

Toxic responses of the respiratory system

Structure

The respiratory tract is a complex system, both in structure and function. It consists of the nasopharynx, the tracheal and bronchial tracts, and the pulmonary acini, which are composed of respiratory bronchioles, alveolar ducts, and alveoli. The nasopharynx serves to remove large particles from the inhaled air, add moisture, and moderate the temperature. The tracheal and bronchial tract serves as the conducting airway to the alveoli.

Functions

The pulmonary acini are the sites where oxygen and carbon dioxide are exchanged between the blood and the air, and are the main sites of absorption of toxicants that exist in the form of gases and vapors. The alveoli are lined with epithelial cells, in addition, there are endothelial cells, macrophages, and fibroblasts.

Apart from its vital function in the exchange of oxygen and carbon dioxide, the respiratory system also can excrete toxicants that have been absorbed from the lungs or via other routes. Although liver is the primary site, pulmonary tissue possesses cytochrome P-450 (CYP-450) enzymes involved in xenobiotic detoxication.

Defense Mechanisms

The trachea and bronchi are lined with ciliated epithelium and covered with a thin layer of mucus secreted by certain cells in the epithelial lining. This lining, with the cilia and mucus, can move particles deposited on the surface up to the mouth. The particle-containing mucus can then be eliminated from the respiratory tract by spitting or swallowing. The respiratory tract has various CYP-450 enzyme systems, which may detoxify certain toxicants. However, many toxicants may be activated by these enzyme systems.

Apart from clearance and detoxication, the respiratory tract also possesses mechanisms to phagocytize and engulf toxicants, notably solid particles. The main effector is the macrophage. Similar to the enzyme systems, the macrophage may also aggravate the toxic effects.

General principles in the pathogenesis of lung damage caused by chemicals

Toxic inhalants, and gases

The sites of deposition of gases in the respiratory tract define the pattern of toxicity of those gases. Solubility, diffusivity, and metabolism/reactivity in respiratory tissues and breathing rate are the critical factor in determining how deeply a given gas penetrates into the lung. Highly soluble gases such as SO₂ do not penetrate farther than the nose (during nasal breathing) unless doses are very high, and are therefore relatively nontoxic to animals, especially obligatory ^{ملازم}nose breathers, such as the rat. Relatively insoluble gases such as ozone and NO₂ penetrate deeply into the lung and reach the smallest airways and the alveoli, where they can elicit toxic responses. Very insoluble gases such as CO and H₂S efficiently pass through the respiratory tract and are taken up by the pulmonary blood supply to be distributed throughout the body.

Particle clearance

Lung defense is dependent on particle clearance, wherein rapid removal lessens the time available to cause damage to the pulmonary tissues or permit local absorption.

Nasal clearance-Particles deposited in the anterior portion of the nose are removed by extrinsic actions such as wiping and blowing. Particles deposited in the posterior portion of the nose are removed by mucociliary clearance that propels mucus toward the glottis, after which the particles are swallowed. Soluble particles may dissolve and enter the epithelium and /or blood before they can be mechanically removed.

Tracheobronchial clearance-particles deposited in the tracheobronchial tree are also removed by mucociliary clearance. In addition to deposited particles, particle-laden ^{مقتل} macrophages are also moved to the oropharynx, where they are swallowed.

Alveolar clearance-Particles deposited in the alveolar region are removed by specialized cells, the alveolar macrophages, lung defense involve both the innate and adaptive and immune systems. Macrophages are the primary effectors of innate lung immunity and their ability to accomplish phagocytosis depends on the recognition of foreign or damage cells by a variety of macrophage surface macromolecules and receptors.

Acute responses of the lung to injury

Trigeminal mediated airway reflexes

Certain gases and vapors stimulate nerve endings in the nose, particularly those of the trigeminal nerve. The result is holding of the breath or changes in breathing patterns, to avoid or reduce further exposure. Transient receptor potential channel receptors may be activated by many irritants causing tickling, itching, and painful nasal sensations. Subfamily A receptors are activated by several irritants activated including acrolein, allyl isothiocyanate (wabasi), allicin (garlic), chlorine, ozone, and hydrogen peroxide.

If continued exposure cannot be avoided, many acidic or alkaline irritants produce cell necrosis and increased permeability of the alveolar walls. Other inhaled chemicals can be more insidious; inhalation of high concentrations of HCl, NO₂, NH₃, or phosgene may at first produce very little apparent damage in the respiratory tract. The epithelial barrier in the alveolar zone, after a latency period of several hours, begins to leak flooding the alveoli and producing a delayed pulmonary edema that is often fatal.

Bronchoconstriction, airway hyperactivity, and neurogenic inflammation

Bronchoconstriction can be provoked by irritants such as acrolein, cigarette smoke and air pollutants, and by cholinergic drugs (acetyl choline), histamine, various prostaglandins and leukotrienes, substance p, and nitric acid. Bronchoconstriction causes a decrease in airway diameter and a corresponding increase in resistance to airflow. Characteristic associated symptoms include wheezing, coughing, a sensation of chest tightness, and dyspnea. Exercise potentiates these problems.

Acute lung injury (pulmonary edema)

Acute lung injury (adult or infant respiratory distress syndrome) is marketed by alveolar epithelial and endothelial cell perturbation اضطراب and inflammatory cell influx that leads to surfactant disruption, pulmonary edema and atelectasis انهيار. Acrolein, HCl, NO₂, NH₃, or phosgens may compromise alveolar barrier function several hours after exposure to low concentrations, and immediate alveolar damage and death with high concentrations.

Chronic responses of the lung to injury

Chronic obstructive pulmonary disease

Characterized by a progressive airflow obstruction, chronic obstructive pulmonary disease involves airway (bronchitis) and alveolar pathology. Chronic bronchitis is defined by the presence of sputum production and cough for at least three months. In emphysema, destruction of the gas exchanging surface area results in a distended, hyperinflated **تضخم** lung that no longer effectively exchanges oxygen and carbon dioxide as a result of both loss of tissue and air trapping. The major cause of human emphysema is, by far, cigarette smoke inhalation, although other toxicants also can elicit this response. A feature of toxicant-induced emphysema is severe or recurrent inflammation.

Lung cancer

Lung cancer is now the leading cause of death from cancer among both men and women. Average smokers have a 10-fold, and heavy smokers a 20-fold, increased risk of developing lung cancer compared with nonsmokers. Many other agents also cause lung cancer.

Human lung cancers may have a latency period of 20–40 years, making the relationship to specific exposures difficult to establish. Two major forms are non-small-cell lung cancer, which account for about 85% of all lung cancers, and may be characterized as squamous cell carcinoma, adenocarcinoma, and large-cell lung cancer.

The potential mechanisms of lung carcinogenesis center on damage of DNA. An activated carcinogen or its metabolic product may interact with DNA.

Asthma

Asthma is characterized clinically by attacks of shortness of breath, which is caused by narrowing of the large conducting airways (bronchi). The clinical hallmarks of asthma is increased airway reactivity of the bronchial muscle in response to exposure to irritants. There may be common mechanisms between asthma and pulmonary fibrosis with regard to the role of recurrent or chronic inflammation in disease pathogenesis.

Pulmonary fibrosis

Fibrotic lungs from humans with acute pulmonary fibrosis contain increased amounts of collagen. In lungs damaged by toxicants, the response resembles adult or infant respiratory distress syndrome. Excess

lung collagen is usually observed not only in the alveolar interstitium, but also throughout the alveolar duct and respiratory bronchioles.

Agents known to produce lung injury in humans

There are about 7900 unique chemicals that are commonly used in industry, many of which represent hazards to the respiratory tract. Exposure prevention is one of the most effective approach to prevent lung injury and disease.

Asbestos: Exposure to asbestos fibers occurs in mining operations and in the construction and shipbuilding industries, where asbestos was at one time widely used for its highly desirable insulating and fireproofing properties. Once asbestos fibers have been deposited in the lung, they may become phagocytized by alveolar macrophages. Short fibers are completely ingested and subsequently removed via the mucociliary escalator. Longer fibers are incompletely ingested, and the macrophages become unable to leave the alveoli. Asbestos-related lung disease thus may be mediated through the triggering of an inflammatory sequence of events or the production of changes that eventually lead to the initiation (DNA damage caused by reactive molecular species) or promotion (increased rate of cell turnover in the lung) of the carcinogenic process.

In humans, asbestos causes three forms of lung disease: asbestosis, lung cancer, and malignant mesothelioma. Asbestosis is characterized by a diffuse increase of collagen in the alveolar walls (fibrosis) and the presence of asbestos fibers, either free or coated with a proteinaceous material (asbestos bodies). Lung cancer develops in workers in the asbestos mining industry and smoking of cigarettes greatly enhances risk.

Silica: Inhaled particles of silicon dioxide (silica) cause a characteristic human lung disease. The disease may be acute or chronic; this is important conceptually because the pathological consequences are manifested quite differently. Acute silicosis occurs only in subjects exposed to a very high level of aerosol containing silicon dioxide particles (most often in form of quartz or sand) small enough to be respirable (usually less than 5 μm) over a relatively short period, generally a few months to a few years. These patients have worsening dyspnea, fever, cough, and weight loss. There is rapid progression of respiratory failure, usually ending in death within a year or two.

Chronic silicosis has a long latency period, usually more than 10 years. Uncomplicated silicosis is almost entirely asymptomatic; little alteration is shown on routine pulmonary function tests even after the disease is radio-graphically demonstrable. The X-ray picture presents

fibrotic nodules, generally in the apical القمة portion of lung. The hilar lymph nodes have peripheral calcifications known as eggshell calcifications. Simple silicosis may progress into complicated silicosis, which is defined as the presence of conglomerate nodules larger than 1 cm in diameter. These nodules usually occur in the upper and mid lung zones. At an advanced stage they may be surrounded by emphysematous bullae. Chronic silicosis is associated with an increased incidence of tuberculosis.

Toxic responses of the skin

Skin as a barrier

The skin protects the body against external insults in order to maintain internal homeostasis. It participates directly in thermal, electrolyte, hormonal, and immune regulation. Rather than merely expelling noxious physical agents, the skin may react to them with various defensive mechanisms that serve to prevent internal or widespread cutaneous damage. If an insult is severe or intense enough to overwhelm the protective function of the skin, acute or chronic injury becomes readily manifest.

Contact dermatitis

Of all occupational skin diseases, contact dermatitis accounts for over 90% of reported causes. Contact dermatitis falls into the two major categories of irritant and allergic forms. Both involves inflammatory processes and can have indistinguishable clinical characteristics of erythema (redness), induration (thickening and firmness), scaling (flaking), and vesiculation (blistering) on area directly contacting the chemical agents.

1- Irritant dermatitis

Irritant dermatitis is the condition that arise from the direct condition of agents to the skin and account for nearly 80% of contact dermatitis cases. A chemical in this category is anticipated to an adverse reaction to anyone if the concentration is high enough and the exposure time long enough.

Exposure is more commonly the result of chronic cumulative irritation from repeated exposures to mild irritants such as soap, detergents, solvents, and cutting oil.

2- Chemical burns

Extremely corrosive and reactive chemicals may produce immediate coagulation necrosis that results in substantial tissue damage, with ulceration and sloughing.

3- Allergic contact dermatitis

Allergic contact dermatitis is a delayed (T-cell mediated) hypersensitivity reaction. To induce sensitization, chemical haptens must penetrate the skin and become attached to carrier protein.

Memory T cells are produced over a 1 to 3 week period and enter the circulation. Subsequent exposure to the same antigen results in an amplified immune response characterized by dermal infiltration and spongiosis.

Granulomatous reactions

A granulomatous reaction to a foreign body is one in which invading substances that cannot be readily removed are consequently isolated. These occur infrequently toward a variety of agents introduced into the skin through injection or after laceration جرح or abrasion خدش. Persistent lesions with abundant inflammatory cells can be produced, resembling chronic infectious conditions (e.g. tuberculosis).

Many substances can produce granulomatous reactions, including silica, talc, paraffin or mineral oil, and beryllium.

Photosensitivity

1- Phototoxicity

Phototoxic reactions from exogenous chemicals may be produced by systemic or topical administration or exposure. In acute reactions, the skin may appear red and blister within minutes to hours after ultraviolet light exposure. Chronic phototoxic responses may result in hyperpigmentation and thickening of the affected area. UV A (320- 400nm) is the most commonly responsible; UV B (290-320 nm) may occasionally be involved.

2- Photoallergy

In contrast to phototoxicity, photoallergy is a type IV delayed hypersensitivity reaction, leading typically to eczema. Hence, photoallergy requires prior sensitization to the chemical. Induction and subsequent elicitation of reactions may result from topical exposure as in photocontact dermatitis or from systemic photoallergy.

UV light is necessary to convert a potential photosensitizing chemical into a hapten that elicits يثير an allergic response, photoallergy generally is distinguishable from phototoxicity because the former results from delayed hypersensitivity and amounts of chemical too low to give a toxic response still suffice to elicit allergy.

Acne

Comedogenic chemicals induce comedone lesions, which may be open or closed (blackhead or whitehead, respectively, in the vernacular). Additionally papules, pustules, cysts, and scars may complicate the process. Hair follicles

and associated sebaceous glands become clogged with compacted keratinocytes that are bathed in sebum. The pigmentary change most evident in open comedones is from melanin.

