Preface

Toxicology is the science of the harmful effects of substances and factors on living organisms. The *toxicity* of a substance usually depends on the quantity or concentration of that substance, as well as the duration and frequency of exposure; not all living things are equally sensitive to all toxic substances. Many substances are essential for humans at low doses but may be toxic at higher doses. The famous maxim of *Theophrastus Bombastus von Hohenheim* (1493–1541), known as Paracelsus, that *"Only the dosage makes something a poison or a remedy,"* was undisputed until quite recently. However, this maxim is now being challenged as, for example, in the case of gene-altering substances where only one molecule is thought to suffice, theoretically, to cause a cell to degenerate and thus initiate tumor formation. The same principle may also apply to where a single molecule might be enough to trigger an allergic reaction.

The *Illustrated Handbook of Toxicology* includes a full discussion of threshold and nonthreshold toxicology, modern toxicological methods (omics techniques) such as genomics, proteomics and metabolomics, and biological weapons. In addition, the effects of relevant toxicants on the environment and human health are explained and richly illustrated. Additional expert risk assessments provided along with updated (hazardous substance) exposure thresholds for those affected add another important dimension to the utility of the Handbook. These expert assessments are very helpful in providing meaningful context to complex toxicological concepts to the interested reader.

The first part (General Toxicology) provides updated fundamental information on toxicology.

The second part (Special Toxicology) deals with the different groups of harmful and poisonous substances, including the effects of radiation and noise. The full-color toxicological illustrations bring to life various toxicological phenomena. All the chemical formulas are in line with Römpp's Dictionary of Chemistry. This *Illustrated Handbook of Toxicology* is the book of first choice for students of medicine, dentistry, veterinary medicine, pharmacy, biology, chemistry, food chemistry, and other sciences. It is also an invaluable resource for practicing physicians, pharmacists, and scientists. The easy-to-read text, clear tables, and full color illustrations further enhance the utility and accessibility of this handbook to a broad audience.

This *Illustrated Handbook of Toxicology* provides the interested reader with a broad range of topics that will be useful not only for students but also for toxicologists, environmental physicians, political decision-makers and their advisers, whose work is directed toward protection of the environment and human health.

Our thanks go to the authors and our colleagues for their suggestions; to Dr. Juergen Durner and Dr. Mario Seiss for reviewing the chemical formulae; Dr. Tanja Huesch and Mr. Stefan Schulz for the research; in particular Dr. Christina Schoeneborn and Dr. Bettina Hansen of Georg Thieme Verlag; the illustrators Ms. Ruth Hammelehle and Mr. Thomas Heinemann for their outstanding work in producing the color plates for this book.

