principle have convinced many industrial establishments to control their hazardous emissions. The principle consists of requiring that the polluter pays the cost of pollution damage, including damage to health. The charges for the full health and environmental costs should be reasonable but sufficiently high that polluters do not simply consider the cost as the price for doing business (in other words a “Pay to Pollute” principle).

Any industry generating hazardous chemicals must comply with regulations and standards established by the government. It is essential to monitor compliance with these limits and regulations. Various means can be used, such as permits, to operate with inspection of the industrial facility, or environmental monitoring of the regulated chemical. Future land-use management through zoning or other measures should also be a consideration. In the end, it is always important to remember that the best solution is prevention and that it is almost always more effective and less costly to prevent an environmental disaster than to correct one.

Regulations can include the phasing-out or banning of toxic chemicals that pose an unacceptable and unmanageable risk to human health or the environment. Regulations must also be established to prevent accidents, and should include specific plans for emergency response procedures.

6.4 **Pesticides — A Regulatory Definition**

A pesticide is any substance or mixture of substances intended to prevent, destroy or control pests. Pests include vectors of human or animal disease, unwanted species of plants, and animals that
interfere with the production, processing, storage, transport or marketing of food, agricultural commodities, wood and wood products or animal feedstuffs. Pesticides also include chemicals that may be administered to animals for the control of insects, arachnids or other pests in or on their bodies. They also include substances intended for use as plant growth regulators, defoliants, desiccants or agents for thinning fruit or preventing the premature fall of fruit, as well as substances applied to crops either before or after harvest to protect them from spoilage during storage and transport.

Pesticides may be named according to the target species of pests they are designed to kill, such as insecticides, larvicides, fungicides, rodenticides, acaricides, molluscicides, herbicides, avicides, nematocides. They are also named according to the chemical class to which they belong: organochlorine, organophosphorus, thiocarbamate, pyrethroid, phenoxy, etc. DDT is an organochlorine insecticide. A pesticide that is distributed in the air is called a fumigant.

Pesticides consist of an active ingredient (the pesticide chemical), which is usually mixed with other chemicals to facilitate its use and application. It is then known as a formulation. Formulations usually need further dilution.

6.4.1 Environmentally sound management of pesticides

Among the wide variety of chemicals that can endanger health and the environment, pesticides stand in a prominent place. Although they are intended to destroy or control an undesirable insect, plant or other species, at the same time they are often a necessity for food production and public health protection, as in malaria control. Pesticides may be misused but, through some key action programmes, the safe and beneficial use of pesticides has been achieved in many countries of the world.

Because of international concern for the potential health and environmental impacts of pesticides, the Food and Agriculture Organization of the United Nations (FAO) has published the *International Code of Conduct on the Distribution and Use of Pesticides* (1990). The Code of Conduct should serve as a point of reference in the regulation, marketing and use of pesticides, and it should be of particular value to countries which do not yet have adequate means for controlling the importation, distribution, storage, formulation and disposal of pesticides.

The Code of Conduct includes provisions for “Prior Informed Consent” (PIC), a procedure in which a pesticide that has been banned or severely restricted in some industrialized country cannot be exported to another country without its prior agreement.
While the Code of Conduct may not solve all problems, it goes a long way toward providing basic guidance to developing countries for the environmentally sound management of pesticides.

6.4.2 Registration

No pesticide should be used in a country without its prior registration. Registration means the process whereby the responsible national government authority approves the sale and use of a pesticide. This is preceded by an appropriate evaluation of comprehensive scientific data demonstrating that the product is effective for the purposes intended and yet not unduly hazardous to human or animal health or to the environment.

Countries that do not have a well-developed registration and review framework often rely on the evaluations performed by the FAO/WHO Joint Meeting on Pesticide Residues (JMPR) for the use of pesticides in agriculture. JMPR establishes levels of pesticides that can be ingested daily by humans, for a lifetime, without appreciable risk (see also section 4.1.2), and proposes, based on good agricultural practice, maximum residue levels of pesticides in foods. After comments by governments, these levels may be adopted as Codex maximum residue limits (MRLs) by the Codex Alimentarius Commission (CAC). It is important to note that only those pesticides for which the Codex Alimentarius Commission has adopted MRLs have had the benefit and scrutiny of review by the JMPR.

In addition to agricultural uses, many pesticides are used for the control of insects and other pests of public health importance, such as molluscs, mosquitos, flies, fleas, bedbugs and lice. Registration for the use of pesticides in public health programmes is also needed. WHO has published specifications for the physico-chemical characteristics of such pesticides and test methods for determining these characteristics, as well as practical guidance on application procedures, treatment cycle and precautions to be taken.