Pigmentary disturbance

Several factors influence pigmentation of the skin. Melanin is produced through a series of enzymes pathways beginning with tyrosine. Errors in this pathway or exposure to tyrosine analogs may results in abnormal pigmentation. Hyperpigmentation results from increased melanin production or deposition of endogenous or exogenous pigments in the upper dermis. Exogenous hyperpigmentation can arise from deposition of metals and drugs in dermal tissue. Conversely, hypopigmentation is a loss of pigmentation from melanin loss, melanocyte damage, or vascular abnormalities. Leukoderma (vitiligo) and depigmentation denote complete loss of melanin from the skin, imparting يعرف a porcelain-white appearance.

Urticaria

For those allergens to which IgE antibodies have been elicited يثار by previous or ongoing exposure, subsequent contact can lead to development of urticaria (hives), typically in minutes, through an immediate type I hypersensitivity reaction.

Food allergies and pharmaceuticals are major causes of acute uticaria, but may other causes are known. Certain food allergies (e.g. nuts, fish, and shellfish) are capable of producing the life-threatening response, anaphylactic shock. Some agents (e.g. opiates) can bring about direct release of histamine from mast cells without antibody mediation, while others (nonsteroidal anti-inflammatories) may do so through effects on arachidonic acid metabolism or by uncertain mechanisms.

Contact urticaria in an occupational setting can arise from exposure to plant or animal proteins and appear more common in atopic individuals. Among the numerous occupations where this response occurs include hairdressers and those involving routine handling of food, plant, or animal products. Healthcare is an occupation in which allergic contact dermatitis to latex rubber is a common problem.

Toxic epidermal necrolysis

Toxic epidermal necrolysis (TEN) represents one of the most life-threatening dermatologic diseases that is caused by drugs and chemicals. At the most

severe end of a spectrum, TEN involves detachment of $\geq 30\%$ of the epidermal surface from the dermis, commonly accompanied by severe erosions of mucous membrane and has a fatality rate = 30%.

Nearly 200 drugs have been reported to cause the syndrome with major contributors being anticonvulsants, nonsteroidal anti-inflammatories, antibacterial sulfonamides, and allopurinol.

Skin cancer

1- Radiation

X-ray could cause severe burns, squamous cell carcinoma, and basal cell carcinomas. X-ray-induced non-melanoma skin cancer continued to be observed.

2- UV-induced skin cancer

The most common UV-induced skin cancers are non-melanoma skin cancers and cutaneous malignant melanoma.

Skin cancer incidence is highest in the tropics and in pale – complexioned white. Even when it does not causes cancer in normal individuals, sun exposure leads to premature aging of the skin. For this reason, sunbathing is discouraged and the use of sun-block is encouraged.

3- Polycyclic aromatic hydrocarbons

Substances rich in polycyclic hydrocarbons (cool tar, creosote) are skin carcinogens in humans and animals. Oxidation biotransformation of polycyclic aromatic compounds produces electrophilic epoxides that can form DNA adducts.

4- Arsenic

High exposure from smelting صهر operations and from well water ماء derived from rock strata طبقات الصخور with a high arsenic content are associated with arsenical keratosis (premalignant lesions), black-foot disease (a circulatory disorder reflecting endothelial cell damage), and squamous cell carcinoma of the skin and several other organs (bladder, lung, and liver).

Toxic effects of pesticides

Introduction

Pesticides can be defined as any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating pests. Pests can be insects, rodents, weeds, and a host of other unwanted organisms. Pesticides may be more identified as insecticides (insects), herbicides (weeds), fungicides (fungi, molds), and rodenticides (rodents), but there are also acaricides (mites العث), molluscides (snails, other mollusks الرخويات), miticides (mites), larvicides (larvae), and pediculocides (lice).

Exposure

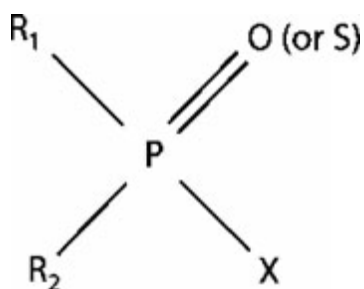
Exposure to pesticides can occur via the oral or dermal routes or by inhalation. High oral doses, leading to severe poisoning and death, are achieved as a result of pesticide ingestion for suicidal intents, or of accidental ingestion, commonly due to storage of pesticides in improper containers. Chronic low doses on the other hand, are consumed by the general population as pesticide residues in food, or as contaminants in drinking water. Regulations exist to ensure that pesticide residues are maintained at levels below those that would cause any adverse effects. Workers involved in the production, transport, mixing and loading, and application of pesticides, as well as in harvesting of pesticide-sprayed crops, are at highest risk for pesticide exposure dermal exposure during normal handling or application of pesticides, or in case of accidental spillings تسرب, occurs in body areas not covered by protective clothing, such as the face or the hands. Furthermore, deposition of pesticides on clothing may penetrate the skin and/or to potential exposure of others, if clothes are not changed and washed upon termination of exposure.

Insecticides

Insecticides play a most relevant role in the control of insect pests, particularly in developing countries. All of the chemical insecticides in use today are neurotoxicants, and act by poisoning the nervous systems of the target organisms. As a class, insecticides have higher acute toxicity toward nontarget species compared to other pesticides. Some of them, most notably the organophosphates, are involved in a great number of human poisonings and deaths each year.

Organophosphorus compounds

The general structure of OP insecticides can be represented by



Where X is the so-called “leaving group,” that is displaced when the OP phosphorylates acetylcholinesterase (AChE), and is the most sensitive to hydrolysis; R1 and R2 are most commonly alkoxy groups (i.e., OCH₃ or OC₂H₅), though other chemical substitutes are also possible; either an oxygen or a sulfur (in this case the compound should be defined as a phosphorothioate) are also attached to the phosphorus with a double bond. Based on chemical differences, OPs can be divided into several subclasses, which include phosphates, phosphorothioates, phosphoramidates, phosphonates, and others.

Signs and symptoms of toxicity and mechanism of action

Organophosphorus insecticides have high acute toxicity, with oral LD₅₀ values in rat often below 50 mg/kg, though for some widely used compounds (e.g., chlorpyrifos, diazinon) toxicity is somewhat lower, due to effective detoxication. For several OPs acute dermal toxicity is also high. Inhibition of AChE by OPs causes accumulation of acetylcholine at cholinergic synapses, with over-stimulation of cholinergic receptors of the muscarinic and nicotinic type. As these receptors are localized in most organs of the body, a “cholinergic syndrome” follows, which includes increased sweating and salivation, profound bronchial secretion, bronchoconstriction, miosis, increased gastrointestinal motility, diarrhea, tremors, muscular twitching, and various central nervous system effects. When death occurs, this is believed to be due to respiratory failure due to inhibition of respiratory centers in the brain stem.

Treatment of Poisoning

In case of dermal exposure, contaminated clothing should be removed, and the skin washed with alkaline soap. In case of ingestion, procedures to reduce absorption from the gastrointestinal tract do not appear to be very effective. Atropine represents the cornerstone of the treatment for OP poisoning; it is a muscarinic receptor antagonist, and thus prevents the action of accumulating acetylcholine on these receptors. Atropine is

preferably given intravenously, though the intramuscular route is also effective.

The administration of pralidoxime (2-PAM) early after OP exposure can help prevent acetylcholinesterase aging but its effectiveness is equivocal and harm may ensue. Diazepam may be used to relieve anxiety in mild cases, and to reduce muscle fasciculation اضطراب حركة العضلات and control convulsions in the more severe cases.

Carbamates

Carbamate insecticides have a variety of chemical structures, but all derive from carbamic acid, the majority being *N*-methylcarbamates. They present different degrees of acute oral toxicity, ranging from moderate to low toxicity such as carbaryl, to extremely high toxicity, such as aldicarb.

Carbamates are susceptible to a variety of enzyme-catalyzed biotransformation reactions, and the principal pathways involve oxidation and hydrolysis. The mechanism of toxicity of carbamates is analogous to that of OPs, in that they inhibit AChE. However, inhibition is transient and rapidly reversible. The sign and symptoms of carbamate poisoning are the same as observed following intoxication with OPs, and include miosis, urination, diarrhea, salivation, muscle fasciculation, and CNS effects. Acute intoxication by carbamates is generally resolved within a few hours. The treatment of carbamate intoxication relies on the use of the muscarinic antagonist atropine.

Pyrethroids

Because of their high insecticidal potency, relatively low mammalian toxicity, lack of environmental persistence, and low tendency to induce insect resistance, pyrethroids have encountered much success in the past thirty years, and now account for more than 25% of the global insecticide market. Pyrethroids are used widely as insecticides both in the house and in agriculture, in medicine for the topical treatment of scabies and head lice, and in tropical countries in soaked bed nets to prevent mosquito bites. Pyrethroids are known to alter the normal function of insect nerves by modifying the kinetics of voltage-sensitive sodium channels.

Upon occupational exposure, the primary adverse effect resulting from dermal contact with pyrethroids is paresthesia. Symptoms include continuous tingling or pricking or, when more severe, burning. The condition reverses in about 24 hours, and topical application of vitamin E has been shown to be an effective treatment.

Organochlorine compounds

The organochlorine insecticides include the chlorinated ethane derivatives, such as DDT and its analogues; the cyclodienes, such as chlordane, aldrin; the hexachlorocyclohexanes, such as lindane.

DDT and Its Analogues

DDT was effective against a wide variety of agricultural pests, as well as against insects that transmit some of the world's most serious diseases, such as typhus, malaria, and yellow fever. DDT has a moderate acute toxicity when given by the oral route. Dermal absorption of DDT is very limited.

Acute exposure to high doses of DDT causes motor unrest, increased frequency of spontaneous movements, abnormal susceptibility to fear and hyper-susceptibility to external stimuli (light, touch, sound). This is followed by the development of fine tremors, progressing to coarse tremors, and eventually tonic-clonic convulsions. Symptoms usually appear several hours after exposure, and death, usually due to respiratory failure, may follow after 24–72 h.

DDT and Public Health: Risk-Benefit Considerations The Stockholm Convention on Persistent Organic Pollutants, ratified in 2004 by 50 states, outlawed the use of 12 industrial chemicals (the “Dirty Dozen”), including DDT. Yet, an exemption clause allows malaria-endemic nations to continue utilizing DDT for indoor residual wall spraying. The United Nations Environment Program estimates that about 25 countries would use DDT under this exemption from its ban. This situation is keeping the debate on the risks and benefits of DDT usage very much alive.

Insect repellents

Insect-transmitted diseases remain a major source of illness and death worldwide. DEET (N,N-diethyl-3-methylbenzamide) is very effective at repelling insects, flies, fleas, and ticks, and protection time increases with increasing concentrations. Sub-chronic toxicity studies in various species did not reveal major toxic effects. No significant effects of DEET were seen in mutagenicity, reproductive toxicity, and carcinogenicity studies. Acute and chronic neurotoxicity studies also provided negative results.

Picaridin

Insect repellent formulations (cream, aerosol, wipe) containing 5% to 20% picaridin are highly effective against a variety of arthropod pest especially mosquitoes, ticks, and flies. Its action in insects is believed to be due to the interaction with specific olfactory receptors of the arthropod. Picaridin containing formulations are deemed **يعتبر** to be safe and effective when used as directed.

Herbicides

Herbicides are chemicals that are capable of either killing or severely injuring plants. Some of the various mechanisms by which herbicides exert their biological effects. *preplanting* herbicides are applied to the soil before a crop محصول is seeded; *preemergent* herbicides are applied to the soil before the time of appearance of unwanted vegetation; and *postemergent* herbicides are applied to the soil or foliage اشجار اوراق after the germination انبات of the crop and/or weeds العشب الضارة. Herbicides are also divided according to the manner they are applied to plants. *Contact* herbicides are those that affect the plant that was treated, while *translocated* herbicides are applied to the soil or to above-ground parts of the plant, and are absorbed and circulated to distant tissues. Nonselective herbicides will kill all vegetation, while selective compounds are those used to kill weeds without harming the crops.

A number of herbicides can cause dermal irritation and contact dermatitis, particularly in individuals prone to allergic reactions. Other compounds have generated much debate for their suspected carcinogenicity or neurotoxicity.

Chlorophenoxy compounds

Chlorophenoxy herbicides are chemical analogues of auxin, a plant growth hormone, and produce uncontrolled and lethal growth in target plants.

Fungicides

Fungicidal chemicals are derived from a variety of structures, from simple inorganic compounds, such as copper sulfate, to complex organic compounds. The majority of fungicides are surface or plant protectants, and are applied prior to potential infection by fungal spores, either to plants or to postharvest crops. Other fungicides can be used therapeutically, to cure plants when an infestation has already begun.

Inorganic and organometal fungicides

Copper sulfate has overall low toxicity and remains one of the most widely used fungicides. Among organotin compounds, triphenyltin acetate is used as a fungicide. Triphenyltin has moderate to high acute toxicity, but may cause reproductive toxicity and endocrine disruption.

Rodenticides

Rats and mice can cause health and economic damages to humans. Rodenticides still play and will likely continue to play an important role in rodent control. To be effective, yet safe, rodenticides must satisfy several criteria: (1) the poison must be very effective in the target species once incorporated into bait in small quantity; (2) baits طعوم containing the poison must not excite bait shyness حذر, so that the animal will continue to eat it; (3) the manner of death must be such that survivors do not become suspicious of its cause; and (4) it should be species-specific, with considerable lower toxicity to other animals.

Fluoroacetic acid and its derivatives

Sodium fluoroacetate (Compound 1080) and fluoroacetamide are the main representatives of this class of rodenticides. They are white in color and odorless, and due to their high mammalian toxicity, their use is restricted to trained personnel. The main targets of toxicity are the central nervous system and the heart.

