الجمهورية الجزائرية الديمقراطية الشعبية
وزارة التعليم العالي و البحث العلمي

Université Ferhat Abbas Sétif 1
Faculté des Sciences de la
Nature et de la Vie

جامعة فرحات عباس، سطيف1
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DÉPARTEMENT OF BIOTECHNOLOGy

Course handout of:
Food toxicology

Level: 3rd Year Bachelor's (LMD)
Biotechnology and food

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"All substances are poisons and there is none that is not a poison. It is the dose that makes the poison." ***Paracelsus (1493–1541)***

2025-2026

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Chapter I: Fundamentals of Toxicology

The relationship between humans and their environment is complex, shaped by ongoing interactions that help sustain a dynamic equilibrium. Yet this environment is not uniform; it contains various harmful agents, including chemicals, toxins, and other hazardous substances, that can seriously influence the health of living beings.

These dynamics underscore the importance of understanding how such agents may affect our well-being and highlight the necessity of taking action to safeguard both our health and the ecosystems we depend on.

1. Definitions

Toxicology can be described as the science of how chemicals negatively affect living organisms. Its roots go back to prehistoric times, when early humans tried consuming various substances in search of safe food. By learning which items provided nourishment without causing sickness or death, ancient communities developed eating habits that enabled the survival and progress of the human species. In today's context, toxicology relies extensively on knowledge from chemistry and biology, aiming for a thorough understanding of harmful effects. Contemporary toxicology largely focuses on examining how particular substances influences specific chemical and biological processes.

Food Toxicology is a scientific discipline dedicated to the study of poisons and toxic compounds, known as xenobiotics. Its primary goal is to detect and assess the adverse health effects in humans caused by exposure to various agents whether physical, chemical, or biological agents. This involves analysing the interplay among different disease-causing agents, including viruses, bacteria, fungi, parasites, pesticides, and other toxic chemicals.

Given these risks, food toxicology is essential for understanding how different agents affect human health and for developing risk reduction strategies. This requires thorough research into the sources of toxicity, the mechanisms of toxin action, and the assessment of exposure levels and potential health impacts.

Thus, food toxicology plays a crucial role in protecting public health by providing essential information about the dangers associated with consuming certain foods or being exposed to environmental contaminants.

The main terminology in toxicology

- **Toxic Agents**

A **toxic agent** is anything that can produce an adverse biological effect. It may be chemical, physical, or biological in form. For example, toxic agents may be Chemical (such as cyanide, Physical (such as radiation) Biological (such as snake venom)

- **Systemic Toxicants and Organ Toxicants**

A **systemic toxicant** affects the entire body or many organs rather than a specific site. For example, potassium cyanide is a systemic toxicant in that it affects virtually every cell and organ in the body by interfering with the cells' ability to use oxygen.

Toxicants may also affect only specific tissues or organs while not producing damage to the body as a whole. These specific sites are known as the **target organs** or **target tissues**.

- Benzene is a **specific organ toxicant** in that it is primarily toxic to the blood-forming tissues.
- Lead is also a specific organ toxicant; however, it has three **target organs:** the central nervous system, the kidneys, and the hematopoietic system.

A toxicant may affect a specific type of tissue (such as connective tissue) that is present in several organs. The toxic site is then considered the target tissue (fig1).

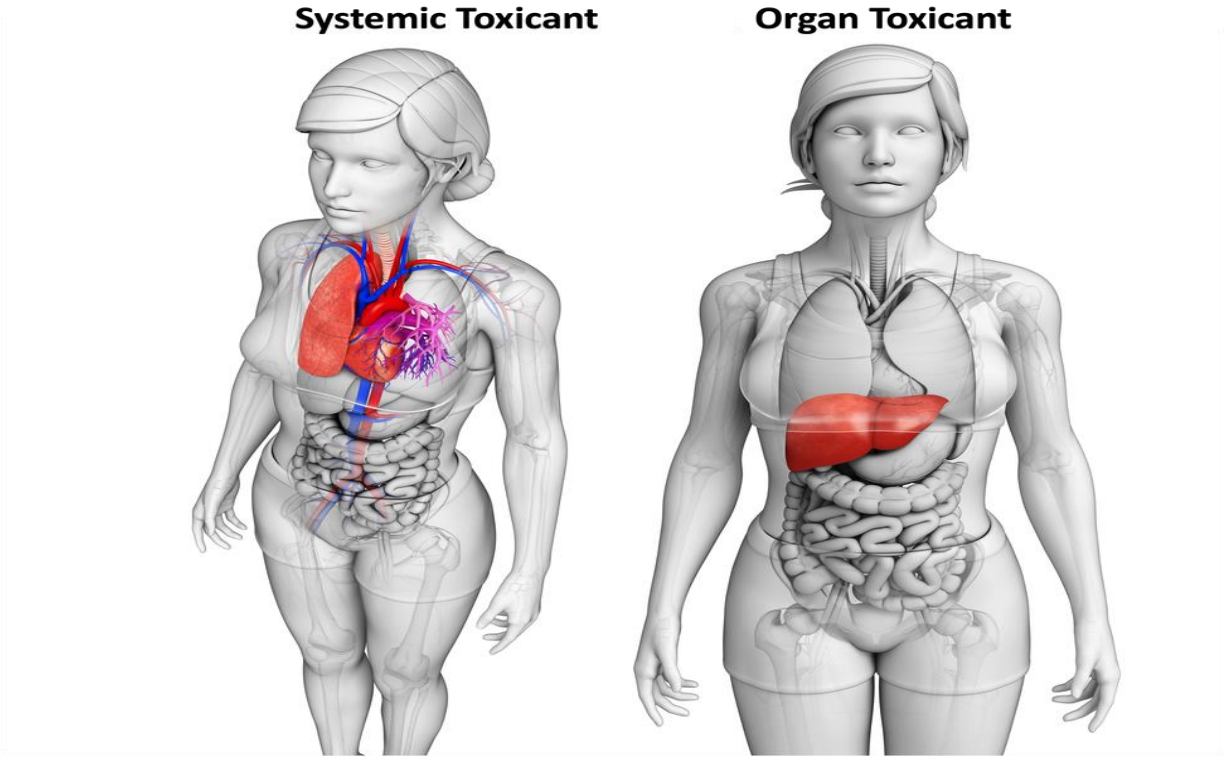

Fig 1. Systemic toxicant and organ toxicant

- **Natural and Man-Made Chemicals**

Often, people mistakenly assume that all man-made chemicals are harmful and natural chemicals are beneficial. In reality, natural chemicals can be just as harmful to human health as man-made chemicals, and in many cases, more harmful. Figure 2 compares the toxicity of several natural and man-made chemicals.