6.4.3 Labelling

All pesticide containers should be clearly labelled. A label should contain the following essential information:

- the trade name and the approved name of the pesticide, the active ingredient(s) and the hazard it presents;
- the target pests;
- the safety precautions necessary when handling or using the pesticide, and the medical treatment in case of poisoning;
- how, when and where to use the pesticide;
- how to mix or dilute the pesticide;
- how to clean application or mixing equipment afterwards, and how to dispose of unwanted pesticide and the washings;
• whether the formulation can be mixed with other pesticides or diluting agents;
• the laws and regulations that apply specifically to the use of the pesticide, including the period of restricted entry into a treated area, and the minimum or withholding period to be observed between treatment and harvest of a crop;
• the name and address in the country of the manufacturer, distributor or agent, and the registration number of the pesticide;
• the date of manufacture and/or formulation, and expiry date;
• any other information required in that country or region.

6.4.4 Education, training and workers protection

The education of workers at all levels is needed with regard to the hazards associated with the use of pesticides and the proper techniques to ensure their safe use. Packaging, transport, transfer, storage, mixing and application of pesticides are hazardous operations that require proper training for the safety of workers. Information about pesticides and how they may be used safely and efficiently is available in most countries. It is produced by governments, international agencies, associations representing manufacturers, agricultural experts, schools and colleges.

It is the responsibility of the employer to provide correct information to workers. If special protective equipment is needed, the employer should provide this, instruct the workers in its proper use, see that it is maintained and replace it if faulty. Priority areas are the use of goggles to prevent eye injuries, the use of respirators in dusty atmospheres, and the use of gloves to protect the hands. Personal protection also includes the use of washable work clothing, and the provision of water and soap for washing exposed skin whenever pesticides or other potentially toxic chemicals are involved.

The general public is becoming increasingly aware of pesticides. This is partly because the effects of their use are not always confined to the area of land treated. Public awareness is not so much about the benefits of pesticide use as about the harm that misuse can cause. Pesticide users should be alert to public concern and set a good example by taking necessary precautionary measures when handling pesticides.

6.4.5 Transportation, storage and disposal

Pesticide containers that are damaged or leaking should be refused for transport. The transport vehicle itself should not damage the containers and protruding sharp edges or nails should be avoided. Containers of pesticides should never be carried in the same truck as food or animal feed.
Pesticides, if not stored adequately, may deteriorate. To avoid storage problems, only the amount needed for a given operation should be ordered. All pesticide storage areas must be securely locked. Storage sites must not be liable to flooding or have any potential for polluting underground water supply sources. They should not be located upstream from a water supply catchment area or in environmentally sensitive areas.

The safe disposal of unwanted pesticides and containers requires the guidance of an expert. Methods used include returning the material safely to the supplier, incineration or burial of pesticides in their containers at carefully selected sites, geologically isolated from water sources and not subject to flooding.

Empty pesticide containers must never be used for storage of food or drinking-water. If containers cannot be returned to suppliers, they can be disposed of by burying, burning or repeated washing, using only carefully supervised and approved procedures and taking care to avoid contamination of water supplies.

6.4.6 Integrated pest management (IPM)

IPM is a methodology that has slowly developed in recent years. It is essentially a combination and development of traditional environmental, biological and chemical pest control methods to reduce reliance on pesticides, and to lessen the real risk that the pest may become resistant to the pesticide. At the same time, the hazard of exposure of those who apply the chemicals is diminished. Examples of IPM includes the use of pest-resistant varieties of crops, biological methods that involve the release of sterile insects or of bacteria that kill the pest species, or the controlled release of insects or animals that consume the pests but not the crop.

6.4.7 Pesticide poisoning

While necessary precautions should always be taken to prevent or minimize exposure to pesticides, pesticide poisoning is not uncommon. Some pesticides are extremely toxic and small amounts can result in acute poisoning. All cases of pesticide poisoning should be seen by a doctor as soon as possible. It is important for the doctor to know to which pesticide the person has been exposed.

Symptoms and signs of poisoning vary with the nature of the pesticide and include headaches, general weakness or tiredness, sweating, vomiting, blurred vision and seizures. First aid and medical treatment are available for poisoning by different types of pesticides (organophosphorus, carbamates, organochlorine, pyrethroids, etc). Primary health care workers should be trained in
first aid treatment, which should be used until the victim can be assessed by an appropriately qualified medical doctor.