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Toxicodynamics II

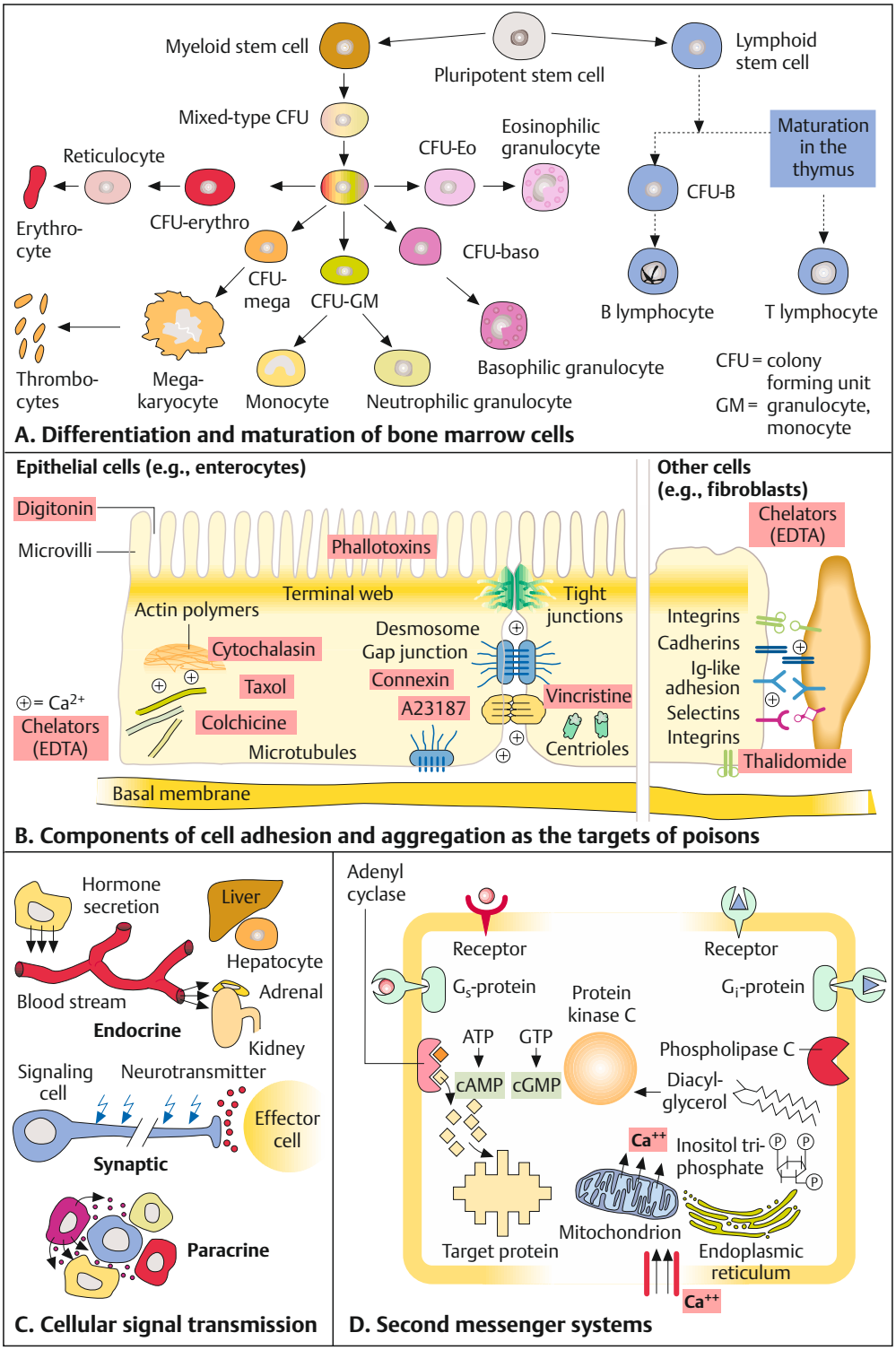
Cellular Effects

At the cellular level, toxic effects are frequently recognized as an **inhibition of cell proliferation**. Above a certain concentration, practically all poisons have an inhibitory effect on cellular growth and division. However, this does not allow us to draw any conclusions about the mechanisms involved.

Tissues with high cell turnover—such as bone marrow, the stem cells of which mature into erythrocytes, leukocytes (granulocytes and lymphocytes), and thrombocytes—are especially susceptible to a **disturbance in cellular differentiation or maturation** (**A**). Stem cells are very sensitive to ionizing radiation and chemicals. Any damage to the respective clones may lead to cell death or to the uncontrolled growth of cells where differentiation has been disturbed (leukemia). In mature blood cells, the immunological selection caused by circulating antigen/antibody complexes may lead to a decreased lifespan, or the complete extinction, of certain clones or precursors. A well-known example is the impaired maturation of blood cells by folic acid antagonists (e.g., methotrexate), which leads to erythropenia or aplastic anemia. Rare cases of agranulocytosis may be associated with exposure to phenothiazine and thyreostatics, while thrombocytopenia may be caused by thiazide diuretics or antiphlogistics, for example.

Other poisons produce functional disturbances in cell clusters by **inhibition of cell adhesion** or **cell aggregation**. At a biochemical level, the mechanical and electrochemical coupling of cells with one another occurs by means of proteins, which are either anchored in the cell membrane (cadherins, ICAMs, connexins, selectins, integrins) or undergo dynamic restructuring in the cytosol as components of the cytoskeleton (microfilaments, microtubules) (**B**). Calcium ions also play an essential role in the aggregation of cells and in the organization of the cytoskeleton. Any disturbance of calcium balance can jeopardize cell adhesion, cell polarity, or even the viability of individual cells. Some well-known examples are components of animal poisons, e.g., hydrolytic activities in snake poison (collagenases, hyaluronidases), whose complex-forming substances disturb the calcium balance. Amanitin, cadmium, and thalidomide act on the cytoskeleton or the adhesion of cells.