Anticoagulants

In addition to their use as rodenticides, coumarin derivatives, including warfarin itself, are used as anticoagulant drugs and have become a mainstay for prevention of thromboembolic disease. Human poisonings by these rodenticides are rare because they are dispersed in grain-based baits. However, there is a significant number of suicide or homicide attempts or of accidental consumption of warfarin.

Fumigants

These agents are active toward insects, mites, nematodes, weed seeds, fungi or rodents, and have in common the property of being in the gaseous form at the time they exert their pesticidal action. They can be liquids that readily vaporize (e.g., ethylene dibromide), solids that can release a toxic gas on reaction with water (e.g., phosphine released by aluminum phosphide), or gases (e.g., methyl bromide).

Sulfur

It is very effective as a fumigant for the control of many plant diseases, particularly fungal diseases, and still represents the most heavily used crop protection chemical in the United States. The primary health effect in humans associated with the agricultural use of elemental sulfur is dermatitis. In ruminants, excessive sulfur ingestion can cause cerebrocortical necrosis.

Toxic effects of solvents and vapors

The term *solvent* refers to a class of liquid organic chemicals of variable lipophilicity and volatility. These properties, coupled with small molecular size and lack of charge, make inhalation the major route of solvent exposure and provide for ready absorption across the lung, gastrointestinal (GI) tract, and skin.

Solvents are classified largely according to molecular structure or functional group. Classes of solvents include aliphatic hydrocarbons, many of which are chlorinated (i.e., halocarbons); aromatic hydrocarbons; alcohols; ethers; esters/acetates; amides/amines; aldehydes; ketones; and complex mixtures that defy يتحدى classification.

The main determinants of a solvent's inherent ملازم toxicity are: (1) its number of carbon atoms; (2) whether it is saturated or has double or triple bonds between adjacent carbon atoms; (3) its configuration (i.e., straight chain, branched chain, or cyclic); and (4) the presence of functional groups. Some class-wide generalizations regarding toxicity can be made. For example, the more lipophilic a hydrocarbon, the more potent a central nervous system (CNS) depressant it is; amides/amines tend to be potent sensitizers; aldehydes are particularly irritating; hydrocarbons that are extensively metabolized tend to be more cytotoxic/mutagenic; and many unsaturated, short chain halocarbons are animal carcinogens

The adverse health effects occur from solvent exposure is dependent on several factors: (1) toxicity of the solvent; (2) exposure route; (3) amount or rate of exposure; (4) duration of exposure; (5) individual susceptibility; and (6) interactions with other chemicals. Adverse health effects may occur acutely and be readily discernible قابل للتمييز, or they may be the result of chronic exposure and have insidious onset.

Solvent abuse

Solvents are among the most popular classes of drugs of abuse, given their presence in a multitude of inexpensive, readily available products that are legal to buy and possess. These products are used for common household and industrial purposes and include paint thinners and removers, dry cleaning fluids, degreasers, gasoline, glues, typewriter fluid, nail polish remover, felt-tip القلم رأس marker fluids, and aerosols such as fabric protector sprays and spray paints. Solvents are often among the first drugs used by children and adolescents.

Solvent abuse is a unique exposure situation in that participants repeatedly subject themselves to vapor concentrations high enough to

produce effects that resemble alcohol intoxication. Solvents can be breathed in through the nose or the mouth by “sniffing” or “snorting” vapors from containers; spraying aerosols directly into the nose or mouth; “bagging” by inhaling vapors from substances sprayed or deposited inside a plastic or paper bag; or “huffing” نفخ from a solvent-soaked rag قماش stuffed محشو into the mouth. Although dependent on the pattern of inhalation, blood levels of solvents typically peak minutes after inhalation begins, and the abuser can begin to experience intoxication after a matter of seconds. While intoxication may last only a few minutes, abusers frequently seek to prolong the “high” by inhaling repeatedly over the course of several hours. In extreme circumstances, death may be a consequence of cardiac arrhythmias, asphyxiation اختناق, and/or cachexia تعب.

Environmental contamination

The majority of the more volatile organic compounds (VOCs) volatilize when products containing them (e.g., aerosol propellants, paint thinners, cleaners, and soil fumigants تبخير) are used as intended. Solvent loss into the atmosphere also occurs during production, processing, storage, and transport activities, resulting in elevated concentrations in air in the proximity of point sources. Winds dilute and disperse solvent vapors across the world.

Solvent contamination of drinking water supplies is of major health concern. Although the majority of a solvent spilled onto the ground evaporates, some may permeate the soil and migrate through it until reaching groundwater.

Classification of the solvents

1- Chlorinated hydrocarbons

Trichloroethylene

It is widely used solvent for metal degreasing. Moderate-to-high doses of TCE, as with other halocarbons, are associated with a number of non-cancer toxicities including autoimmune disorders, immune system dysfunction, and potentially a male reproductive toxicants.

Carbon Tetrachloride

CCl₄ previously enjoyed widespread use as a solvent, cleaning agent, fire extinguisher, synthetic intermediate, grain fumigant, and human anthelmintic. Its use has steadily declined since the 1970s, due to its hepatorenal toxicity, carcinogenicity, and contribution to atmospheric ozone depletion.

It is likely that the mechanism of liver injury by CCl₄ has received more attention than that of any other chemical. Nevertheless, there is still

considerable debate about the relative importance of different actions of CC14, notably covalent binding and lipid peroxidation. CC14 is known to be metabolized by P450-dependent reductive dehalogenation to a trichloromethyl radical (CC13·). This radical can bind covalently to nucleic acids to initiate liver cancer, and bind to lipids and proteins, causing structural damage of membranes and inhibition of a variety of enzymes.

2- Aromatic hydrocarbons

Benzene

Benzene is now used principally in the synthesis of other chemicals. The percentage by volume of benzene in gasoline is 1–2%. Benzene plays an important role in unleaded gasoline due to its antiknock properties. Inhalation is the primary route of exposure in industrial and in everyday settings. Cigarette smoke is the major source of benzene in the home.

The most important adverse effect of benzene is hematopoietic toxicity. Chronic exposure to benzene can lead to bone marrow damage, which may be manifest initially as anemia, leukopenia, thrombocytopenia, or a combination of these. Bone marrow depression appears to be dose dependent in both laboratory animals and humans. Continued exposure may result in marrow aplasia and pancytopenia, an often fatal outcome. There is strong evidence from epidemiological studies that high-level benzene exposures result in an increased risk of acute myelogenous leukemia (AML) in humans.

Toluene

Toluene is present in paints, lacquersورنيش, thinners, cleaning agents, glues, and many other products. Toluene is also used in the production of other chemicals. Gasoline, which contains 5–7% toluene by weight, is the largest source of atmospheric emissions and exposure of the general populaceالناس. Inhalation is the primary route of exposure, though skin contact occurs frequently. Toluene is a favorite of solvent abusers, who intentionally inhale high concentrations to achieve a euphoric effect.

The CNS is the primary target organ of toluene and other alkylbenzenes. Manifestations of acute exposure range from slight dizziness and headache to unconsciousness, respiratory depression, and death.

3- Alcohols

Ethanol

Many humans experience greater exposure to ethanol (ethyl alcohol and alcohol) than to any other solvent. Not only is ethyl alcohol used as an additive in gasoline, as a solvent in industry, in many household products,

and in pharmaceuticals, but it is also heavily consumed in intoxicating beverages المشروبات المسكرة.

Alcohol-induced hepatotoxicity is postulated to be caused by elevation of endotoxin in the bloodstream. Endotoxin, released by the action of ethanol on gram-negative bacteria in the gut, is believed to be taken up by Kupffer cells, causing the release of inflammatory mediators that are cytotoxic to hepatocytes and chemo attractants for neutrophils.

Alcohol-induced damage of the liver and other tissues is believed to result in part from nutritional disturbances, as well as toxic effects. Lack of money, poor judgment, prolonged inebriation, and appetite loss contribute to poor nutrition and weight loss in alcoholics. A high percentage of calories in the alcoholic's diet is furnished by alcohol.

Alcoholism can result in damage of extrahepatic tissues. Alcoholic myopathy is one of the more common consequences, occurring in 50% of alcohol abusers. The condition is characterized by reductions in skeletal muscle mass and strength. Alcoholic cardiomyopathy is a complex process. It results from decreased synthesis of cardiac contractile proteins.

There was "sufficient evidence" for causation of tumors of the oral cavity, pharynx and larynx, esophagus, and liver of humans. Use of alcohol is also linked to a moderate increase in risk of lobular and hormone receptor-positive breast cancer in women.

Methanol

Methanol (methyl alcohol, wood alcohol, and CH_3OH) is primarily used as a starting material for the synthesis of chemicals such as formaldehyde, acetic acid, and methacrylates.

Serious methanol toxicity is most commonly associated with ingestion. Left untreated, acute methanol poisoning in humans is characterized by an asymptomatic latent period of 12–24 hours followed by formic acidemia, ocular toxicity, coma, and in extreme cases death. CH_3OH 's target within the eye is the retina, specifically the optic disk and optic nerve.

4- Glycols

Ethylene glycol

Ethylene glycol (1,2-dihydroxyethane, EG) is a constituent of antifreeze, hydraulic fluids, drying agents, and inks, and is used to make plastics and polyester fibers. The most important exposure route is ingestion, as EG may be accidentally swallowed, taken deliberately بتعمد in suicide attempts, or used as a cheap substitute for ethanol. "Antifreeze" poisoning occurs frequently in cats and dogs that find its taste appealing.

Three clinical stages after an asymptomatic period, during which EG is metabolized: (1) a period of inebriation سُكر، ثمالة, the duration and degree

depending on dose; (2) the cardiopulmonary stage 12–24 hours after exposure, characterized by tachycardia and tachypnea, which may progress to cardiac failure and pulmonary edema; and (3) the renal toxicity stage.

After the absorption EG from the GIT, is converted to oxalic acid. Hypocalcemia can result from Ca^{2+} chelation by oxalic acid to form Ca^{2+} oxalate monohydrate crystals. Deposition of these crystals in kidney tubules and small blood vessels in the brain is associated with damage of these organs.

Glycol ethers

Glycol ethers also find use as solvents in paint thinners, inks, metal cleaning products, liquid soaps, and household cleaners, and are used as jet fuel anti-icing additives and in semiconductor fabrication. Human exposure occurs mainly via inhalation, but also by dermal absorption. In vitro and in vivo toxicity studies demonstrate that some glycol ethers and their oxidative metabolites are reproductive, developmental, hematologic, and immunologic toxicants by all exposure routes.

5- Automotive gasoline and additives

Automotive gasoline is a complex mixture of hundreds of hydrocarbons predominantly in the C4 to C12 range. The most extreme exposures occur to those intentionally sniffing gasoline for its euphoric effects. This dangerous habit can cause acute and chronic encephalopathies that are expressed as both motor and cognitive impairment. Ingestion of gasoline during siphoning events is typically followed by a burning sensation in the mouth and pharynx, as well as nausea, vomiting, and diarrhea resulting from GI irritation. If aspirated into the lungs, gasoline may produce pulmonary epithelial damage, edema, and pneumonitis. Thus, emetic therapy for gasoline ingestion is usually contraindicated.

Chemical carcinogenesis

Overview

Cancer remains a leading cause of morbidity and mortality in the human population. Cancer is a group of diseases in which there is an uncontrolled proliferation of cells. It has been proposed that cancer has six hallmarks: صفة مميزة

- 1- Self-sufficiency in growth signals. لا حاجة الى تحفيز للنمو.
- 2- Insensitivity to antigrowth signals.
- 3- Escape of apoptosis.
- 4- Tissue invasion and metastasis.
- 5- Sustained angiogenesis. نمو الاوعية الدموية.
- 6- Limitless replication potential. تكاثر لا حد له.

Multistage carcinogenesis

The induction of neoplasm is a multistage process that occurs over a long period of time in humans. These steps have been defined as initiation, promotion, and progression.

Initiation

Initiation is a phenomenon of gene alteration, which may result from the interaction of ultimate carcinogens with DNA in the target cells. Chemicals capable of initiating cells are called initiating agents. Initiation without the following steps, promotion, and progression, rarely yields malignant neoplasms.

Once initiated cells are formed, their fate has multiple potential outcome:

- 1- The initiated cell can remain in a state non-dividing states
- 2- The initiated cell may possess mutations incompatible with viability or normal function and be deleted through apoptotic mechanisms or
- 3- The cell may undergo cell division resulting in the proliferation of the initiated cell.

Mutation of pro-oncogenes, such as the ras genes may result in their activation, leading to neoplastic transformation. On the other hand, mutation in tumor suppressor gene, such as the p53 gene may cause in their

inactivation. Inactivation of the p53 tumor suppressor gene leads to induction of cancer. In fact, p53 is the most commonly mutated gene found in human cancers.

Promotion نقل

It involves the selective clonal expansion توسع استنساخي of initiated cells to produce a pre-neoplastic lesion. This is referred to as the promotion stage of the carcinogenesis process. Both exogenous and endogenous agents that function at this stage are referred to as tumor promoters.

Tumor promoters are not mutagenic and generally are not able to induce tumors by themselves, rather they act through several mechanisms involving gene expression التعبير الجيني changes that result in sustained cell proliferation and or inhibition of apoptosis. Typical tumor promoters include phenobarbital and cholic acid.

One distinct characteristic of promotion, in contrast to initiation and progression, is the reversible nature of this stage. In this regard, the existence of the promoted cell population (pre-neoplastic lesion) is dependent on the continued administration of the promoting agents. The regression of pre-neoplastic lesion upon withdrawal of the promoters may be due to increased cell death via apoptosis.

Because tumor promotion has long duration and reversibility, tumor promotion is considered a preferred target for cancer chemoprevention.