Whenever pesticides and other chemicals are used in a country, a Poison Information Centre should be established to provide a support service to health care workers and doctors who are called upon to treat cases of acute poisoning.
After reading this chapter, you should be aware that:

- The environmentally sound management of toxic chemicals, often referred to as "cradle-to-grave" or "life-cycle" management requires the proper management of a chemical from when it is first manufactured to when it is disposed of.

- It is often far easier, far less costly and far less damaging to both human health and the environment to prevent a toxic release rather than try to contain or remediate a release of pollutants.

- A health and environmental impact assessment (HEIA) is a comprehensive study to evaluate, anticipate and prevent the ways in which a chemical production facility will affect air, water and soil quality, as well as traffic patterns, further land utilization in the area and aesthetic considerations in the community.

- Standards and regulations intended to ensure the safe use of chemicals achieve nothing unless they can be implemented at reasonable cost and routinely enforced. This requires appropriate facilities, technical expertise and an appropriate legislative framework.

- The FAO "Code of Conduct" includes provisions for "Prior Informed Consent", a procedure in which a pesticide that has been banned or severely restricted in some industrialized country cannot be exported to another country without its prior agreement.

- Countries that do not have a well-developed pesticide registration and review framework often rely on the evaluations performed by the FAO/WHO Joint Meeting on Pesticide Residues (JMPR) for the use of pesticides in agriculture. The JMPR establishes levels of pesticide residues that can be ingested daily by humans, for a lifetime, without appreciable risk.

- Simple steps in pesticide use will help ensure safe and beneficial use while minimizing risks. These steps include proper labelling, use, storage and disposal of the chemical products, including pesticides.
GLOSSARY

Acceptable Daily Intake (ADI): The dose of a substance that is anticipated to be without appreciable health risk to humans when taken daily over the course of a lifetime.

Acid Rain: Rain having a pH of less than 4.0.

Acute toxicity: Refers to adverse effects on, or mortality of, organisms following soon after a brief exposure to a chemical agent. Either a single exposure or multiple exposures within a short time period may be involved, and an acute effect is generally regarded as an effect that occurs within the first few days after exposure, usually less than 2 weeks.

Additive effect: Combined effect of two or more chemicals equal to the sum of their individual effects.

Adverse: an abnormal, undesirable or harmful change.

Affinity: having a special attraction for a specific element, organ or structure.

Allergic reaction: a hypersensitive immune response induced by exposure to a particular antigen.

Anaerobic: A process that does not require oxygen or free air; conditions in which oxygen is absent.

Antagonism/antagonistic: The combined action of two or more substances to produce an effect less than the sum of their individual effects; the opposite of synergism.

Anthropogenic: originating from the activity of humans.

Antibody: a molecule produced by lymphocytes that interacts only with the antigen that induced its synthesis.

Antigen: any substance that is capable, under appropriate conditions, of inducing a specific immune response. Antigens may be substances such as toxins and foreign proteins, or particulates such as bacteria.

Aplastic anaemia: A form of anaemia in which the bone marrow fails to produce adequate numbers of peripheral blood elements. Therefore, the number of erythrocytes per unit volume of blood, the quantity of haemoglobin and blood production are disturbed.

Arthropods: Organisms such as insects, arachnides (spiders and mites) and crustaceans.

Asbestosis: A form of lung disease caused by inhaling fibres of asbestos. Characterized by interstitial fibrosis of the lung tissue from minor involvement of the basal areas to massive scarring.

Asphyxia: A condition due to lack of oxygen in respired air, resulting in death.

Autoimmunity: The loss of the natural ability to distinguish between self and non-self.

Axon: Fibre which extends out from the body of a neuron.

Benign (tumour): A non-cancerous tumour.

Biological transformation (biotransformation): The series of chemical changes of a substance or compound that occur within an organism (plant or animal).

Blood-brain barrier: a selective barrier between the nervous system and the rest of the body that protects the nervous system from certain toxic substances.

Bronchitis: Inflammation of one or more bronchi of the lungs.
Byssinosis: A type of pulmonary disease among textile workers due to inhalation of textile dust. Characterized by tightness of the chest, wheezing, and coughing. In chronic cases, permanent dyspnoea (shortness of breath) occurs. Also known as brown lung, cotton-dust asthma, cotton-mill fever, and Monday fever.

Calcification: The process by which living tissue becomes hardened with deposits of calcium salts within its substance. Scar tissue is an example of tissue undergoing calcification.

Carcinogen: Any substance capable of producing cancer or a chemical that causes or induces cancer.

Central nervous system: The nervous system consisting of the brain and spinal cord.