Some toxic effects are best described as **inhibition of signal transmission** (**C**): communication between neighboring cells is either paracrine (by mediators, cytokines) or takes place by means of gap junctions, while communication between distant organs is either endocrine (by hormones) or synaptic (by transmitter substances). The mechanisms of signal transmission differ with respect to the selectivity, range, spreading rate, and duration of the toxic effect. Gap junctions provide direct continuity between the transmitting and receiving cells; this type of transmission is therefore only possible between directly adjacent cells. Many cellular messengers bind as a *first messenger* to special structures (receptors) on the cell membrane of the recipient cell, from where signal transmission into the cell takes place. The binding of a messenger to receptors may influence the function of ion channels, G-proteins, or enzymes (**D**). Signal transmission into the cell is mediated by a *second messenger*, e.g., cyclic AMP (cAMP) or calcium ions. Other messengers—such as steroid hormones, thyroxin, nitric oxide (NO), and carbon monoxide (CO)—pass directly through the cell membrane and act inside the cell. Poisons can interfere at many levels of signal transmission, by blocking or falsifying the signal. Examples include ouabain, curare, forskolin, nicotine, and calcimycin.



Psychosocial Consequences for the "Environmentally Poisoned"

As "environmentally poisoned" individuals are convinced that they are continuously threatened by pollutants, they develop behavioral disorders with psychosocial consequences (**A**). Psychiatric disorders caused by environmental pollutants do not all have the same origin. According to modern diagnostic criteria for psychiatric disorders, they include affective disorders, anxiety disorders, somatoform disorders, and—in rare cases—psychotic disorders. If the poisons themselves actually cause psychiatric disorders, these should be classified as organically caused psychiatric disorders. Within the group of people with affective disorders, "environmentally poisoned" individuals are usually those suffering from adjustment disorder with a depressive emotional response (formerly known as neurotic depression).

Exteriorization of Problems

A psychiatric disorder can be triggered by "environmental poisoning." The underlying cause may be a subconscious, repressed conflict that should be resolved. However, if it cannot be resolved, the person is looking for causes in the environment. An "environmental poison" is particularly suitable for this purpose: one exteriorizes the problem and invests all one's energy into fighting this "environmental poison." This may temporarily suppress the depressive mood (**B**).

Toxicophobia, Somatotropic Disorders, and Hypochondriasis

Toxicophobia. This anxiety disorder is characterized by a fear of being poisoned, although this is not in fact the case. It may be chronic, or occur suddenly in the form of panic attacks, for example, triggered by odors (**C**).

Somatotropic disorder. The clinical symptoms of this disorder are bodily complaints or an irrational fear of disease.

Hypochondriasis. When the fear is particularly incomprehensible and the patient always interprets all bodily sensations as severe illness, the condition is called hypochondriasis (**D**).