Progression

Progression is the last irreversible stage of carcinogenesis which usually develops from the cells in the stage of promotion.

Progression results from continuing evolution التحول of a basically unstable karyotype النمط النووي, leading to morphologically alteration in cellular genomic structure. Either benign or malignant neoplasm are observed in this stage.

Agents that only cause the transition of a cell from the stage of promotion to that of progression are termed progressor agents. Progressor agents may include hydrogenperoxid, hydroxylurea and arsenic salts.

Due to significant genetic alteration, cells in the progression stage may gain the ability to undergo invasiveness and metastasis to eventually lead to the formation of a clinical cancer.

Mechanism of chemical carcinogenesis

The development of neoplasia requires two major events: the formation of an initiated, mutated cell and the selective proliferation of the mutated cell to form a neoplasm. Both these events can be induced or acted upon by chemical carcinogens.

Chemical carcinogens may be classified based on their chemical nature into: 1- Organic chemical carcinogens, such as bezo(a)pyrine, aflotoxine B1, and benzene. 2- Inorganic chemical carcinogens including arsenic , cadmium, chromium and nikel. 3- Hormonal carcinogen, typified by estrogens.

Chemicals that induce cancer have also been broadly classified into one of two categories—genotoxic or DNA reactive, and nongenotoxic or epigenetic carcinogens—based on their relative abilities to interact with genomic DNA.

1- Genotoxic carcinogens

Mutagenesis

A genotoxic carcinogen is able to interact with DNA directly or indirectly, leading to mutations. The induction of the mutation is due to primarily to chemical or physical alteration in the structure of DNA that result in inaccurate replication of that region of the genome.

The process of mutagenesis include two major steps: structural DNA alteration, and cell proliferation that lead to the fixation of the DNA alteration.

DNA repair

The interaction of ultimate carcinogens with DNA results in the formation of various DNA adducts اضافي.

Because of the existence of this DNA repair machinery, the structural damage induced by carcinogens may be effectively repaired and thus mutagenesis can be prevented.

On the other hand, the persistence of DNA-carcinogen adducts is indicative of the insufficiency of DNA repair.

Classes of genotoxic carcinogens

a- Polyaromatic hydrocarbons

Polyaromatic hydrocarbons such as benzo(*a*)pyrene are found at high levels in charcoal broiled foods مشوي, cigarette smoke, and in diesel exhaust.

b- Alkylating agents

Whereas some alkylating chemicals are direct-acting genotoxic agents, many require metabolic activation to produce electrophilic metabolites that can react with DNA. Alkylating chemicals (indirect) including the nitrogen mustards (e.g., chlorambucil, cyclophosphamide) have been used in cancer chemotherapy. The alkylation of DNA by nitrogen mustard requires the formation of highly reactive metabolites.

c- Aromatic amines and amides

Aromatic amines and amides encompass a class of chemicals with varied structures. Classically, exposure to these chemicals was through the dye industry, although exposure still occurs through cigarette smoke and other environmental sources.

The aromatic amines undergo phase-I (hydrolysis, reduction, and oxidation) and phase-II (conjugation) metabolism. Phase-I reactions occur mainly by cytochrome P450-mediated reactions, yielding hydroxylated metabolites that are often associated with adduct formation in proteins and DNA and produce liver and bladder carcinogenicity.

2- Non-genotoxic (epigenetic) carcinogens

There are many chemicals that can cause cancer but do not directly affect DNA. These carcinogens are designated non-genotoxic (epigenetic). They have the following characteristics:

- 1- They are non-mutagenic.
- 2- They show no evidence of direct chemical reactivity with DNA.
- 3- There are no chemical structural features between these chemicals.
- 4- They exhibit a clear dose threshold effect.
- 5- Their carcinogens potential is generally lower than that of genotoxic carcinogens.

These carcinogens act by sustained cytotoxicity, receptor mediated, hormonal action, modulation of methylation status, and oxidative stress.

a- Cytotoxicity

Chloroform induced liver and kidney tumors and melamine induced bladder tumors are classic examples of chemical carcinogens that are as functioning via cytolethal mode of action.

Chemicals that function through this mechanism produce sustained cell death, that is accompanied ومصاحب by persistent regenerative growth, resulting in the potential for the acquisition اكتساب of spontaneous DNA mutation and allowing mutated cells to accumulate and proliferate.

مما أدى الى امكانية الحصول على طفرة DNA العفوية

b- Receptor mediated

1) P450 inducers: phenobarbital-like carcinogens

Phenobarbital is a commonly studied non-DNA reactive compound that is known to cause tumors by a non-genotoxic mechanism involving liver hyperplasia. One feature seen following phenobarbital exposure is the induction of P450 enzymes, particularly CYP2B.

2) Peroxisome proliferator activated receptor α (PPAR α)

A wide array of chemicals are capable of increasing the number and volume of peroxisomes in the cytoplasm of cells. These chemicals, termed peroxisome proliferators, include chemicals such as herbicides, chlorinated solvents (e.g., trichloroethylene), plasticizers (e.g., diethylhexylphthalate and other phthalates), lipid lowering fibrate drugs (e.g., ciprofibrate, clofibrate), and natural products.

The currently accepted mode of action for this class of chemicals involves agonist binding to the nuclear hormone receptor, peroxisome proliferator-activated receptor alpha (PPAR α).

c- Hormonal mode of action

Hormonally active chemicals include biogenic amines, steroids, and peptide hormones that cause tissue specific changes through interaction with a receptor. In addition, a number of non-DNA reactive chemicals can induce neoplasms in rodents through receptor-mediated mechanisms, and/or perturbation اضطراب of hormonal balance.

Trophic hormones are known to induce cell proliferation at their target organs. This action may lead to the development of tumors when the mechanisms of hormonal control are disrupted and some or other hormone shows persistently increased levels. Several well-studied examples include the induction of ovarian neoplasms via decreased estradiol and increased LH levels and the induction of thyroid tumors in rats by phenobarbital-type P450 inducers.

A number of chemicals that reduce thyroid hormone concentrations (T4 and/or T3) and increase thyroid-stimulating hormone (TSH) have been shown to induce neoplasia in the rodent thyroid. TSH demonstrates proliferative activity in the thyroid, with chronic drug-induced TSH increases leading to progression of follicular cell hypertrophy, hyperplasia, and eventually neoplasia.

d- Oxidative stress and chemical carcinogenesis

Experimental evidence has shown that increases in reactive oxygen in the cell, through either physiological modification or through chemical carcinogen exposure, contribute to the carcinogenesis processes.

Reactivity's of reactive compounds including the superoxide anion ($\bullet\text{O}_2^-$), hydroperoxyl radical ($\text{HO}_2 \bullet$), hydrogen peroxide (H_2O_2), and the hydroxyl radical ($\bullet\text{OH}$), all derived through the reduction of molecular oxygen.

Oxygen radicals can be produced by both endogenous and exogenous sources and are typically counterbalanced by antioxidants. Antioxidant defenses are both enzymatic (e.g., superoxide dismutase, glutathione peroxidase, and catalase) and nonenzymatic (e.g., vitamin E, vitamin C, β -carotene, glutathione). Importantly, many of these antioxidants are provided through dietary intake.

Chemical carcinogenesis in human

A number of factors have been implicated in the induction of cancer in humans. Infectious agents, lifestyle, medical treatments, environmental and occupational exposure account either directly or indirectly for the majority of cancers seen in humans.

Of these, the component that contributes the most to human cancer induction and progression is **lifestyle**: tobacco use, alcohol use, and poor diet.

Tobacco usage either through smoking tobacco, chewing tobacco, or tobacco snuff-type products is estimated to be responsible for 25–40% of all human cancers. In particular a strong correlation between tobacco usage and mouth, larynx, lung, esophageal, and bladder cancer exists. It has been estimated that 85–90% of all lung cancer cases in the United States are a direct result of tobacco use. The induction of pancreatic cancer also appears to have a linkage to tobacco use. Alcohol consumption contributes anywhere from 2 to 4% of cancers of the esophagus, liver, and larynx.

Poor diets whether high fat, low protein, high calories, or diets lacking in needed antioxidants and minerals account for anywhere from 10 to 70% of human cancers. Diet contaminated by molds such as *Aspergillus flavis* (which produces aflatoxin B1) have been linked epidemiologically to a higher incidence of liver cancer. It also appears that aflatoxin B1 exposure coupled with hepatitis B virus infection produces an increased incidence of liver cancer compared to aflatoxin B1 or hepatitis B exposure individually.

In particular **high fat and high calorie diets** have been linked to breast, colon, and gall bladder cancer in humans. Diets poor in antioxidants and/or vitamins such as vitamin A and vitamin E probably also contribute to the onset of cancer.

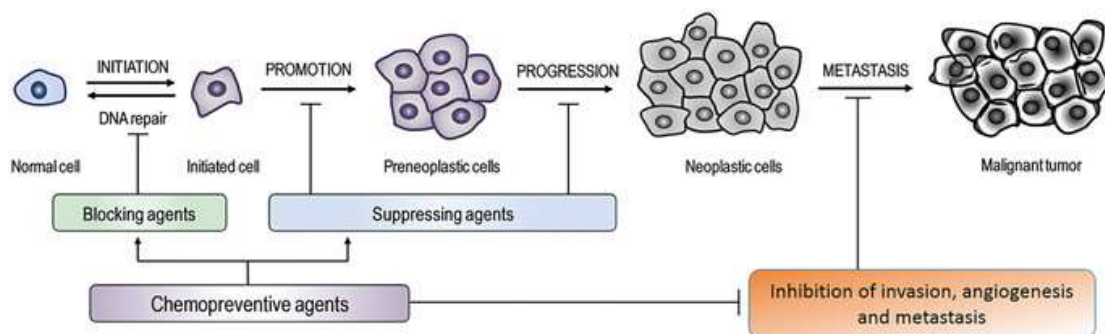
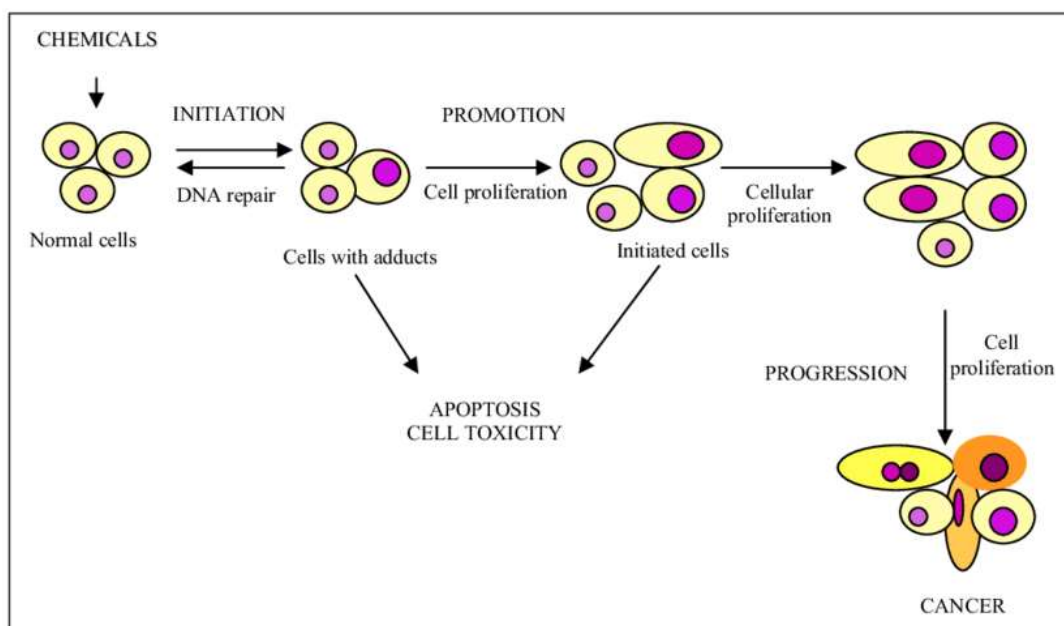
The method of cooking may also influence the production of carcinogens produced in the cooking process. Carcinogenic heterocyclic amines and polycyclic aromatic hydrocarbons are formed during broiling and grilling of meat. Acrylamide, a suspected human carcinogen has been found in fried foods at low concentrations.

The linkage between occupational exposure to **asbestos** and the development of bronchiogenic carcinoma and as well as malignant mesothelioma has been clearly established.

The appearance of bronchiogenic carcinoma was much higher in shipyard workers who were exposed to both asbestos as well as cigarette smoking. Aromatic amines used in the chemical and dye industries have been shown to produce or induce bladder cancer in humans. Prolonged high exposure to benzene in an occupational setting has been linked to the formation of acute myelogenous leukemia in humans.

A number of **medical therapy** and medical diagnostic tools have also been linked to the induction of human cancer. Cancer chemotherapeutic drugs, such as the alkylating agent cyclophosphamide, have been associated with bladder tumors and leukemia in patients receiving these treatments. The

use of oral contraceptives containing synthetic estrogens as their major or only component has been implicated in the induction of liver cell adenomas. In addition, an association exists between prolonged use of estrogenic oral contraceptives and an increased incidence of premenopausal breast cancer. Androgenic steroids and synthetic testosterone compounds have been implicated in hepatocellular carcinoma induction.



Toxic responses of the blood

Blood as a target organ

Hematotoxicology is the study of adverse effects of drugs, nontherapeutic chemicals and other agents in our environment on blood and blood-forming tissues.

The various blood cells (erythrocytes, granulocytes, and platelets) are each produced at a rate of approximately 1–3 million per second in a healthy adult this characteristic makes hematopoietic tissue a particularly sensitive target for cytoreductive or antimitotic agents, such as those used to treat cancer, infection, and immune-mediated disorders.