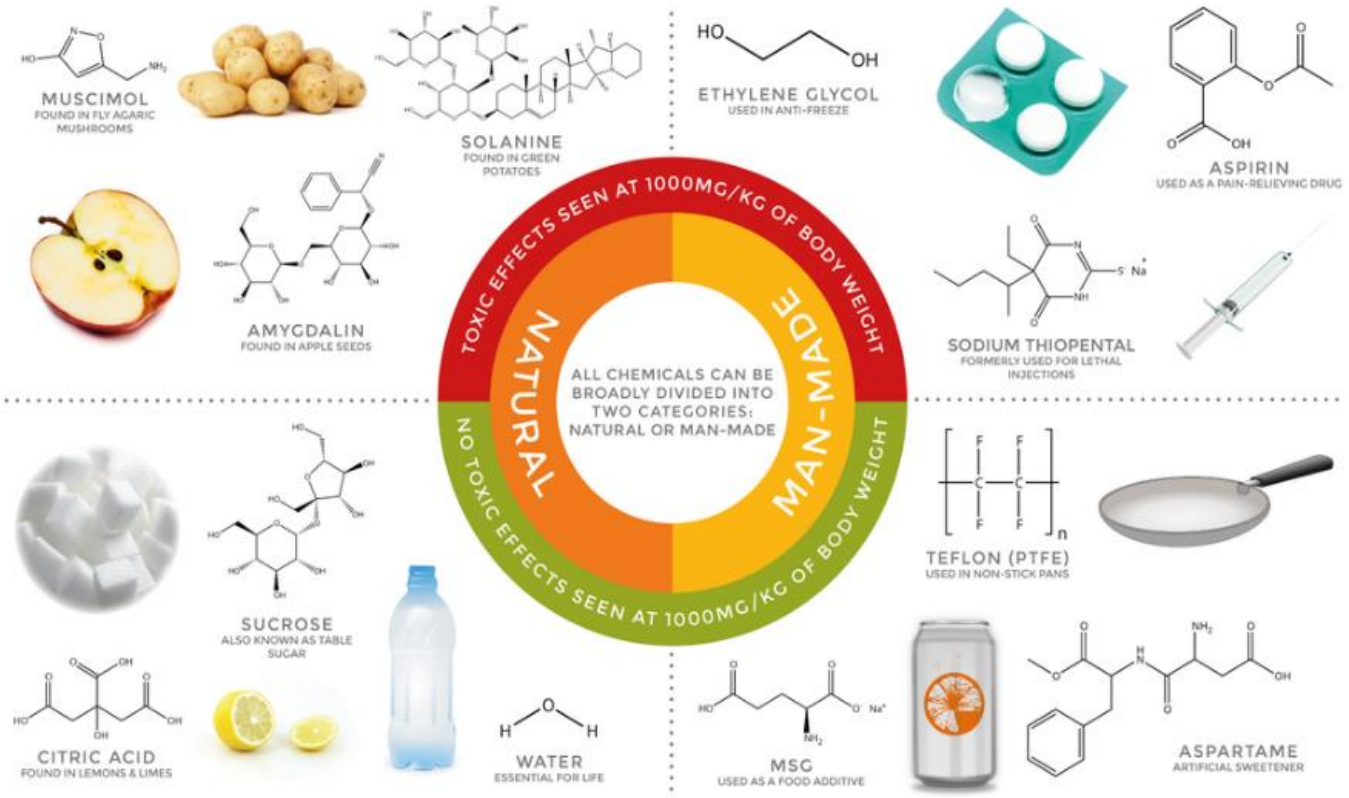

Fig 2. Natural and man-made chemicals

- **Dose-effect relationship**

The dose-effect relationship is a fundamental element in toxicology, because it represents a key concept: the relationship between dose and effect at the individual level. Increasing the dose can increase the intensity or severity of an effect. A dose-effect curve can be plotted for the whole organism, the cell, or the target molecule. Some toxic effects, such as death or cancer development, are not progressive; they represent "all-or-nothing" effects. The dose-response relationship refers to the relationship between the dose and the percentage of individuals exhibiting a specific effect. As the dose increases, a greater number of individuals in the exposed population are affected. Dose-response relationships differ according to organism types and strains, tissue types, and cell populations.

The figure below indicates that the threshold for effect onset, the slope of the relationship in its linear phase, and the maximum effect are the important values characterizing the relationship for a given compound. This graphical representation shows the activation of the same receptors by a chemical compound (fig3).