Somatoform Disorders

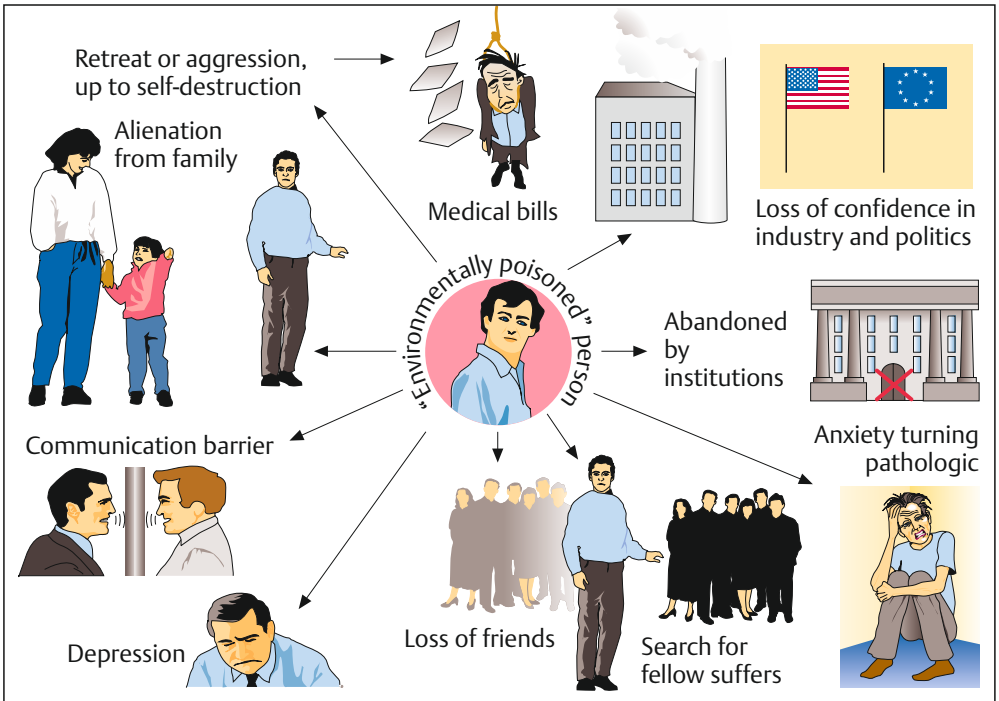
Somatization disorder is suspected when there have been multiple physical symptoms over a period of at least 6 months and the patient is less than 30 years old. When the first manifestation occurs in patients older than 30 years, it is called undifferentiated somatoform disorder. Patients with these somatoform disorders make up the largest portion of "environmental victims." For those patients who ascribe their complaints to pollutants (*attribution*), the cause of their disease is already absolutely clear (*fixed disease concept*). The main symptoms of somatization disorders are in the gastrointestinal tract, while other symptoms are only secondary (see environmental poisons, p. 40).

According to depth psychology, somatization disorders may have their origins in early childhood:

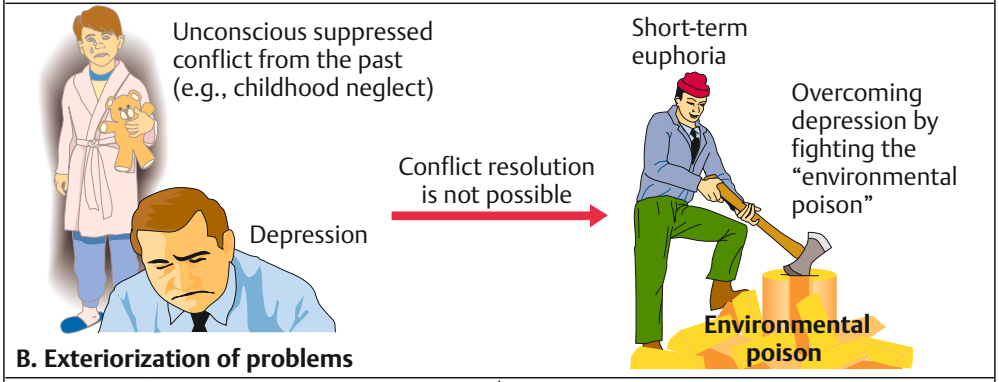
1. The mother behaves toward the child in a very *possessive* and *overbearing* way, and the child (who, indeed, had been in the mother's possession during pregnancy) has no chance to separate and realize its own body (*lack of identity*).

2. Another relationship pattern exists that could be called *lack of relationship*: the child is not noticed, but is ignored or even despised. The conflicts thus created in the child are so prominent that they need to be vigorously suppressed.

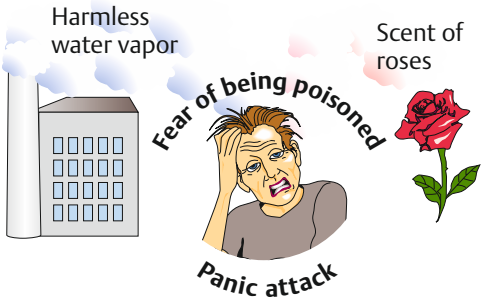
It is therefore very difficult to persuade patients with somatization disorder to enter therapy. In most cases, it is better for these patients to let them hold on to their fixed disease concept, rather to confront them with psychogenic causes of their disease.