Hematotoxicity may be regarded as *primary*, where one or more blood components are directly affected, or *secondary*, where the toxic effect is a consequence of other tissue injury or systemic disturbances. Primary toxicity is regarded as among the more common serious effects of xenobiotics, particularly drugs.

Hematopoiesis

The production of blood cells, or hematopoiesis, is a highly regulated sequence of events by which blood cell precursors proliferate and differentiate. The bone marrow is the principal site of hematopoiesis in humans and most laboratory and domestic animals.

The spleen has little function in blood cell production in the healthy human, but plays a critical role in the clearance of defective or senescent cells الخلايا الهزيمة, as well in host defense.

Whereas the central function of bone marrow is hematopoiesis and lymphopoiesis, bone marrow is also one of the sites of the mononuclear phagocyte system, contributing monocytes that differentiate into a variety of phagocyte cells in other tissues.

Toxicology of the erythron

The Erythrocyte

Erythrocytes (red blood cells, or RBCs) make up 40–45% of the circulating blood volume and serve as the principal vehicle of transportation of oxygen from the lungs to the peripheral tissues. In addition, erythrocytes are involved in the transport of carbon dioxide from tissues to the lung.

Erythrocyte are also involved as a carrier and/or reservoir for drugs and toxins. Xenobiotics may affect the production, function and survival of erythrocytes.

1- Alterations in red cell production

Erythrocyte production is a continuous process that is dependent on frequent cell division and a high rate of hemoglobin synthesis. Adult hemoglobin (hemoglobin A), the major constituent of the erythrocyte cytoplasm, is a tetramer composed of two α - and two β -globin chains, each with a heme residue.

An imbalance between α - and β -chain productions is the basis of congenital thalassemia syndromes and results in decreased hemoglobin production and microcytosis **صغر حجم الكريات الحمراء**. Xenobiotics can affect globin-chain synthesis and alter the composition of hemoglobin within erythrocytes.

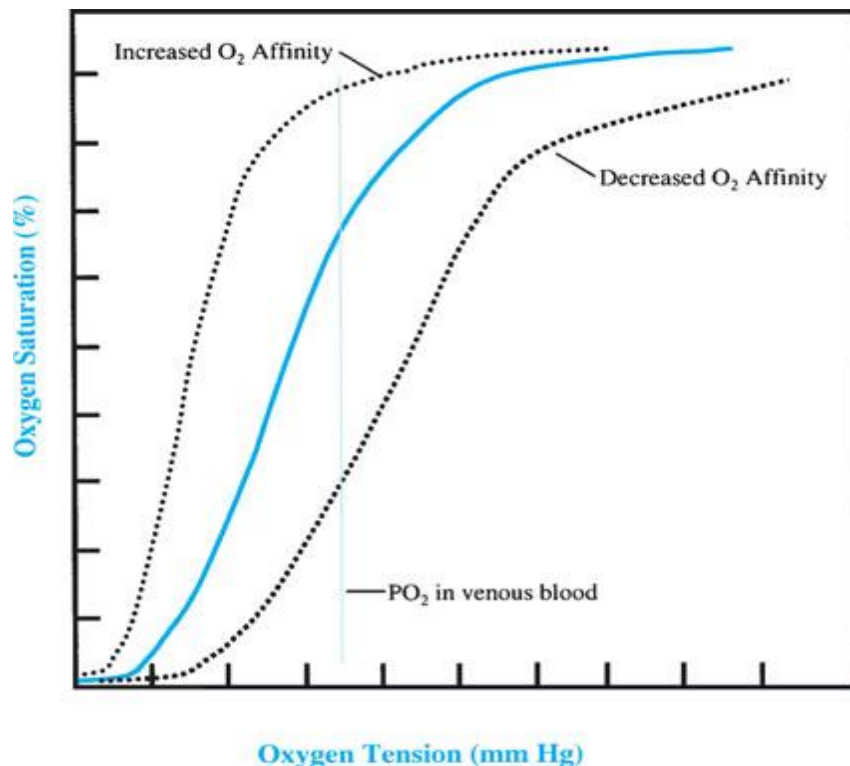
Synthesis of heme requires incorporation of iron into a porphyrin ring. Defects in the synthesis of the porphyrin ring of heme can lead to *sideroblastic anemia*, with its characteristic accumulation of iron in bone marrow erythroblasts **ارومة الحمراء**. The accumulated iron precipitates within mitochondria causing injury. A number of xenobiotics can interfere with one or more of the steps in erythroblast heme synthesis and result in sideroblastic anemia.

Hematopoiesis requires active DNA synthesis and frequent mitoses. Folate and vitamin B12 are necessary to maintain synthesis of thymidine for incorporation into DNA. Deficiency of folate and/or vitamin B12 results in *megaloblastic anemia*, with its characteristic morphologic and biochemical changes, which commonly affect erythroid, myeloid, and megakaryocytic lineage **ذرية**. A number of xenobiotics may contribute to a deficiency of vitamin B12 and/or folate, leading to megaloblastic anemia.

Drug-induced *aplastic anemia* may represent either a predictable or idiosyncratic reaction to a xenobiotic. This life threatening disorder is characterized by peripheral blood pancytopenia **قلة في كريات الدم**, reticulocytopenia **فشل في نخاع العظم**, and bone marrow hypoplasia. Chemicals such as benzene and radiation have a *predictable* effect on hematopoietic progenitors **السلف، الاصل**, and the resulting aplastic anemia corresponds to the magnitude of the exposure to these chemicals. In contrast, idiosyncratic aplastic anemia does not appear to be related to the dose of the chemical initiating the process.

2- Alterations in the respiratory function of hemoglobin

Hemoglobin is necessary for effective transport of oxygen and carbon dioxide between the lungs and tissues. Thus the individual globin units show cooperativity in the binding of oxygen, resulting in the familiar sigmoid shape of the oxygen dissociation curve (Fig. 1). The ability of hemoglobin to safely and efficiently transport oxygen is dependent on both intrinsic (homotropic) and extrinsic (heterotropic) factors that affect the performance of this system.



Homotropic effects One of the most important homotropic properties of oxyhemoglobin is the slow but consistent oxidation of heme iron to the ferric state to form methemoglobin. Methemoglobin is not capable of binding and transporting oxygen. In addition, the presence of methemoglobin in a hemoglobin tetramer has allosteric effects that increase the affinity of oxyhemoglobin for oxygen, resulting in a leftward shift of the oxygen dissociation curve (Fig. 1). The combination of decreased oxygen content and increased affinity impairs delivery of oxygen to tissues when the concentration of methemoglobin rises beyond critical levels.

The normal erythrocyte has metabolic mechanisms for reducing heme iron back to the ferrous state. Failure of these control mechanisms leads to

increased levels of methemoglobinemia by various chemicals as nitrates and dapson. Most patients tolerate low levels (<10%) of methemoglobinemia without clinical symptoms. Higher levels lead to tissue hypoxemia that is eventually fatal.

Heterotropic effects There are three major heterotropic effectors of hemoglobin function: pH, erythrocyte 2,3-bisphosphoglycerate(2,3-BPG) and temperature.

A decrease in pH (e.g., lactic acid, carbon dioxide) lowers the affinity of hemoglobin for oxygen; that is, it causes a right-shift in the oxygen dissociation curve facilitating the delivery of oxygen to tissues (Fig. 1).

Binding of 2,3-BPG to deoxyhemoglobin results in reduced oxygen affinity (a shift to the right of the oxygen dissociation curve), which promotes oxygen delivery to peripheral tissues.

The oxygen affinity of hemoglobin decreases as the body temperature increases. This facilitates delivery of oxygen to tissues during periods of extreme exercise, and febrile illnesses associated with increased temperature. Correspondingly, oxygen affinity increases during hypothermia, which may lead to decreased oxygen delivery under these conditions.

The respiratory function of hemoglobin may also be impaired by blockade of the ligand binding site following interaction with other substances, most notably carbon monoxide. Carbon monoxide has a relatively low rate of association with deoxyhemoglobin but has high affinity once bound. The affinity is about 200 times that of oxygen, and thus persistent exposure to a low level of carbon monoxide (for example, 0.1%) may lead to 50% saturation of hemoglobin. Consequently, the oxygen dissociation curve is shifted to the left, further compromising oxygen delivery to the tissues.

3- Alterations in erythrocyte survival

a- Nonimmune hemolytic anemia

Microangiopathic anemias Intravascular fragmentation of erythrocytes gives rise to the microangiopathic hemolytic anemias. The hallmark of this process is the presence of schistocytes (fragmented RBCs) in the peripheral blood

The erythrocytes appear to be destroyed by mechanical trauma in the feet. Sufficient hemoglobin may be released to cause hemoglobinuria.

Major thermal burns are also associated with a hemolytic process. The erythrocyte membrane becomes unstable as the temperature increases. With major burns there can be significant heat dependent lysis of erythrocytes. Small RBC fragments break off, with resealing of the cell membrane. These cell fragments usually assume a spherical shape and are not as deformable as normal erythrocytes. Consequently, these abnormal cell fragments are removed in the spleen, leading to anemia.

Infectious diseases: A variety of infectious diseases may be associated with significant hemolysis, either by direct effect on the erythrocyte or development of an immune-mediated hemolytic process.

Erythrocytes are parasitized in malaria and babesiosis, leading to their destruction.

Oxidative hemolysis Molecular oxygen is a reactive and potentially toxic chemical species; consequently, the normal respiratory function of erythrocytes generates oxidative stress on a continuous basis. The major mechanisms that protect against oxidative injury in erythrocytes include NADH-diaphorase, superoxide dismutase, catalase, and the glutathione pathway or development of an immune-mediated hemolytic process.

The most common enzyme defect associated with oxidative hemolysis is glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, a relatively common sex-linked disorder characterized by alterations in the primary structure of G-6-PD that diminish its functional activity. It is often clinically asymptomatic until the erythrocytes are exposed to oxidative stress. The stress may come from the host response to infection or exposure to xenobiotics.

Nonoxidative chemical-induced hemolysis Exposure to some xenobiotics is associated with hemolysis without significant oxidative injury. Arsenic hydride is a gas that is formed during several industrial processes. Inhalation of the gas can result in severe hemolysis, with anemia, jaundice, and hemoglobinuria هيموكلوبين في البول. The mechanism of hemolysis in arsine toxicity is not understood. Lead poisoning is associated with defects in heme synthesis and a shortening of erythrocyte survival. The cause of the hemolysis is uncertain, but lead can cause membrane damage and interfere with the Na⁺/K⁺ pump. These effects may cause premature removal of erythrocytes from the circulation.

b- Immune hemolytic anemia

Immunologic destruction of erythrocytes is mediated by the interaction of IgG or IgM antibodies with antigens expressed on the surface of the erythrocyte. In the case of autoimmune hemolytic anemia the antigens are intrinsic components of the patient's own erythrocytes

A number of mechanisms have been implicated in xenobiotic mediated antibody binding to erythrocytes. Some drugs, of which penicillin is a prototype, appear to bind to the surface of the cell, with the "foreign" drug acting as a *hapten* and eliciting an immune response. The antibodies that arise in this type of response only bind to drug-coated erythrocytes. Other drugs, of which quinidine is a prototype, bind to components of the erythrocyte surface and induce a conformational change in one or more components of the membrane.

A third mechanism, for which α -methyldopa is a prototype, results in production of a *drug-induced autoantibody* that cannot be distinguished from the antibodies arising in idiopathic مجهول السبب autoimmune hemolytic anemia.

Toxicology of the leukon جملة الكريات البيض

Components of blood leukocytes

The leukon consists of leukocytes, or white blood cells. They include granulocytes (which may be subdivided into neutrophils, eosinophils, and basophils), monocytes, and lymphocytes.

Toxic effects on granulocytes

The high rate of proliferation of neutrophils makes their progenitor granulocyte pool particularly susceptible to inhibitors of mitosis. Such effects by cytotoxic drugs are generally nonspecific as they similarly affect cells of the dermis, gastrointestinal tract, and other rapidly dividing tissues. Agents that affect both neutrophils and monocytes pose إشير إلى a greater risk for toxic sequel عاقبة such as infection.

Two innovations ابتكار have had a dramatic impact on cancer chemotherapy and the dose-limiting myelotoxicity associated with these drugs: 1) the development of drugs with cancer-cell-specific molecular targets that are relatively bone marrow sparing, 2) the use of hematopoietic growth factors, the co-treatment with which يخفف or successfully rescues patients from effects of myelosuppression.

Leukemogenesis as a toxic response

1- Human leukemias

Leukemias are proliferative disorders of hematopoietic tissue that are monoclonal in origin and thus originate from individual bone marrow cells. Poorly differentiated phenotypes have been designated as “acute,” whereas well differentiated ones are referred to as “chronic” leukemias. It provides the diagnostic framework for classifying chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), along with various subtypes of these disorders.

2- Leukemogenic agents محدث الابيضاض

Most alkylating agents used in cancer chemotherapy can cause MDS and/or AML, including cyclophosphamide, melphalan, busulfan, chlorambucil,

Exposure to high-dose γ - or x-ray radiation has long been associated with ALL, AML, and CML, as demonstrated in survivors of the atom bombings of Nagasaki and Hiroshima.

Toxicology of platelets and hemostasis

Hemostasis is a multicomponent system responsible for preventing the loss of blood from sites of vascular injury and maintaining circulating blood in a fluid state. The major constituents of the hemostatic system include circulating platelets, a variety of plasma proteins, and vascular endothelial cells. The hemostatic system is a frequent target of therapeutic intervention as well as inadvertent غير متعمد expression of the toxic effect of a variety of xenobiotics.