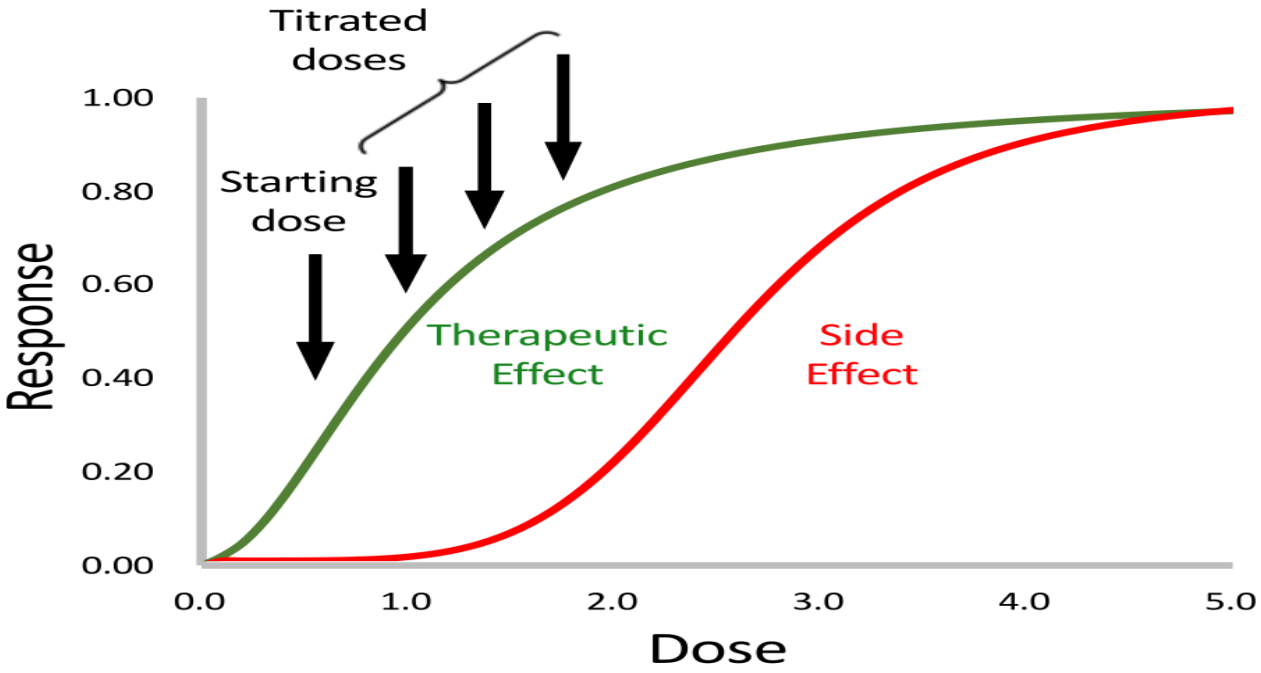

Fig 3. Exemple of relation dose-effet

2. Modes of penetration of toxic substances

The harmful substances or xenobiotic can enter the body through ingestion, inhalation, or skin absorption, leading to a range of physiological responses. The consequences of such exposure can be severe, resulting in disturbances of one or more vital functions, and in some cases, causing irreversible damage or even death.

For a toxic substance to exert its harmful effects, it must first enter the body. The main routes of entry are:

2.1. Respiratory route" or "Inhalation route

Inhalation is the primary route of entry for gases, vapours, and aerosols (both solid and liquid). It is the fastest and most penetrating route because the absorption surface area of the lungs, which is very large, and the pulmonary capillaries are almost directly in contact with the outside air. Inhaled substances quickly reach various target organs the brain, kidneys, placenta, etc. without passing through the liver, which is the major organ for xenobiotic metabolism.

Exposure level depends on the concentration of a toxic substance in the air and the duration of exposure. The risk is influenced by the product's volatility (paint solvents) and physical properties. Only particles smaller than 4.25 micrometres can reach the lung alveoli;

larger particles are trapped and removed by the mucociliary elevator to the oropharyngeal junction.

The respiratory system's structures involved include (fig4).

- **Lungs and alveoli**: The alveoli provide a large surface area for absorption. Fine particles (<4.25 µm) penetrate deep into the alveolar region, where they can enter the bloodstream or cause local damage.
- **Mucociliary elevator**: This defense mechanism (mucus and cilia lining the airways) traps larger particles and transports them upward to the throat, where they are swallowed or expelled, preventing them from reaching the alveoli.
- **Oropharyngeal junction**: The point where cleared particles are redirected to the digestive tract, reducing pulmonary exposure.

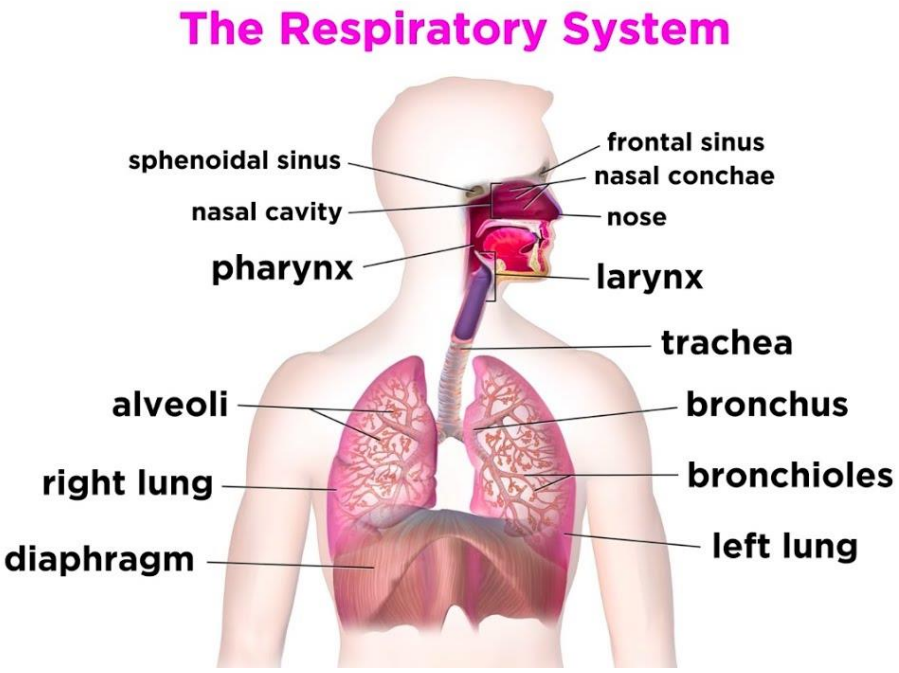

Fig 4. The respiratory system's structures

2.2. **Percutaneous route** or **Transdermal route**

Cutaneous administration is another form of the topical route of xenobiotic and is applied to the layer of skin referred to as *cutis*, which includes the epidermis and dermis. As the body's largest organ, the skin covers the entire external surface. It is composed of three layers—the epidermis, dermis, and hypodermis—each with distinct anatomical features and functions

(fig 5). The skin's complex architecture forms the body's first line of defense against pathogens, ultraviolet (UV) radiation, chemicals, and physical trauma. In addition, this organ helps regulate body temperature and controls the loss of water to the external environment.

Skin thickness varies by body region, depending on the epidermal and dermal layers. The thickest skin is on the hairless palms and soles, due to an extra epidermal layer called the stratum lucidum. Other regions have "thin skin"; among these, the back is the thickest because it has a thick epidermis. The skin's barrier function makes it prone to inflammatory and infectious conditions. Wound healing, sensory changes, and appearance (cosmesis) are key surgical concerns. Understanding skin anatomy is essential across all medical fields.