Cavities: Occur after the destruction of calcified tissue of the tooth surface by decalcification of the enamel of the teeth. Cavities can penetrate through the enamel, dentin and pulp of the teeth.

Chelation: A process by which a metallic ion is sequestered and firmly bound into a ring within a chelating molecule. Chelates are used in chemotherapeutic treatments for metal poisoning (e.g., lead poisoning).

Chronic: Occurring over a long period of time, either continuously or intermittently; used to describe ongoing exposures and effects that develop only after a long exposure.

Cradle to grave: The environmentally sound management of toxic chemicals from when a chemical is first manufactured to when it is finally disposed.

Dental fluorosis: A condition due to exposure to excessive amounts of fluorine or its compounds, causing the mottling and blackening of the tooth enamel.

Dermat: Of the skin; through or by the skin.

Dermatitis: A condition characterized by inflammation of the skin. Can be caused by contact exposure to an allergen.

Dust: A pesticide formulation consisting of an active ingredient impregnated on a finely ground carrier such as clay, talc or calcium carbonate.

Eczema: A type of dermatitis occurring as a reaction to many endogenous and exogenous agents. Characterized by oedema and inflammation, oozing, crusting and scaling of the dermis.

End-point: A biological effect used as an index of the effect of a chemical on an organism.

Enhanced greenhouse effect: An alteration and increase of the earth's atmospheric temperature due to an increase in the concentration of greenhouse gases such as water, carbon dioxide, CFCs and methane. The effect is said to be enhanced because the concentrations of greenhouse gases are steadily increasing.

Epidemiology: The study of the distribution and determinants of health-related states or events in populations.

Eutrophication: The stimulation of excessive growth of plants and algae in natural waters by an oversupply of inorganic nitrogen and phosphate compounds found in fertilizers and other similar compounds.

Exposure: Contact with a chemical. The main routes of exposure for humans are dermal absorption (skin), ingestion (by mouth) and inhalation (breathing).


Health and environmental impact assessment (HEIA): A comprehensive study to anticipate, evaluate and prevent the ways in which proposed industrial development could adversely impact on the surrounding environmental or human health quality.
Hepatotoxicant: A toxicant or substance that specifically damages the liver, typically through the accumulation of fat or death of liver cells.

Hepato-carcinogen: A substance or compound capable of causing cancer of the liver. The liver is especially susceptible due to its anatomical relationship to the most important port of entry, the gastrointestinal tract, and its very high concentration of xenobiotic-metabolizing enzymes. Many of these enzymes produce very reactive intermediates which can react with liver proteins and DNA to produce cancer.

Hepatocyte: Liver cell.

Hormone: A chemical substance secreted by a gland and which exerts control on other body systems.

Hydrocarbons: An organic compound that contains only carbon and hydrogen.

Hyperpigmentation: Abnormally increased pigmentation.

Immunosuppression: Inhibition of the immune response.

Independent effect: When two or more chemicals act by different modes of action and produce different effects.

Ingestion: Intake of a substance by mouth; absorption from the digestive tract.

Inhalation: Drawing of air into the lungs.

Inhalation toxicology: A route of exposure in which the toxicant is drawn into the lungs.

Keratosis: Any horny growth, such as a wart or callous.

LD₅₀: Lethal dose, low. The lowest dose which causes death in test animals.

Leaching: The movement of a chemical downward through soil as a result of water movement, potentially causing contamination of groundwater resources.

Leukocyte: White blood cell; the major component of the immune system.

Local effect: Effect of a chemical which is limited to the area of contact.

Leukaemia: A progressive, malignant disease of the blood-forming organs (bone marrow). Characterized by distorted proliferation and development of leukocytes and their precursors in the blood and bone marrow.

LOAEL: Lowest-observed-adverse-effect level; the lowest dose in an experiment that produces an observable adverse effect.

Lung fibrosis: The formation of fibrous tissue within the lungs. Characterized by chronic inflammation and progressive fibrosis of the pulmonary alveolar walls, combined with progressive dyspnoea (shortness of breath).

Malignant (tumour) A tumour characterized by cells showing both growth and a tendency to invade and destroy other tissues.

Mesothelioma: A malignant tumour derived from mesothelial tissue (peritoneum, pleura, pericardium). Pleural mesotheliomas have been linked to exposure to asbestos.

Metastasis: The process by which individual tumour cells, or clumps of cells, are shed from the primary tumour.
**Mobility**: Relates to the movement of a chemical in the environment. It is dependent on the environmental matrix in which the chemical is located and its chemical and physical properties.

**Mucociliary clearance**: Removal of mucus from the respiratory tract by cilia.

**Mutagen**: An agent that causes a permanent genetic change in a cell other than that which occurs during normal genetic recombination.