1- Toxic effects on platelets

The thrombocyte Platelets are essential for formation of a stable hemostatic plug in response to vascular injury.

Thrombocytopenia may be due to decreased production or increased destruction.

Exposure to xenobiotics may cause increased immune mediated platelet destruction through any one of several mechanisms. Some drugs function as haptens, binding to platelet membrane components and eliciting an

immune response that is specific for the hapten. The responding antibody then binds to the hapten on the platelet surface, leading to removal of the antibody-coated platelet from the circulation

A second mechanism of immune thrombocytopenia is initiated by a change in a platelet membrane glycoprotein caused by xenobiotica. This elicits an antibody response, with the responding antibody binding to this altered platelet antigen in the presence of drug, resulting in removal of the platelet from the circulation by the mononuclear phagocytic system.

Heparin-induced thrombocytopenia (HIT) represents another mechanism of immune-mediated platelet destruction. When heparin (an anticoagulant) binds to certain clotting factors, a neoepitope (antigen) is exposed and an immune response is mounted against the neoepitope. The results in platelet activation and aggregation instead of heparin's normal function of preventing clot formation, which can lead to a risk of thrombosis.

Thrombotic thrombocytopenic purpura (TTP) is a syndrome characterized by the sudden onset of thrombocytopenia, a microangiopathic hemolytic anemia, and multisystem organ failure, which often includes neurologic dysfunction. The syndrome tends to occur following an infectious disease but may also occur following administration of some drugs.

2- Toxic effects on fibrin clot formation

Decreased synthesis of coagulation proteins: The majority of proteins involved in the coagulation cascade are synthesized in the liver. Therefore, any chemical that impairs liver function may cause a decrease in production of coagulation factors. The common tests of the coagulation cascade, the prothrombin time (PT) and activated partial thromboplastin time (aPTT), may be used to screen for liver dysfunction and a decrease in clotting factors.

3- Toxicology of agents used to modulate hemostasis

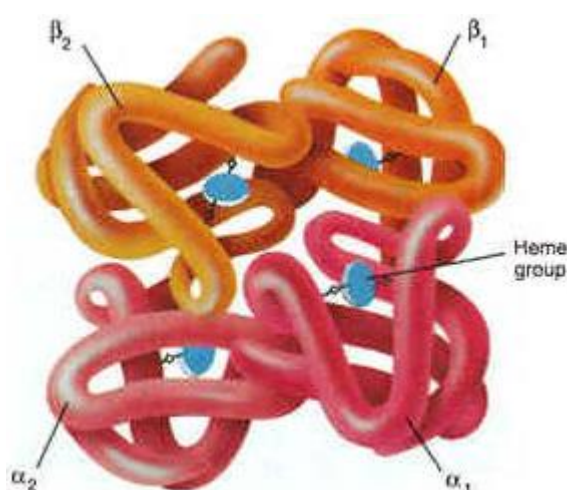
Oral Anticoagulants Oral anticoagulants (warfarin) interfere with vitamin K metabolism by preventing the reduction of vitamin K epoxide, resulting in a functional deficiency of reduced vitamin K. These drugs are widely used for prophylaxis and therapy of venous and arterial thrombosis. The therapeutic window for oral anticoagulants is relatively narrow, and there is considerable inter-individual variation in the response to a given dose. Number of factors, including concurrent medications and genetics, affect the individual response to oral anticoagulants. For these reasons, therapy

with these drugs must be routinely monitored to maximize both safety and efficacy.

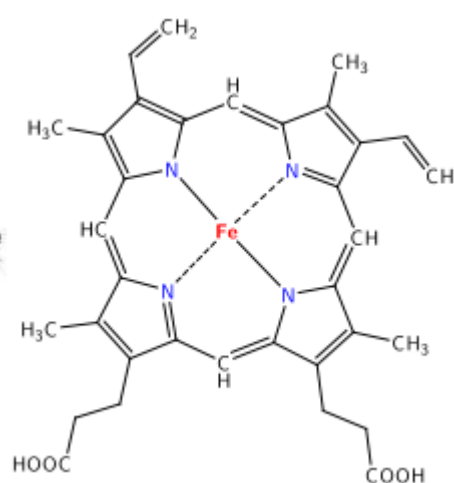
Mechanism or interference with oral anticoagulant include induction or inhibition, interference with absorption of warfarin from the gastrointestinal tract; displacement of warfarin from albumin in plasma, which temporarily increases the bioavailability of warfarin until equilibrium is reestablished; diminished vitamin K availability, and inhibition of the reduction of vitamin k epoxide, which potentiate the effect of oral anticoagulant.

Fibrinolytic agents: Fibrinolytic drugs are used in the treatment of acute thromboembolic disease with the goal of dissolving the pathogenic thrombus. Each of these drugs works by converting plasminogen, an inactive zymogen (inactive precursor), to plasmin, an active proteolytic enzyme. Plasmin is normally tightly regulated and is not freely present in the circulation. However, administration of fibrinolytic drugs regularly results in the generation of free plasmin leading to systemic fibrin(ogen)olysis, which is characterized by prolongation of PTT and thrombin time.

Streptokinase is a protein derived from group C β -hemolytic streptococci and is antigenic in humans. Antibody formation to streptokinase occurs commonly in association with streptococcal infections as well as due to exposure to streptokinase.



Hemoglobin



Hem = Porphyrin + Fe

Toxic responses of the nervous system

Mechanisms of neurotoxicity

Neuropathies

Certain toxicants are specific for neurons, or sometimes a particular group of neurons, resulting in their injury or, when intoxication is severe enough, their death. The loss of a neuron is irreversible and includes degeneration of all of its cytoplasmic extensions, dendrites and axons, and of the myelin ensheathing the axon.

Methyl Mercury The neuronal toxicity of organomercurial compounds, such as methyl mercury (MeHg), was tragically revealed ^{يظهر} in large numbers of poisonings in Japan and Iraq. The residents of Minamata Bay in Japan, whose diet was largely composed of fish from the bay, were exposed to massive amounts of methyl mercury when mercury-laden ^{مثقل} industrial effluent ^{تصريف} was rerouted ^{اعادة توجيه} into the bay. Methyl mercury injured even more people in Iraq, with more than 400 deaths and 6000 people hospitalized. In this epidemic, as well as in several smaller ones, the effects occurred after the consumption of grain that had been dusted with methyl mercury as an inexpensive pesticide.

Methyl mercury is efficiently absorbed by the gastrointestinal tract and can easily make its way across blood-brain barrier and into the brain via transporters within the barrier. It can result in severe mental retardation and paralysis. It tends to disturb multiple cellular site resulting in detriments ^{ضرر} in calcium signals, mitochondrial function, as well as an accumulation of oxidative stress, all of which can damage the neuron.

Carbon monoxide Exposure to carbon monoxide, which binds to hemoglobin, inhibits its ability to deliver oxygen to tissues. Neurological symptoms of carbon monoxide poisoning include depression, trouble with memory, as well as motor deficits. For reasons that are still unclear, the neuropathological effects of carbon monoxide appear to selectivity target neurons of the globus pallidus ^{الكرة الصفراء}. If the globus pallidus is damaged, it can cause movement disorders.

MPTP The neurotoxic effects MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) were identified in the early 1980s following the injection of a synthetic heroin by intravenous drug users that had been accidentally contaminated with MPTP during the drug's synthesis. Within days of injecting the drug, patients developed symptoms of Parkinson's

disease with a devastating loss of dopamine neurons in the midbrain, similar to that seen in Parkinson's disease. From a neurotoxicological stand point, MPTP and its neurotoxic metabolite, MPP (1-methyl-4-phenylpyridinium, is quite interesting because instead of having a global neurotoxic effects on multiple neuron population it is extremely selective for the dopamine neuron that reside in the midbrain.

Facilitating this selectivity is the fact that the dopamine transporter is only present on dopamine neurons and the highest concentration of dopamine neurons is found in the midbrain as well as other parts of the basal ganglia, making these regions and these cells more susceptible to MPTP.

Axonopathies

The neurotoxic disorders termed *axonopathies* are those in which the primary site of toxicity is the axon itself. The axon degenerates, and with it the myelin surrounding that axon; however, the neuron cell body remains intact. سليم Because longer axons have more targets for toxic damage than shorter axons, one would predict that longer axons would be more affected in toxic axonopathies. Indeed, such is the case. The involvement of long axons of the CNS, such as ascending sensory axons or descending motor axons.

***n*-hexane** a simple alkane, in a work setting develop a progressive sensorimotor distal axonopathy. Intentional inhalation of materials containing *n*-hexane is also common, and produces the same neurotoxic effects. *n*-hexane is not toxic rather its metabolite 2,5-hexadione is the toxic compound, begins in the hands and feet

Carbon Disulfide: The most significant exposures of humans to CS₂ have occurred in the vulcan rubber and viscose rayon حرير industries. Manic psychoses were observed in the former setting and were correlated with very high levels of exposure.

Acrylamide: is a vinyl monomer used widely in water purification, paper manufacturing, mining, and water proofing. It is also used extensively in biochemical laboratories, and is present in many foods prepared at high temperatures. Although it can be dangerous if not handled carefully, most toxic events in human have been observed as peripheral neuropathies in factory workers exposed to high doses.

Myelinopathies

Hexachlorophene Hexachlorophene resulted in human neurotoxicity when newborn infants, particularly premature infants, were bathed with the compound to avoid staphylococcal skin infections. Following skin absorption of this hydrophobic compound, hexachlorophene enters the NS and results in intra-myelinic edema, splitting the intra-period line (extracellular) of myelin in both the CNS and the PNS. The intra-myelinic edema leads to the formation of vacuoles, creating a “spongiosis” of the brain.

Lead: Lead exposure in animals results in a peripheral neuropathy with prominent segmental demyelination. In young children, acute massive exposures to lead result in severe cerebral edema, perhaps from damage to endothelial cells. Chronic lead intoxication in adults results in peripheral neuropathy, often accompanied by manifestations outside the NS, such as gastritis, colicky abdominal pain, anemia, and the prominent deposition of lead in particular anatomic sites, creating lead lines in the gums and in the epiphyses of long bones in children.

Neurotransmission-Associated neurotoxicity

Neurotransmission at the axon terminal can be divided into discrete events such as release of neurotransmitter from the terminal, interaction of the neurotransmitter with the receptors on the postsynaptic neurons, and termination of the neurotransmitter effects through either removal of the transmitter from the synapse or degradation of the transmitter within the synapse.

α -Latrotoxin is the major neurotoxin found in the widow spider species (black widow). α -Latrotoxin exerts its neurotoxicological effects by targeting the calcium channels located at the presynaptic terminal. It facilitates the inward flow of calcium, allowing a flood of calcium and a heightened release of acetylcholine at the muscle, resulting in severe muscle contractions, as well as vomiting and cardiac problems.

Cocaine: The dopamine transporter functions to terminate the action of dopamine by removing it from the synapse and sequestering عزل it back into the presynaptic terminal. By blocking the dopamine transporter, dopamine remains in the synapse where it can repeatedly/continually bind to dopamine receptors and continue to elicit a physiological response. It was believed that this excess exposure to dopamine is what accounts for the euphoric feelings described by cocaine users. While a single use of

cocaine may not cause damage to the neurons, repeated or chronic use has been demonstrated to have deleterious consequences.

Like cocaine, **amphetamine** exert their effects in the CNS, altering catecholamine neurotransmission by competing for uptake via plasma membrane transporters and by disrupting the vesicular storage of dopamine. Amphetamine have been associated with an increased risk of abnormal fetal growth and development, cerebrovascular disease, and psychiatric and neurologic problems in chronic abusers.

Some compound can be bind to receptors located on the postsynaptic membrane and can inhibit the normal binding of the neurotransmitters, thus reducing its ability to induce a physiological response. As the antipsychotic medication **haloperidol** is an antagonist for the dopamine receptors in the brain. Blockade of these receptors prevents dopamine from binding and facilitating movement. As a result one of the major side effects of the drug are deficits in movement.

Several compound found in the environment, as chlorinated cyclodiene insecticides as chloridane and endosulfan, block the binding of GABA with it postsynaptic receptor, causing seizures, nausea and dizziness.

Domoic acid is a neurotoxic compound produced and released by algae طحالب. Shellfish محار can take up and accumulate high levels of domoic acid, which is passed on to the human population when they consume shellfish that have been exposed. Domoic acid mimics the effects of the neurotransmitter glutamate, which can then over activate glutamate receptors and result in severe neurological deficits within the hippocampus and can even cause death.

Toluene, an aromatic hydrocarbon, which is widely abused as an inhalant, binds to the GABA receptors and potentiates the release of GABA in the nervous system. Mild exposure to toluene can cause dizziness, while prolonged exposure can result in unconsciousness and respiratory depression.

Exposure to organophosphate insecticide chlorpyrifos effectively inhibits or inactivate acetylcholinesterase and perpetuates يديم the neurological effects of continuous acetylcholine binding to receptors. Excessive exposure to chlorpyrifos can cause symptoms ranging from salivation and lacrimation to diarrhea, vomiting as well as alteration in movement and unconsciousness. Interestingly, , several of the chemicals that are most well recognized as being used in biological warfare, such as VX, tabun, and sarine nerve gas, are all acetylcholinesterase inhibitors and

were originally manufactured for use as insecticides, but were discontinued after severe lethality to humans was discovered.