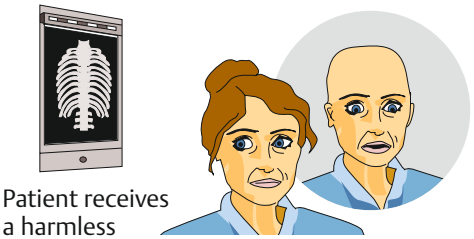
A. Psychosocial effects on an "environmentally poisoned" person



B. Exteriorization of problems



C. Toxicophobia



D. Hypochondriasis

Halogenated Aliphatic Hydrocarbons

Basics. Among the halogen compounds containing fluorine, chlorine, or bromine, the chlorinated organic compounds are particularly important in toxicology. Chlorine is extremely reactive, and chlorine-containing compounds are therefore used in the chemical industry as reactive starting materials or intermediates. Unlike polyhalogenated *cyclic* compounds (see p. 112), which are the subject of international concern because of their global distribution and persistence in the environment, chlorinated *aliphatic* compounds are of immediate importance because of their acute and chronic toxic effects on parenchymatous organs. These effects are facilitated by the high vapor pressure of these compounds, which enhances their uptake and elimination. Other factors are various metabolic reactions, the products of which then determine the type and extent of the toxic effects. Even substances that are chemically closely related are metabolized differently, and hence also have different toxicities. The genotoxic effects of certain metabolites are accompanied by carcinogenic effects and therefore pose a special problem. Current risk assessments of chlorinated organic compounds take this into account (**A**). Polychlorinated alkanes, alkenes, and alkynes are largely used as *solvents* because of their good lipid-dissolving properties (**B**). Uptake is predominantly by inhalation; dermal or oral exposures are rare (accidents or attempted suicides). The high vapor pressure of these compounds usually produces rapid, concentration-dependent narcotic effects, the duration of which is determined by the speed of exhalation.

Trichloromethane (Chloroform)

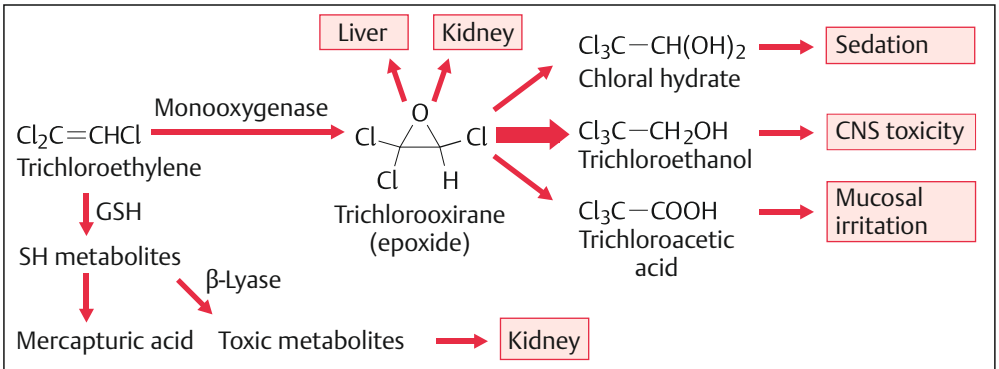
Like other chlorinated hydrocarbons, trichloromethane ($CHCl_3$) has been in use since 1847 as an anesthetic. Because of its toxic effects, primarily on the liver and kidneys, other halogenated compounds with wider therapeutic ranges are currently used for anesthesia, e.g., halothane (see p. 108).

Absorption and metabolism. Upon absorption after inhalation, ingestion, or uptake through the skin, trichloromethane is metabolically activated in the liver. The secondary product trichloromethanol is converted to phosgene by dehydrochlorination; this reactive metabolite causes damage to cells and cellular components (**C**).