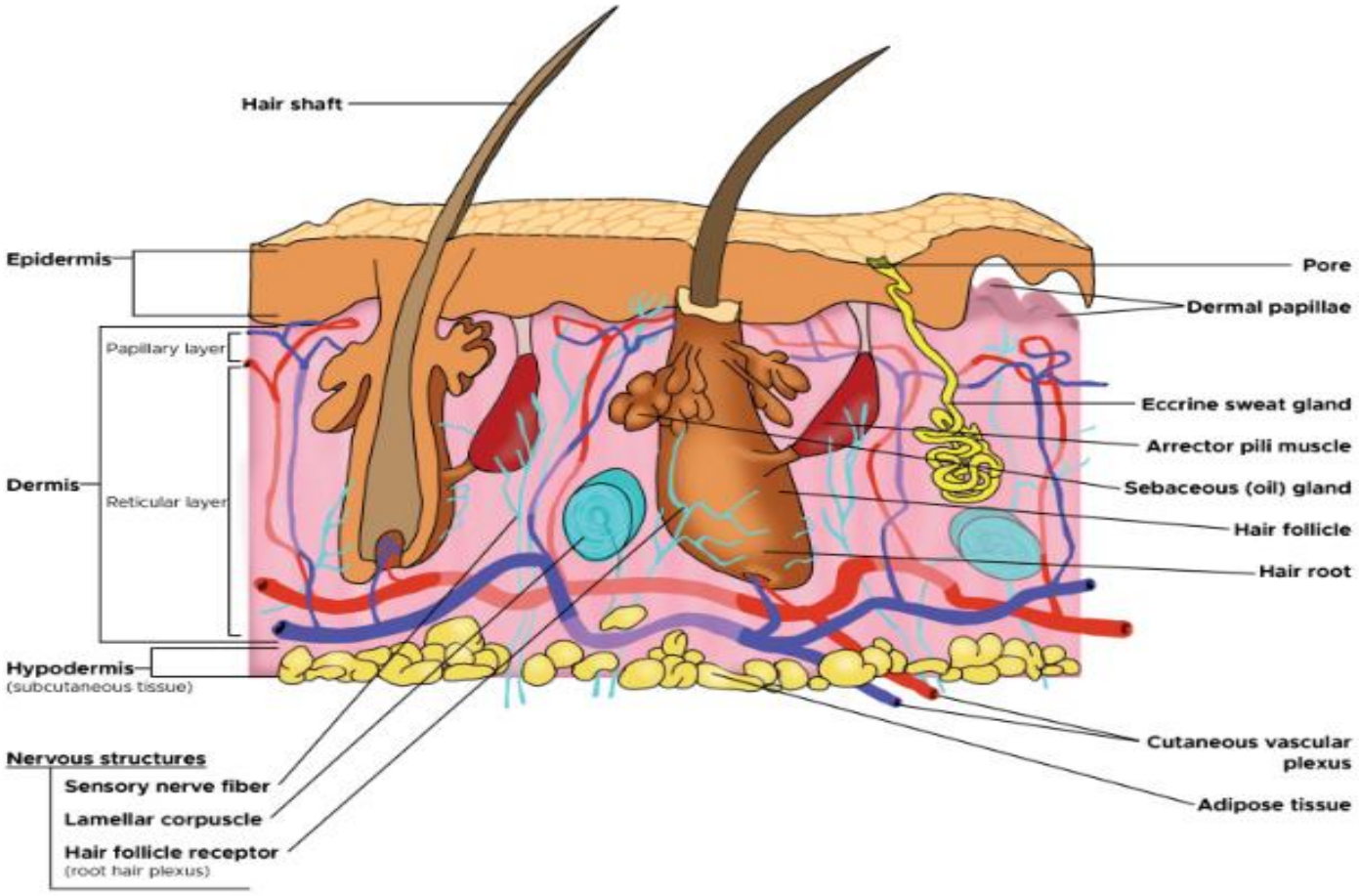

Fig 5. Layers of the Skin. This is a cross-section view of the hair follicles, hair roots and shafts, sweat glands, pores, epidermis, dermis, and hypodermis. The papillary and reticular layers are also included. The eccrine sweat gland is located

2.3. Trophies or oral administration way

Toxic substances enter the digestive tract through water, food, and medications. Except for highly caustic products, their effects occur only after absorption.

Oral administration is a convenient, cost-effective, and the most commonly used route. The primary site of absorption for food and drugs is usually the small intestine. Bioavailability is influenced by the amount of substance absorbed across the intestinal epithelium. In the stomach, weak acids diffuse easily, unlike weak bases. In the intestine, weak bases are the most readily absorbed. Additionally, active transport processes may be involved for certain toxic substances like lead.

A key feature of digestive absorption is the first-pass effect (first-pass metabolism), the toxic substance, absorbed through the digestive tract, passes through the liver, reaches the heart, and after pulmonary circulation, distributes throughout the body.

In the intestinal mucosa and the liver, the substance encounters enzymes that can transform it into one or more metabolites sometimes active, but most often inactive. This is first-pass metabolism (Fig 6). The liver is then the primary organ for inactivation and transformation, but also a major target organ for toxic substances.