**Myoneural junction**: The small gap between muscle and nerve fibres.

**Nephron**: The functional unit of the kidney; includes a glomerulus and long tubule.

**Neuron**: The functional unit of the nervous system; conducts or transmits nerve impulses.

**Neurotoxin**: Any substance that is capable of destroying or adversely affecting nerve tissue.

**Neurotransmitter**: Chemical responsible for the transfer of information along the nervous system.

**NOAEL**: No-observed-adverse-effect level; the highest dose in an experiment that does not produce an observable adverse effect.

**NOEL**: No-observed-effect level of a pollutant is the concentration at or below which there is no defined effect, either deleterious or beneficial, on a member of a population exposed to the pollutant in question.

**Neoplasm**: New growth or tumour resulting from the accumulation of rapidly reproducing cells within an area.

**Occupational exposure**: Exposure to chemicals while in a workplace setting.

**Ozone layer**: At approximately 25–30 km in altitude, there is a relatively high concentration of ozone (approximately 10 ppm), which is referred to as the "ozone layer".

**Peripheral nervous system**: Nervous system structures outside of the central nervous system.

**Peripheral vascular disorder**: Disruption of the blood vessels in the extremities and outer layer of the body.

**Personal protective equipment**: Special equipment used by workers to protect them from potential chemical exposure.

**pH**: Hydrogen ion concentration; used to express the degree of acidity or alkalinity of a material.

**Phagocytosis**: The process by which neutrophils and macrophages invade and ingest foreign particles.

**Photoallergic reaction**: A type of hypersensitivity involving exposure to a chemical substance and radiant energy (light).

**Prior informed consent (PIC)**: A United Nations Food and Agricultural Organization Code of Conduct provision which includes a procedure whereby a pesticide that has been banned or severely restricted in some industrial countries cannot be exported to another country without its prior agreement.

**Provisional Acceptable Daily Intake (PADI)**: The maximum dose of a substance that is anticipated to be without health risk to humans when taken daily over the course of a lifetime. PADIs are set by the US Environmental Protection Agency.

**Respiratory toxicology**: The response of the lungs to an inhaled toxicant.

**Risk**: The probability of the occurrence of an unwanted adverse effect.

**Safety**: Often referred to as the opposite of risk, it is the practical certainty that adverse effects will not result when a substance is used in the quantity and in the manner proposed for its use.
**Scrubbing:** A process by which acid gases are neutralized with a base, typically calcium hydroxide.

**Skeletal fluorosis:** A condition due to exposure to excessive amounts of fluorine or its compounds, causing skeletal changes including weakening and softening of bones due to impaired mineralization.

**Subchronic:** Intermediate between acute and chronic toxicities; subchronic toxicity studies involve repeated daily exposure of animals to a chemical for part (not exceeding 10%) of a life span. In rodents, this period extends up to 90 days of exposure.

**Synergistic/synergism:** An interaction of two or more chemicals that results in an effect that is greater than the sum of their effects taken independently.

**Systemic toxicity:** Poisoning that is either generalized or occurs at a site distant from the point of entry of the toxicant.

**Target organ:** Organ in which toxic injury manifests itself in terms of a adverse effect.

**Tolerable Daily Intake (TDI):** The amount of a chemical that can be ingested daily over a lifetime without appreciable risk.

**Teratogen:** Any substance capable of producing non-heritable structural abnormalities of prenatal origin, present at birth or manifested shortly thereafter.

**Teratogenicity:** The ability of a substance to produce irreversible, non-heritable birth defects or anatomical or functional disorders as a result of an effect on the developing embryo or fetus.

**Threshold:** The lowest dose of a chemical at which a specified measurable effect is observed and below which it is not observed.

**Tolerance:** (1) A legal limit, established by the US Environmental Protection Agency, for the maximum amount of a pesticide residue which may be present in or on a food. Temporary tolerances, which cover residues resulting from an experimental use, generally expire after one year. (2) Capacity to withstand pesticide treatment without adverse effect on normal growth and function.

**Toxicity:** (1) The capacity or property of a substance to cause adverse effects. (2) The specific quantity of a substance which may be expected, under specific conditions, to do damage to a specific living organism.

**Toxin:** A toxicant produced by a living organism.

**Uncertainty factor:** A number (equal to or greater than one) used to divide NOAEL or LOAEL values derived from measurements in animals or small groups of humans, in order to estimate a NOAEL value for the whole human population; also called margin-of-safety.

**Volatile:** Capable of vaporizing or evaporating readily.
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