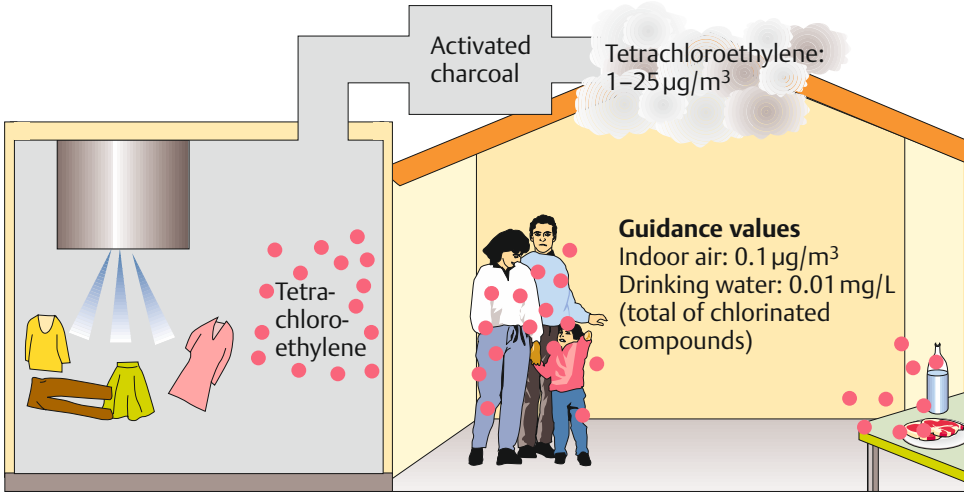
Acute toxicity (D). Symptoms of poisoning with inhaled trichloromethane include excitation, unconsciousness, and respiratory paralysis. Of particular importance is the cardiotoxic effect after exposure to high concentrations of a trichloromethane–air mixture (> 2.5 v/v), which causes sudden cardiac arrest due to the sensitization to catecholamines. Exposure for several hours causes a drop in blood pressure and shock. Examination of the liver reveals toxic hepatitis with centrilobular necroses, similar to poisoning with tetrachloromethane. In severe cases, acute liver atrophy with hepatic coma sets in. After dermal exposure, ulcers and inflammation of the skin may develop.

Chronic toxicity (D). The liver and kidneys are especially sensitive. The maximum workplace concentrations take this into consideration. Trichloromethane has genotoxic effects, and it is carcinogenic in experimental animals. Like other chlorinated methane derivatives, trichloromethane is considered to be a possible human carcinogen.

Therapy. Intensive monitoring of vital signs is essential. Treatment of poisoning by ingestion consists of rapid detoxification by induction of vomiting and gastric lavage; poisoning by inhalation calls for fresh air and hyperventilation therapy. In case of a fire, it is important that first aid workers wear protective masks (to prevent toxic pulmonary edema if phosgene is formed).