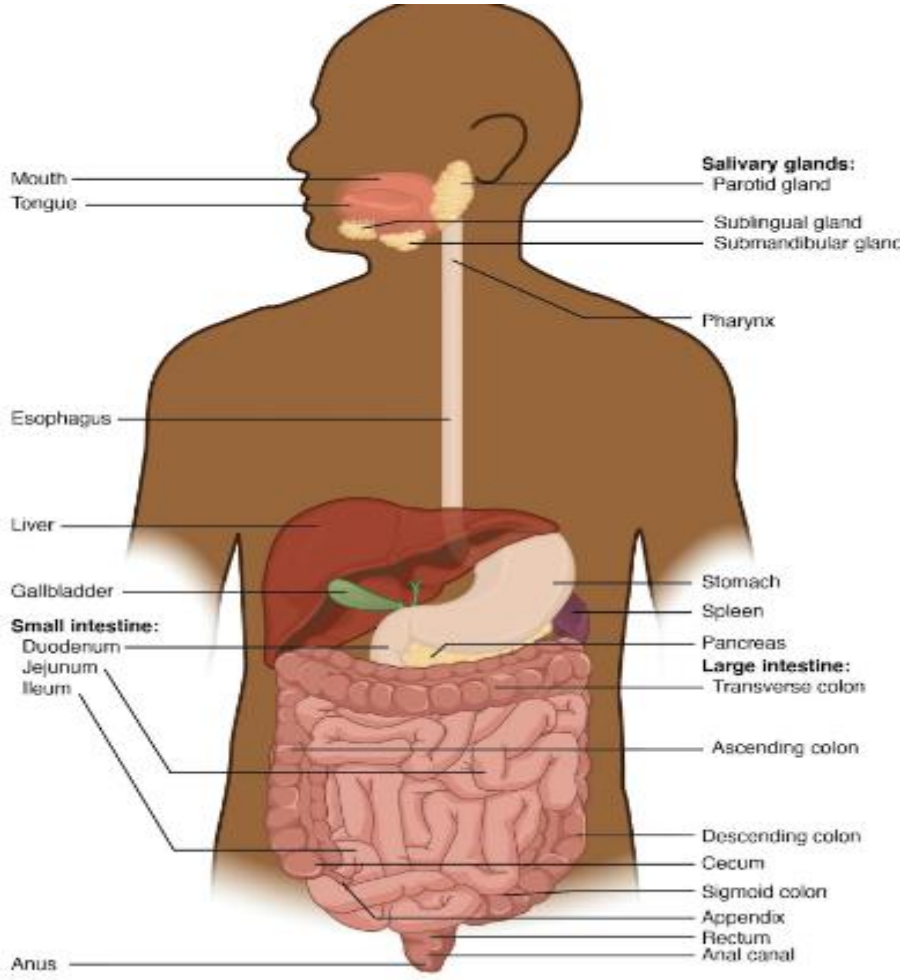

Fig 6. Components of the Digestive System. All digestive organs play integral roles in the life-sustaining process of digestion.

3. Types of toxicity

Toxicity encompasses all the harmful effects of a toxic substance on a living organism. In other words, it is the inherent capacity of a chemical substance to produce adverse effects in a living organism, which makes it a dangerous substance.

So toxic effect is the disruption and dysfunction of the balance of the body's adaptation processes in response to various aggressive situations (biological, chemical, physical).

Several key parameters determine the toxic effect of a substance on the body.

- Dose
- Route of absorption
- Type and severity of lesions

- Time required for the appearance of a lesion
- Route of penetration

Different forms of toxicity exist, including acute or subacute toxicity and long-term toxicity, which result from the absorption of a single dose or repeated small doses (Table 1).

Acute toxicity

Results from a single or very short-duration exposure to a relatively high dose of a substance. Its effects are often immediate and dramatic, possibly leading to rapid death. Acute toxicity results from the absorption of a large dose of a substance by oral, pulmonary, or cutaneous routes, either as a single exposure or several very close exposures.

It can cause dramatic manifestations, even rapid death. Experimentally, it is estimated by the lethal dose 50 (LD_{50}), which varies according to the animal species and the route of administration.

Subacute toxicity

Consequence of repeated exposure over a period ranging from 24 hours to 28 days. The effects are generally less immediate than those of acute toxicity.

Subchronic toxicity

Occurs after repeated exposure over a period of 28 to 90 days.

Chronic toxicity

Results from repeated and prolonged exposure, beyond 90 days. It manifests as insidious effects, often after a long latency period, and may be due to the accumulation of small doses in the body (tab1).

Table 1. Acute/Subacute Toxicity vs. Long-Term Toxicity – Comparison of Exposure, Effects, and Examples

Criterion	Acute and Subacute Toxicity	Long-TermToxicity
Exposure pattern	Single dose or several very close exposures	Repeated absorption of very small doses over a prolonged period
Absorbed dose	high dose	too low to cause acute effects
Observed effects	Immediate (within hours or days). Not applicable (rapid effects: coma, convulsions, respiratory arrest, death)	Slow, insidious (weeks, months, or years) Growth disturbances. Behavioural changes. Altered body fluid chemistry. Histological damage to liver, kidneys, nerve centres, bone marrow, endocrine glands. Blood count abnormalities. Impaired reproduction. Reduced lifespan
Mechanism	Direct massive injury; no prior accumulation needed	Cumulative poisons: retention in the body due to physical affinity (lipid solubility), chemical binding to cellular components, or kidney damage impairing elimination
Experimental assessment	Lethal dose, especially **LD50** (dose that kills 50% of test animals)	No LD50; long-term effects studied on multiple parameters (growth, behavior, organ function, reproduction, lifespan)
Examples	- Carbon monoxide (CO) - Chlorine (Cl_2) - Hydrocyanic acid (HCN) - Massive ingestion of many products	- Methyl alcohol - Digitalis glycosides - Mineral derivatives of arsenic and fluorine - Heavy metals: lead, mercury, cadmium, thallium

3.1. Taxonomic variation

Taxonomic variation in toxicity refers to the differences in toxic responses observed among different species, genera, families, or higher taxonomic groups when exposed to the same chemical substance. This variation is a fundamental concept in toxicology, and risk assessment, as it explains why a compound may be highly toxic to one organism but relatively harmless to another.

In addition, there are many Causes of Taxonomic Variation such as:

- **Metabolic differences**

- **Receptor structure and distribution**
- **Absorption, distribution, and excretion**
- **Detoxification and activation pathways**
- **Physiological and anatomical factors**

3.2. Influence de l'état de l'individu

The influence of an individual's condition on their susceptibility to toxins is a key principle in toxicology. Susceptibility is not uniform across a population; it varies based on intrinsic biological factors such as age, sex, genetics, and pre-existing health conditions, as well as lifestyle factors like nutrition.

3.3. Facteurs extrinsèques

Intrinsic toxicity is determined by the chemical and biological structure of the substance itself. For example, certain plants contain naturally toxic compounds, such as glycoalkaloids in potatoes, which can be toxic at high doses. In contrast, **extrinsic toxicity** is influenced by external factors. For example, the dose ingested or chronic exposure can transform a theoretically harmless compound into a dangerous one (tab 2).

Table 2. The main Differentiates between Extrinsic and Intrinsic Factors

Criterion	**Intrinsic Factors (Inherent to the organism)**	**Extrinsic Factors (Related to the environment and exposure)**
Definition	Factors specific to the individual or species (genetic and biological)	Factors external to the organism (exposure conditions and environment)
Nature	Generally non-modifiable	Potentially modifiable, controllable, or avoidable (prevention possible)
Origin	Inside the body	Outside the body
Main examples	- Age and life stage - Sex - polymorphisms - Nutritional status	- Dose of the toxic substance - Duration of exposure (acute vs. chronic) - Route of exposure (oral, inhalation, dermal) - Interaction with other substances - Physicochemical factors -

4. Different phases of action of a toxic substance

4.1. Exposure phase

The **exposure phase** refers to the contact between a xenobiotic and the external surfaces of the body such as the skin, respiratory tract, or digestive tract before any absorption occurs (Fig 7).