Astrocytes

Astrocytes perform and regulate a wide range of physiologic functions in the CNS. The astrocytes appear to be a primary means of defense in the CNS following exposure to neurotoxicants as a spatial buffering system عازل مكان for osmotically active ions and as a depot مستودع for the sequestration حجز and metabolic processing of endogenous molecules and xenotoxics.

Nitrochemicals: Organic nitrates are used for peripheral vasodilation and reduction of blood pressure (nitroglycerine) in treatment of cardiovascular disease. The dinitrobenzenes are important synthetic intermediates in the industrial production of dyes, plastics, and explosive.

Toxic responses of the liver

Introduction

The liver is the main organ where exogenous chemicals are metabolized and eventually excreted. As a consequence, liver cells are exposed to significant concentrations of these chemicals, which can result in liver dysfunction, cell injury, and even organ failure. The liver, with its multiple cell types and numerous functions, can respond in many different ways to acute and chronic insults.

Liver pathophysiology

Mechanisms and types of Toxin-induced liver injury

The response of the liver to chemical exposure depends on the intensity of the insults, the cell population affected, and the duration of the chemical exposure (acute vs. chronic).

a- Cell death Based on morphology, liver cells can die by two different modes, oncototic necrosis (“necrosis”) or apoptosis. Necrosis is characterized by cell swelling, leakage of cellular contents, nuclear disintegration (karyolysis), and an influx of inflammatory cells. When necrosis occurs in hepatocytes, the associated plasma membrane leakage can be detected biochemically by assaying plasma or serum for liver cytosol- derived enzymes such as aspartate or alanine aminotransferase (AST, ALT) or γ -glutamyltranspeptidase (GGT). In contrast, apoptosis is characterized by cell shrinkage, nuclear fragmentation, formation of apoptotic bodies, and a lack of inflammation.

b- Canalicular cholestasis ركود الصفراء This form of liver dysfunction is defined physiologically as a decrease in the volume of bile formed or an impaired secretion of specific solutes into bile. Cholestasis is characterized biochemically by elevated serum levels of compounds normally concentrated in bile, particularly bile salts and bilirubin. When biliary excretion of the yellowish bilirubin pigment is impaired, this pigment accumulates in skin and eyes, producing jaundice, and spills into urine, which becomes bright yellow or dark brown. Toxicant-induced cholestasis can be transient or chronic; when substantial, it is associated with cell swelling, cell death, and inflammation.

c- Bile duct damage Another name for damage to the intrahepatic bile ducts is *cholangiodestructive cholestasis*. A useful biochemical index of

bile duct damage is a sharp elevation in serum activities of enzymes localized to bile ducts, particularly alkaline phosphatase. In addition, serum levels of bile acids and bilirubin are elevated, as observed with canalicular cholestasis. Initial lesions following a single dose of cholangiodestructive chemicals include swollen biliary epithelium, debris حطام of damaged cells within ductal lumens, and inflammatory cell infiltration of portal tracts. Chronic administration of toxins that cause bile duct destruction can lead to biliary proliferation and fibrosis resembling primary biliary cirrhosis.

d- Sinusoidal damage The sinusoid is, in effect, a specialized capillary with numerous fenestrae for high permeability. The functional integrity of the sinusoid can be compromised by dilation or blockade of its lumen or by progressive destruction of its endothelial cell wall. Dilation of the sinusoid will occur whenever efflux of hepatic blood is impeded. Blockade will occur whenever blood cells become caught in the sinusoids. Such changes have been illustrated after large dose of acetaminophen.

e- Disruption of the cytoskeleton Phalloidin and microcystin disrupt the integrity of hepatocyte cytoskeleton by affecting proteins that are vital to its dynamic nature. The detrimental effects of these two potent hepatotoxicants are independent of their biotransformation and are exclusive for hepatocytes, because there is no appreciable uptake of either toxin into other types of cells. Tight binding of phalloidin to actin filaments prevents the disassembly phase of the normally dynamic rearrangement of the actin filament constituent of the cytoskeleton. Phalloidin uptake into hepatocytes leads to striking alterations in the actin-rich web of cytoskeleton adjacent to the canalicular membrane; the actin web becomes accentuated and the canalicular lumen dilates.

Microcystin uptake into hepatocytes leads to hyperphosphorylation of cytoskeletal proteins secondary to this toxicant's covalent binding to the catalytic subunit of serine/threonine protein phosphatases. Reversible phosphorylations of cytoskeletal structural and motor proteins are critical to the dynamic integrity of the cytoskeleton. Extensive hyperphosphorylation produced by large amounts of microcystin leads to marked deformation of hepatocytes due to a unique collapse of the microtubular actin scaffold into a spiny central aggregate.

f- Fatty liver Fatty liver (steatosis) is defined biochemically as an appreciable increase in the hepatic lipid (mainly triglyceride) content, which is <5% by weight in normal human liver.

Currently, the most common cause of hepatic steatosis is insulin resistance due to central obesity and sedentary lifestyle.

g- Fibrosis and cirrhosis Hepatic fibrosis (scarring) occurs in response to chronic liver injury and is characterized by the accumulation of excessive amounts of fibrous tissue, specifically fibril-forming collagens. With continuing collagen deposition, the architecture of the liver is disrupted by interconnecting fibrous scars. When the fibrous scars subdivided the remaining liver mass into nodules of regenerating hepatocytes, fibrosis has progressed to cirrhosis and the liver has limited residual capacity to perform its essential functions. The primary cause of hepatic fibrosis/cirrhosis in humans worldwide is viral hepatitis. However, biliary obstruction and in particular alcoholic and nonalcoholic steato-hepatitis are of growing importance for the development of hepatic fibrosis. In addition, fibrosis can be induced by chronic exposure to drugs and chemicals including ethanol and by heavy metal overload.

h- Tumors Chemically induced neoplasia can involve tumors that are derived from hepatocytes, bile duct cells, or the rare, highly malignant angiosarcomas derived from sinusoidal lining cells. Hepatocellular cancer has been linked to chronic abuse of androgens, alcohol, and a high prevalence of aflatoxin-contaminated diets.

Critical factors in toxicant-induced liver injury

Location and specialized processes for uptake and biliary secretion produce higher exposure levels in the liver than in other tissues of the body, and strikingly high levels within certain types of liver cells. Then the abundant capacity for bioactivation reactions influences the rate of exposure to proximate toxicants.

a- Uptake and concentration Hepatic “first pass” uptake of ingested chemicals is facilitated by the location of the liver downstream of the portal blood flow from the gastrointestinal tract. Lipophilic compounds, particularly drugs and environmental pollutants, readily diffuse into hepatocytes because the fenestrated epithelium of the sinusoid enables close contact between circulating molecules and hepatocytes.

Phalloidin and microcystin are illustrative examples of hepatotoxins that target the liver as a consequence of extensive uptake into hepatocytes by sinusoidal transporters.

Vitamin A hepatotoxicity initially affects stellate cells, which actively extract and store this vitamin. Early responses to high-dose vitamin A therapy are stellate cell engorgement, activation, increase in number, and protrusion into the sinusoid. Iron poisoning produces severe liver damage. Hepatocytes contribute to the homeostasis of iron by extracting this essential metal from the sinusoid by a receptor-mediated process and maintaining a reserve of iron within the storage protein ferritin.

Acute Fe toxicity is most commonly observed in young children who accidentally ingest iron tablets.

b- Bioactivation and detoxification One of the vital functions of the liver is to eliminate exogenous chemicals and endogenous intermediates. Therefore, hepatocytes contain high levels of phase-I enzymes, which have the capacity to generate reactive electrophilic metabolites. Hepatocytes also have a wide variety of phase-II enzymes, which enhance the hydrophilicity by adding polar groups to lipophilic compounds and target these conjugates to certain carriers in the canalicular or plasma membrane for excretion. Generally, phase-II reactions yield stable, nonreactive metabolites.

The balance between phase-I reactions, which generate the electrophile, and conjugating phase-II reactions determines whether a reactive intermediate is safely detoxified or may cause cell dysfunction or injury. Because the expression of phase-I and -II enzymes and of the hepatic transporters can be influenced by genetics (e.g., polymorphism of drug-metabolizing enzymes) and lifestyle (e.g., diet, consumption of other drugs and alcohol), the susceptibility to potential hepatotoxins can vary markedly between individuals. Several prominent and important examples are discussed.

Acetaminophen one of the most widely used analgesics, acetaminophen (APAP) is a safe drug when used at therapeutically recommended doses. However, an overdose can cause severe liver injury and even liver failure in experimental animals and in humans. Because >90% of a therapeutic dose of APAP is conjugated with sulfate or glucuronide, the limited formation of a reactive metabolite, i.e., *N*-acetyl-*p*-benzoquinone imine (NAPQI), poses no risk for liver injury. In fact, long-term studies with acetaminophen in osteoarthritis patients did not reveal any evidence of liver dysfunction or cell injury even in patients consuming the maximal recommended daily dose of APAP for 12 months. In contrast, after an overdose, the formation of large amounts of NAPQI leads first to depletion of cellular glutathione (GSH) stores and subsequently causes covalent binding of NAPQI to intracellular proteins.

Ethanol Morbidity and mortality associated with the consumption of alcohol is mainly caused by the toxic effects of ethanol on the liver. This targeted toxicity is due to the fact that >90% of a dose of ethanol is metabolized in the liver. Three principal pathways of ethanol metabolism are known. Alcohol dehydrogenase (ADH) oxidizes ethanol to acetaldehyde. Acetaldehyde is further oxidized to acetate in a NAD-dependent reaction by acetaldehyde dehydrogenase (ALDH). This pathway is mainly regulated by the mitochondrial capacity to utilize

NADH and regenerate NAD⁺. The formation of excess reducing equivalents and acetate stimulates fatty acid synthesis and is a major factor in the development of alcohol-induced steatosis. Both ADH and ALDH exhibit genetic polymorphisms and ethnic variations, which play a role in the development of alcoholism and liver damage

Allyl alcohol An industrial chemical used in the production of resins, plastics, and fire retardants, allyl alcohol is primarily used as a model hepatotoxin due to its preferential periportal (zone 1) hepatotoxicity. The alcohol is metabolized by ADH to acrolein, a highly reactive aldehyde, which is then further oxidized by ALDH to acrylic acid. The fact that the toxicity depends on depletion of hepatic GSH levels is prevented by inhibitors of ADH but enhanced by inhibitors of ALDH suggests that acrolein formation is the critical event in liver injury.

Carbon tetrachloride Cytochrome P450-dependent conversion of CCl₄ to •CCl₃ and then to CCl₃OO• is the classic example of xenobiotic bioactivation to a free radical that initiates lipid peroxidation by abstracting a hydrogen atom from the polyunsaturated fatty acid of a phospholipid. CCl₄-induced lipid peroxidation increases the permeability of the plasma membrane to Ca²⁺, leading to severe disturbances of the calcium homeostasis and necrotic cell death.

c- Regeneration The liver has a high capacity to restore lost tissue and function by regeneration. Loss of hepatocytes due to hepatectomy or cell injury triggers proliferation of all mature liver cells. This process is capable of restoring the original liver mass.

d- Inflammation The activation of resident macrophages (Kupffer cells), NK and NKT cells and the migration of activated neutrophils, lymphocytes, and monocytes into regions of damaged liver is a well-recognized feature of the hepatotoxicity produced by many chemicals. The main reason for an inflammatory response is to remove dead and damaged cells. However, under certain circumstances these inflammatory cells can aggravate the existing injury by release of directly cytotoxic mediators or by formation of pro and anti-inflammatory mediators.

e- Idiosyncratic liver injury Idiosyncratic drug hepatotoxicity is a rare but potentially serious adverse event, which is not clearly dose dependent, is at this point unpredictable and affects only very few of the patients exposed to a drug or other chemicals. However, idiosyncratic toxicity is a leading cause for failure of drugs in clinical testing and it is the most frequent reason for posting warnings, restricting use, or even withdrawal of the drug from the market. In addition, idiosyncratic hepatotoxicity is observed after consumption of herbal remedies and food supplements. There are no

known mechanisms of cell injury specific for idiosyncratic hepatotoxins. A number of drugs including halothane (anesthetic), nitrofurantoin (antibiotic), and phenytoin (anticonvulsant) are thought to cause injury mainly by immune (allergic) mechanisms. Other drugs, e.g., isoniazid (antituberculosis), disulfiram (alcoholism), valproic acid (anticonvulsant), or troglitazone (antidiabetic), are considered nonimmune (nonallergic) idiosyncratic hepatotoxins.

principles of toxicology

Toxicology: is the study of the adverse effects of chemical, biological, or physical agents on living organisms and the environment.

Toxicologist: is an individual trained to examine and communicate the nature of a toxicant's properties and identify approaches to prevent or mitigate harm done to human, animal, and environmental health.

Toxicants: Substances produce adverse biological effects (not from biological origin)

Toxins: are poisons that originate from plants and microbial organisms and include venoms released by animals in order to injure predators.

Poisons: Any agent causes immediate death or illness

Toxicology testing (safety testing, toxicity testing)

Conducted to determine the degree to which a substance can damage a living or non-living organisms.

It is often conducted by researchers to comply with governing regulations

Toxicity tests are routinely performed by pharmaceutical manufacturers in the investigation of a new drug.

Acute toxicity tests in which a single dose is used in each animal on one occasion only for the determination of gross behavior and LD50 or median lethal dose

Sub acute tests in which animals (usually rats and dogs) are dosed daily, starting at around expected therapeutic level and increasing stepwise every two to three days until toxic signs are observed

Chronic tests in which two species, one rodent and one non rodent are dosed daily for six months

Sub-disciplines of toxicology

The professional activities of toxicologists fall into three main categories: mechanistic, hazard assessment, and regulatory.