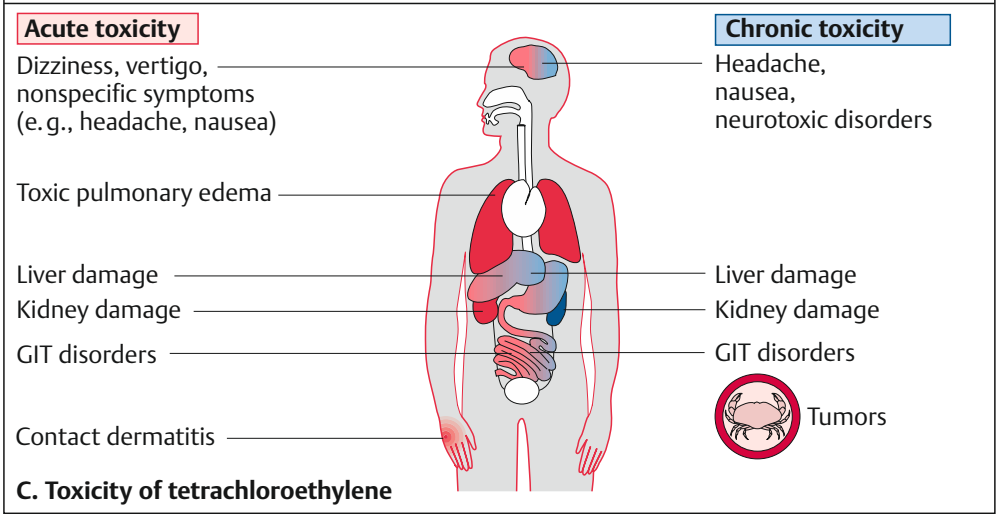


A. Biotransformation and toxicity of trichloroethylene



Dry cleaning facility

B. Occurrence of and exposure to tetrachloroethylene



C. Toxicity of tetrachloroethylene

Hydrogen Sulfide

Hydrogen sulfide (H_2S) is a colorless, flammable gas formed during the reaction of mineral acids with sulfides of heavy metals, as well as during the decomposition of protein (sewer gas contains up to 10% H_2S). Considerable amounts of H_2S are also formed during the papermaking process. In addition, H_2S accumulates in cellars, canals, and containers. The warning sign—an offensive smell of rotten eggs (sensitivity threshold ~ 0.025 mL/m³)—diminishes as the result of rapid habituation. First aid helpers attempting to rescue victims from poisoned areas are therefore prone to accidents.

Effect (A). Concentrations of more than 10–50 mL/m³ cause irritation, possibly pulmonary edema, and intracellular hypoxia; the mechanisms are unknown. Concentrations of more than 500 mL/m³ cause unconsciousness and quick development of central respiratory paralysis. H_2S is rapidly oxidized in the body and eliminated as sulfate.

After chronic exposure (e.g., of workers in synthetic fiber manufacturing facilities), corneal damage, increased airway resistance, pulmonary edema, pneumonia, and myocardial degeneration have been observed.

Therapy. Nonspecific measures (keeping the airways free, correction of acidosis).

Fumigants

Some gaseous compounds are used as fumigants for controlling insects, rodents, and other pests in areas that cannot be reached otherwise. Fumigants are very dangerous poisons, and in many industrialized countries their sale is restricted and their use requires a permit (**B**). Details of how to carry out fumigation procedures are described in national legislation and regulations. For example, ships in transit may be fumigated only with phosphine, containers in transit may be treated only with phosphine or methyl bromide, and ethylene oxide may be used only in fumigation chambers.

In industrialized countries, widely used fumigants include the following (**C**):

Methyl bromide (bromomethane). In the 1960s, the use of this insecticide (a colorless, nonflammable gas; boiling point 4.5 °C; density 3 kg/L) caused more lethal accidents in California than the use of organophosphates (see p. 200). The extremely poisonous methyl bromide is commonly mixed with chloropicrin, a potent irritant that serves as a warning agent. The target organ of the systemic effects of methyl bromide is the central nervous system. A likely mechanism of action for poisoning of the central nervous system is the reaction with endogenous sulfhydryl groups. Dithiol compounds (e.g., dimercaptopropanol, dimercaptosuccinic acid [DMSA]) are being considered as possible agents for treatment.