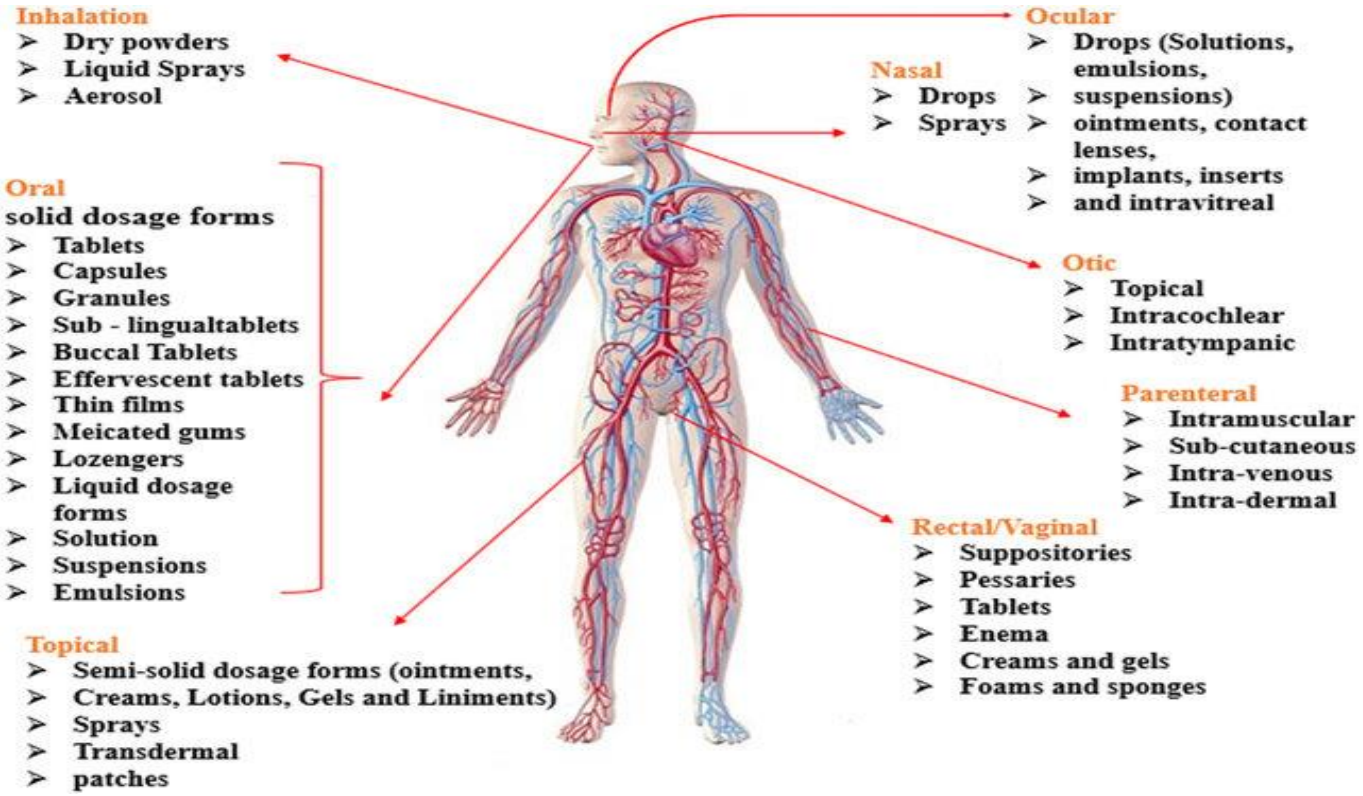

Fig 7. Different routes of exposure

Once a human organism is exposed to a toxic product, different phases follow one another.

4.2. Phase toxicocinétique

Absorption phase

Absorption refers to all the phenomena involved in the transfer of the xenobiotic from its site of administration into the bloodstream.

This process is highly dependent on both the substance's physicochemical properties, such as its lipid solubility, and the specific biological barriers it encounters, like the highly vascularized alveolar sacs in the lungs. Several key mechanisms govern this passage.

In addition, Toxic substances produce effects on the human organism from the moment they are absorbed, mainly through the skin, the digestive tract, and the lungs. Toxic effects result from biochemical interactions between the toxic molecule and the structures of the organism.

Phase toxicocinétique

It begins after absorption and results in the presence of the toxic substance in the internal environment. The nature and intensity of the effects of a xenobiotic on an organism are related to the concentration of the active compound at the target organs. This concentration depends on the dose administered and on factors such as absorption, distribution, metabolism, and excretion (ADME). The fraction of the substance that passes from the exposure phase to the toxicokinetic phase determines its chemical availability.

4.3. Toxicodynamic phase or Interaction with the target tissue

Toxicodynamics refers to the relationship between the concentration of a toxicant at its site of action and the resulting adverse effects over time. It evaluates the mechanisms, duration of action, and the biological response elicited by the chemical stimulus. Thus, the nature and cause of the response are derived from the molecular mechanism and consequent physiological mode of action of the chemical.

5. Biochemical aspects of the different phases

5.1. Biochemical aspects of the exposure phase

The penetration of molecules or ions of toxic substances from the work or living environment into such a highly coordinated biological system can reversibly or irreversibly disrupt normal cellular biochemical processes. This depends on the molecules or ions of toxic substances present in the environment, which enter the body through the skin and mucous membranes, or through the epithelial cells of the respiratory and gastrointestinal tracts, depending on the entry point.

All toxicokinetic and toxicodynamic processes occur at the molecular-cellular level. Many factors influence these processes, and they can be divided into two basic groups:

- Chemical constitution and physicochemical properties of toxic substances
- Cell structure, in particular the properties and function of the membranes surrounding the cell and its internal organelles.

To define chemical structure, many parameters can be selected as descriptors, which can be divided into different groups:

- **Physicochemical:**

✓ General: melting point, boiling point, vapor pressure, dissociation constant (pKa)
✓ Electrical: ionization potential, dielectric constant, dipole moment, mass-to-charge ratio, etc.
✓ Quantum chemistry: atomic charge, bond energy, resonance energy, electron density, molecular reactivity, etc.

- **Steric:** molecular volume, shape and surface, substructure shape, molecular reactivity, etc.

- **Constitutional:** number of bonds, number of rings (in polycyclic compounds), degree of branching, etc.