A mechanistic toxicologist identifies the cellular, biochemical, and molecular mechanisms by which chemicals exert toxic effects on living organisms.

A hazard assessment toxicologist conducts toxicity testing that provides comprehensive information for the evaluation of a chemical's safety and to meet important regulatory requirements.

A regulatory toxicologist has the responsibility for deciding, on the basis of data provided by descriptive and mechanistic toxicologists, whether a drug or other chemical poses a sufficiently low risk (or, in the case o

Spectrum of undesired effects

Allergic reactions

Chemical allergy is an immunologically mediated adverse reaction to a chemical resulting from previous sensitization to that chemical or to structurally similar ones.

Chemical Idiosyncrasy

Genetically determined abnormal reactivity to a chemical. The response observed is usually qualitatively similar to that observed in all individuals but may take the form of extreme sensitivity to low doses or extreme insensitivity to high doses of the chemical.

Immediate Versus Delayed Toxicity

Immediate toxic effects occur or develop rapidly after a single administration of a substance, whereas delayed toxic effects occur after the relapse of some period of time.

Carcinogenic effects of chemicals usually have long latency periods after the initial exposure, before tumors are observed in humans.

Reversible Versus Irreversible Toxic Effects

If a chemical produces pathological injury to a tissue, the ability of that tissue to regenerate largely determines whether the effect is reversible or irreversible.

Local Versus Systemic Toxicity

Local effects are those that occur where contact is first made by the toxicant and the biological system. Such effects are produced by the ingestion of toxic substances or the inhalation of irritant materials. By comparison, systemic effects require the absorption and distribution of a toxicant from its entry point to a distant site where the deleterious effects are produced.

Interactions of Chemical

Additive effect

When the combined effect of two chemicals is equal to the sum of the effects of each agent given alone (example: $2 + 3 = 5$)

Synergistic effect

When the combined effects of two chemicals are much greater than the sum of the effects of each agent given alone (example: $2 + 2 = 20$).

Potentiation

When one substance does not have a toxic effect on a certain organ or system but when added to another chemical makes that chemical much more toxic (example: $0 + 2 = 10$).

Antagonism

Functional antagonism

When two chemicals counterbalance each other by producing opposite effects on the same physiologic function (NE in falling B.P).

Chemical antagonism or inactivation

Chemical reaction between two compounds that produces a less toxic product (Chelating).

Dispositional antagonism

When the absorption, biotransformation, distribution, or excretion of a chemical is altered so that the concentration and/or duration of the chemical at the target organ are diminished (IPECAC)

Receptor antagonism

When two chemicals that bind to the same receptor produce less of an effect when given together than the addition of their separate effects (example: $4 + 6 = 8$) or when one chemical antagonizes the effect of the second chemical (example: $0 + 4 = 1$). Often are termed *blockers*.

Tolerance

Repeated exposure to a chemical can reduce its pharmacologic and/or toxicologic actions, a process called tolerance. Cross-tolerance occurs when structurally related chemicals cause diminished responses. Typically, days or weeks of repeated exposure are required for tolerance to occur.

Characteristics of exposure

Toxicity to a biological system requires that sufficient concentrations of the “active” form of a chemical accumulate at the site of action for a requisite period of time. Whether a toxic response occurs is dependent on multiple factors: chemical and physical properties of the chemical, the exposure scenario, how the chemical is metabolized by the system, the concentration of the active form at the particular target site(s), and the overall susceptibility of the biological system to injury

Route and Site of Exposure

Toxic chemicals enter the body via the gastrointestinal tract (ingestion), the lungs (inhalation), and the skin (topical, percutaneous, or dermal). Chemicals generally produce the greatest effect and the most rapid response when given directly into the bloodstream (the intravenous route). Chemicals can also enter the body to varying degrees through other routes. An approximate descending order of effectiveness for the other routes would be inhalation, intraperitoneal, subcutaneous, intramuscular, intradermal, oral, and dermal.

Duration and frequency of exposure

Toxicologists usually divide the exposure of experimental animals to chemicals into four categories:

Acute exposure is defined as exposure to a chemical for less than 24 h

Subacute exposure refers to repeated exposure to a chemical for 1 month or less

Subchronic for 1 to 3 months

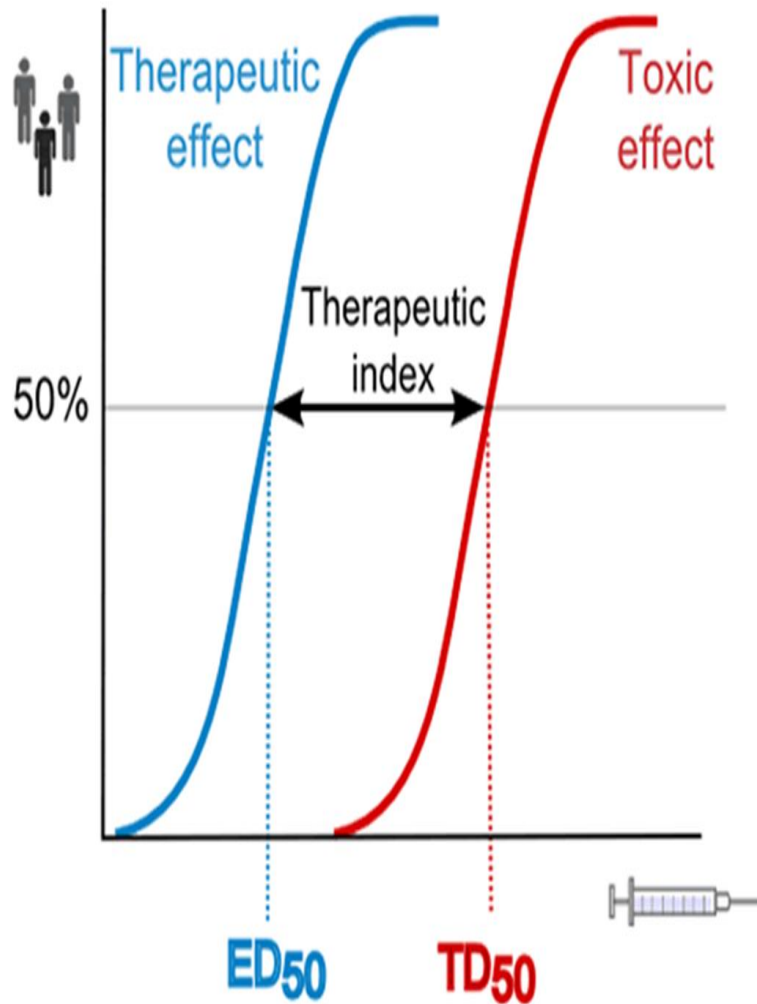
Chronic for more than 3 months

Dose–response relationships

Dose–response relationships are defined as the association between the amount of a toxicant administered and the extent to which changes are observed in a biological system.

Dose–response relationships are routinely divided into two types: (1) the individual dose–response relationship, which describes the response of an individual organism to increasing doses of a chemical, often referred to as a “graded” response because the measured effect is continuous over a range of doses, and (2) a quantal dose–response relationship, which characterizes the distribution of individual responses to different doses in a population of organisms.

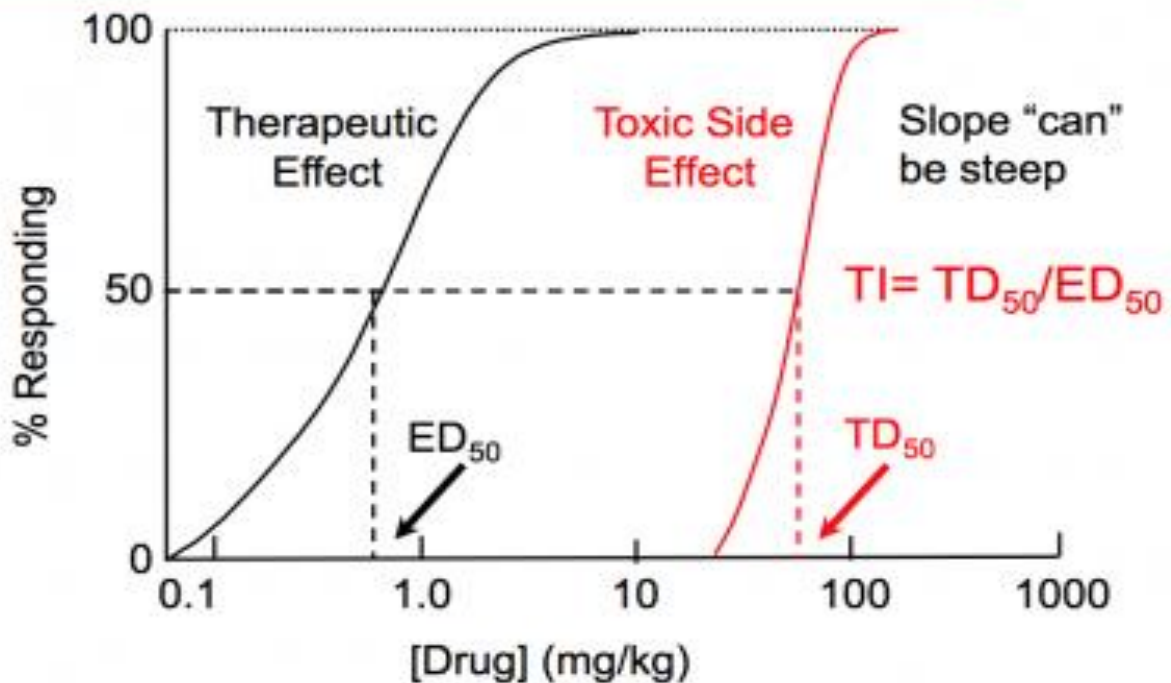
Therapeutic Index = LD50 / ED50 ■



PharmacologyCorner.com

LD50 – Median Lethal Dose, quantity of the chemical that is estimated to be fatal to 50% of the organisms

Drug Safety - Therapeutic Index



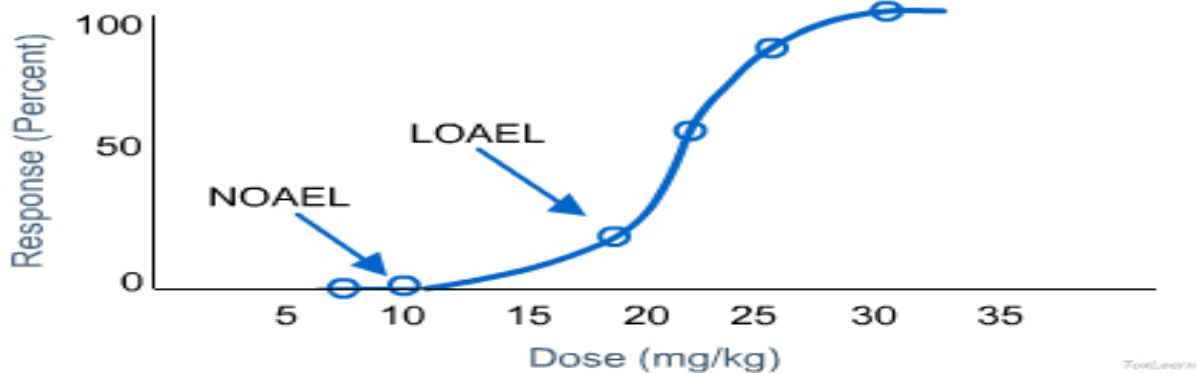
NOAEL Value – No Observed Adverse Effect Level,

The highest dose of a chemical that, in a given toxicity test, causes no observable effect in test animals

The NOAEL for the most sensitive test species and the most sensitive indicator of toxicity is usually employed for regulatory purposes

LOAEL Value – Lowest Observed Adverse Effect Level,

The lowest dose of a chemical that, in a given toxicity test, does cause an observable effect in test animals



Variation in toxic responses

Selective Toxicity

Selective toxicity means that a chemical produces injury to one kind of living matter (such as a cell or organism) without harming another form of life even though the two may exist in intimate contact. علاقة تشابه

By taking advantage of the biological diversity between species, it is possible to develop chemicals that are lethal for an undesired species and harmless for other species. Selective toxicity results because the chemical (1) is equally toxic to both organisms but accumulates preferentially in the target or (2) alters a unique cellular or a biochemical feature that is absent or irrelevant in the unaffected species. Differences in the absorption, biotransformation, or excretion of the toxicant, or intracellular metabolism or transport may dictate accumulation of the ultimate toxic compound in affected tissues.

Species Differences

Experimental animals are routinely used in toxicology as surrogates for humans; however, it is important to recognize the quantitative and qualitative differences in response to toxic substances among various species. Even among phylogenetically similar species (e.g., rats, mice, guinea pigs, and hamsters), large differences in response may be observed.

Modifying Factors

Not all humans respond to toxicants in the same manner and to the same degree as each other. Multiple factors that modify one's susceptibility to adverse outcomes include genetic variation among a population, age and life stages, sex and hormonal status, microbiome, and circadian rhythm.

Management

- Decontamination: removal of the toxin from the patient or the patient must be removed from the toxic environment.
- Emesis (vomiting): this induced with syrup of ipecac which causes vomiting by acting on the chemoreceptor trigger zone.
- Orogastric lavage: by rinsing the patient's stomach with water or saline lavage solution by means of a tube inserted through the patient's mouth or nose.
- Activated charcoal: it binds many chemicals and prevents their absorption into the bloodstream and excreted together with the feces. Charcoal bind well to nonpolar drugs and toxins and binds poorly to polar substances.

- Enhanced elimination: is also called ion trapping, acidification of the urine enhances the excretion of basic drugs while alkalization of the urine enhance the acidic drug excretion.