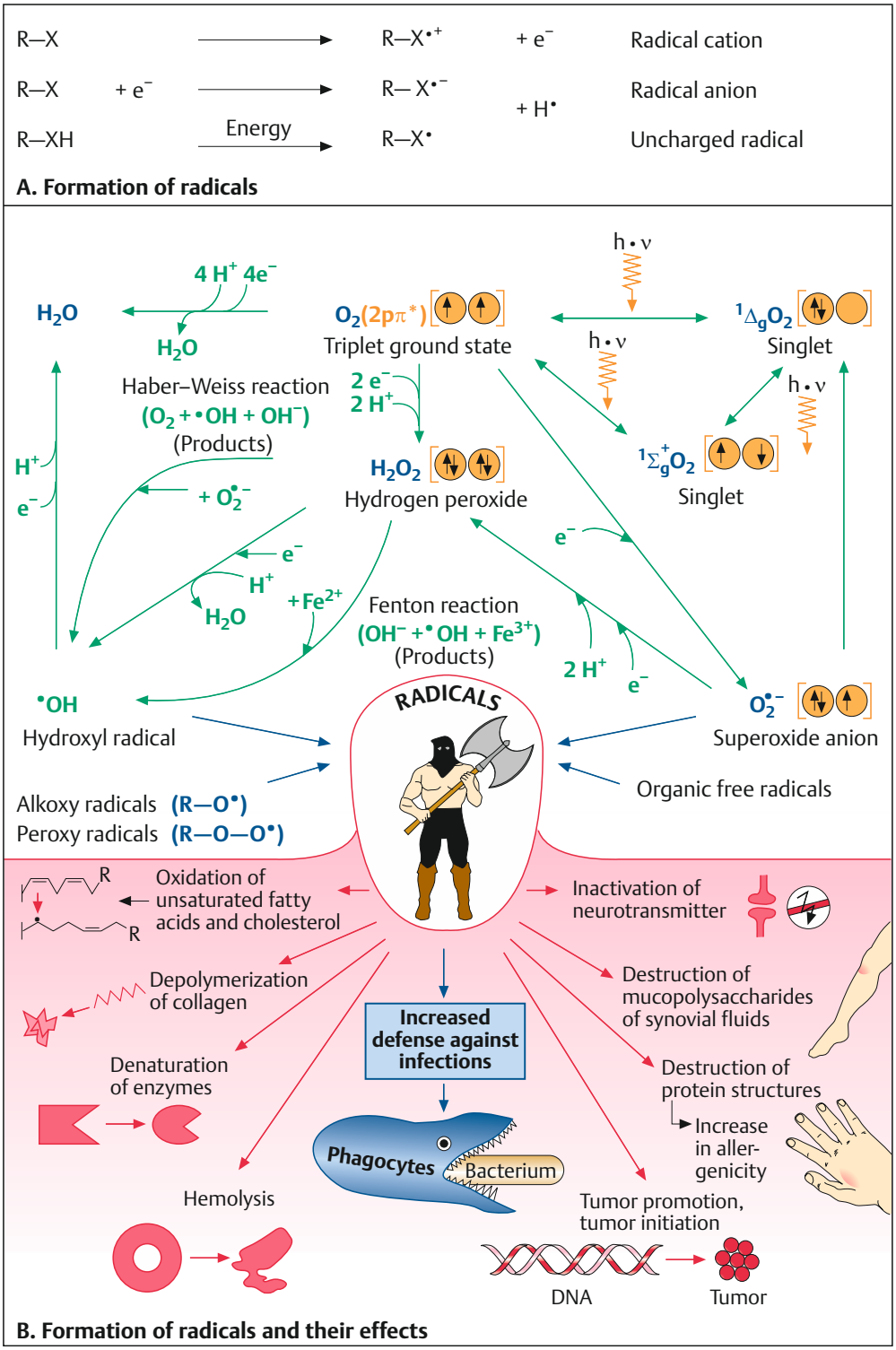
Hydrogen cyanide and formaldehyde. For details, see p. 140 and pp. 94, 136, respectively.

Ethylene oxide (Oxirane). This is a colorless gas (boiling point 11 °C; density 1.5 kg/L) with a high olfactory threshold (at ~ 700 mL/m³). It is a strong irritant, and it forms explosive mixtures with air. Ethylene oxide is mutagenic and carcinogenic.

Phosphorus hydrides: hydrogen phosphide (PH_3), phosphines, and phosphine-producing pesticides. Phosphine is the common name for hydrogen phosphide (a colorless, heavy gas; formerly called phosphorus [tri]hydride). In the presence of traces of water, the gas is slowly released from aluminum phosphide tablets. It is a metabolic poison and neurotoxin that is more toxic than methyl bromide but considered safer to handle.

The following fumigants are also used: vinyl cyanide (acrylonitrile, CH_2CHCN), carbon disulfide (CS_2), tetrachloromethane (carbon tetrachloride, CCl_4, see p. 104), trichloronitromethane (CCl_3NO_2), and ethylene dibromide (1,2-dibromoethane, $CH_2BrCH_2Br_2$), and dibromochloropropane ($ClCH_2CHBrCH_2Br$).

Detection. The gaseous compounds mentioned above can be determined quantitatively by means of gas chromatography or infrared spectroscopy, and semiquantitatively using colorimetric indicator tubes (Draeger tubes).



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