- **Structure and properties of membranes**

The cytoplasmic membrane of eukaryotic cells is a lipid bilayer (phospholipids, sphingolipids, cholesterol) that delimits the cell and its organelles. Lipids are amphipathic: hydrophilic polar heads on the surface, apolar lipophilic tails inside. Intrinsic or extrinsic proteins are inserted into it, playing structural, enzymatic, transport, or receptor roles. The membrane is dynamic: it can remodel according to functional needs. Lipophilic substances cross the bilayer directly; hydrophilic molecules and ions pass through pores. The opening or closing of these pores allows the membrane to regulate exchanges and respond to environmental changes.

The following processes and mechanisms are involved in the transport of substances, including toxic substances, across membranes:

❖ **Passive Diffusion which means** Moves down the concentration gradient through the lipid bilayer. And Most xenobiotics (especially lipophilic), non-ionized molecules like many drugs and environmental pollutants

- **Facilitated Diffusion** Utilizes a carrier protein to move down the concentration gradient. Sugars (fructose) and amino acids that are too large or polar for simple diffusion.

- **Active Transport** Uses carrier proteins to move against the concentration gradient, Essential nutrients (e.g., glucose, some amino acids) and drugs similar in structure to natural substrates (e.g., levodopa).

- **Endocytosis** Engulfs substances by invaginating the cell membrane, forming a vesicle. Large, non-lipid-soluble particles, macromolecules (proteins, some nanoparticles), and substances like vitamin B12 via pinocytosis or phagocytosis (fig8)

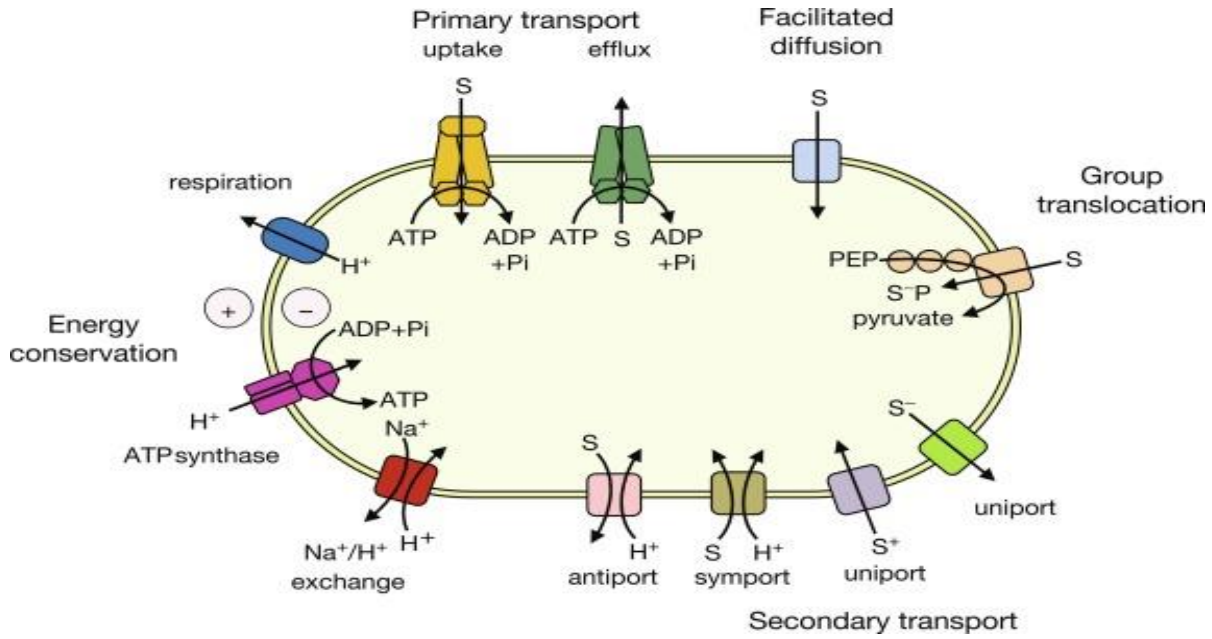

Fig 8. Membrane Transport.

5.2. Biochemical aspects of the toxicokinetic phase

Toxicokinetics includes the phenomena of absorption, tissue distribution, metabolism, and excretion of xenobiotics. It allows us to determine the amount of toxic substance likely to reach its target and to specify in what form (initial compound or metabolites) it arrives there.

To understand the mechanism of action of xenobiotics, it is necessary to consider the metabolic and detoxification pathways, which paradoxically can lead to highly toxic metabolic intermediates. The toxicity of a compound will therefore depend on its mode of absorption, but also on its metabolism.

Absorption

Depending on physicochemical properties (molecular mass, degree of ionization, reactivity, solubility) and exposure sources, xenobiotics can be absorbed in different ways (cutaneous, oral, pulmonary, etc.) and distributed into various tissues actively or passively. Differences exist depending on the nature of the barrier to be crossed (skin, lung, intestinal wall, etc.) and the size of the molecules, with small molecules being able to cross one or more membranes passively.

Lipophilic substances can more easily cross a membrane whose constituents are lipids, whereas ionized substances will be stopped except at membrane pores for the smallest molecules. The cell membrane thus constitutes an effective barrier protecting cells against water-soluble xenobiotics.

Conversely, hydrophobic molecules can accumulate and reach a toxicity threshold. The relationship between the external dose and the internal dose depends essentially on the level of absorption, itself affected by the lipophilic nature of the substance or the efficiency of efflux pump systems.

Indeed, during their evolution, organisms have developed systems limiting the accumulation of xenobiotics: these include membrane transporters allowing rapid exit of unwanted molecules as well as detoxification systems (fig 9).

Distribution

Tissue distribution is the process by which an absorbed substance (or its metabolites, see following paragraph) is distributed among the different organs and tissues. As with absorption, diffusion mechanisms depend primarily on the physicochemical properties of the substances.

Note that if the compound is absorbed orally, it will pass directly into the liver via the portal system and will then be distributed throughout the body (first-pass hepatic effect); if it is inhaled (pulmonary route), it will be distributed throughout the body before reaching the liver.

The elimination of non-ionized lipophilic substances (which are easily absorbed and distributed) requires the intervention of detoxification systems to render them water-soluble and thus excreted via the biliary and urinary routes. This process of xenobiotic metabolism and

excretion involves numerous enzymatic systems. It is classically divided into two phases. During the first phase, the lipophilic xenobiotic is oxidized, reduced, or hydrolyzed; then, during the second phase, it is conjugated with a sulfate or acetate group, with glutathione, or with an amino acid.

5.2.1 Transport and distribution processes

From the entry site and after absorption, the xenobiotic is distributed into the general circulation: substances are transported by the blood to the various tissues of the body. The term "distribution" summarizes transport in the blood (plasmatic phase) followed by diffusion into tissues (tissue phase).

Blood transport

Blood acts as a transport vehicle via plasma, red blood cells, and circulating proteins capable of binding the substance. This is referred to as binding to plasma proteins. This binding is reversible.

The administered substance comes into contact with proteins capable of binding exogenous substances such as drugs. The administered substance is then found either in free form or bound to proteins. Note that only the free xenobiotic is toxicologically active; thus, the importance of this distribution step in the fate of the toxicant in the body becomes apparent.

Binding to plasma proteins

There is a significant number of plasma proteins. The main proteins involved in protein binding are albumin, alpha1-glycoprotein, lipoproteins, and globulins.

- **Albumin** is the most abundant and has numerous sites capable of interacting with drugs.
- **Alpha1-glycoprotein** is the smallest in size and is very rich in carbohydrates.
- Conversely, **lipoproteins** are large in size and contain variable amounts of lipids, explaining their classification; we distinguish HDL (high density lipoprotein), LDL (low density lipoprotein), and VLDL (very low density lipoprotein).
- Finally, **globulins** are an important group of proteins capable of binding drugs, and alpha-, beta-, and gamma-globulins are distinguished based on their molar mass.

Toxicant-protein binding depends on several factors: the affinity of the toxicant for binding sites, the number of "available" binding sites, and the concentration of the toxicant.

- **Affinity**, as its name indicates, defines the ability of the toxicant to bind to the protein. Binding to proteins can be very strong even if affinity is low: it is sufficient that the toxicant concentration is high, or that the number of available sites is large. Binding to proteins can be weak with very high affinity.
- The quantity of proteins available for binding can vary depending on physiological and pathological conditions, notably hypoalbuminemia.

Binding is defined by the percentage of binding, which can range from 0 to 100%. For example, plasma protein binding of certain anti-inflammatory drugs is 95%. The binding of acetaminophen (paracetamol) is, on the contrary, zero. A substance is considered highly bound if its binding percentage exceeds 75%. This binding to plasma proteins is important because only the drug in its free form is active, as it can reach its membrane or intracellular target. The bound form acts as a reservoir that does not cross membranes.

Binding to formed elements

Binding to formed elements (blood cells) appears to be less significant than that to plasma proteins.

To summarize, when the drug reaches the plasma, it can either be bound to plasma proteins, bound to formed elements, or be found in free form, i.e., in an active, diffusible form into tissues.

Tissue diffusion

Tissue diffusion or distribution is the process by which the drug distributes throughout all tissues and organs. Tissue diffusion involves the same mechanisms as diffusion in the blood. The limiting factors of tissue diffusion are:

- Binding to tissue proteins, which determines the free form
- The physicochemical characteristics of the molecule, namely its molar mass, lipophilicity (partition coefficient), pKa of the molecule (which determines its ionized or non-ionized state) and therefore its ability to cross vascular and cellular membranes

- Organ irrigation and blood flow
- The participation of membrane transporters that bring drugs into cells (influx transporters) or export them out of cells (efflux transporters)

Protein binding and tissue distribution

Tissue distribution of a drug will be greater when the plasma concentration of the drug in free form is high. This free form is inversely proportional to the fraction bound to proteins, whether plasma proteins or tissue proteins. The intensity of binding is one of the factors modulating tissue distribution.

Finally, for the same drug, the bound amount may differ from one tissue to another depending on affinity. Take the example of brain tissue: it is rich in lipids and has high affinity for liposoluble molecules. Distribution to this organ will therefore be greater for liposoluble molecules.

Binding to various receptors

A distinction must be made between a first group of receptors whose function is the adaptation of the body to the influx of xenobiotics and whose activation is responsible for the induction of enzymatic systems for xenobiotic elimination, and a second group that includes receptors for endogenous compounds such as hormone receptors, which are nevertheless susceptible to being modulated by pollutants such as pesticides (Figure 20.2).

Xenobiotic receptors include **AhR** (Aryl hydrocarbon Receptor – receptor for dioxins, aromatic hydrocarbons); **PXR** (Pregnane X Receptor – receptor for pesticides, drugs, etc.); **CAR** (Constitutive Androstane Receptor). The binding of xenobiotics to their receptors (PXR, CAR, AhR) triggers signal transduction leading to the induction of enzymes and transporters necessary for their elimination, but this signaling also involves all the processes necessary for a cell's adaptation to stress. In this sense, xenobiotic receptors are considered **xenosensors** because they coordinate an appropriate cellular response. Among xenosensors, PXR is a key player in adaptive systems. Indeed, it is activated by a large number of structurally and functionally varied molecules. This very broad specificity towards xenobiotics characterizes the xenosensor functions of PXR (Kliewer et al., 2002). It coordinates defense processes at the hepatocyte level by co-regulating detoxification mechanisms, enabling

the transcription of genes encoding XMEs (CYP3A4, CYP2B6, GST, MDR, etc.) and cell survival and death pathways.

Xenobiotics can also bind to receptors with known physiological functions, such as the estrogen receptor (ER), androgen receptor (AR), retinoid receptor (RAR), peroxisome proliferator-activated receptors (PPARs), and the thyroid hormone receptor (T3R). This constitutes an illegitimate activation of these receptors leading to endocrine or metabolic disruption. Certain non-genotoxic carcinogens are endocrine disruptors because they bind directly to ER receptors, progesterone receptors, AhR, or the thyroid hormone receptor (fig10).

As xenoestrogens, several pesticides are considered endocrine disruptors. In this category, we find fungicides (alachlor, atrazine, benomyl, vinclozolin, etc.), insecticides (DDT, methoxychlor, chlordecone, dieldrin, endosulfan, chlordane, toxaphene, etc.). They are active either by themselves or through their metabolites (Sonnenschein & Soto, 1998). Some are capable of activating both types of estrogen receptors, ER alpha and ER beta. Endosulfan, alachlor, and chlordecone are competitive ligands for the progesterone receptor. Certain fungicides (vinclozolin), herbicides (linuron, etc.), insecticides (p,p'-DDE, a metabolite of DDT, pyrethroids such as permethrin, etc.) are androgen antagonists (Curtis, 2001). However, most substances exhibit varied effects on other hormones (cortisol, thyroxine, insulin, etc.).

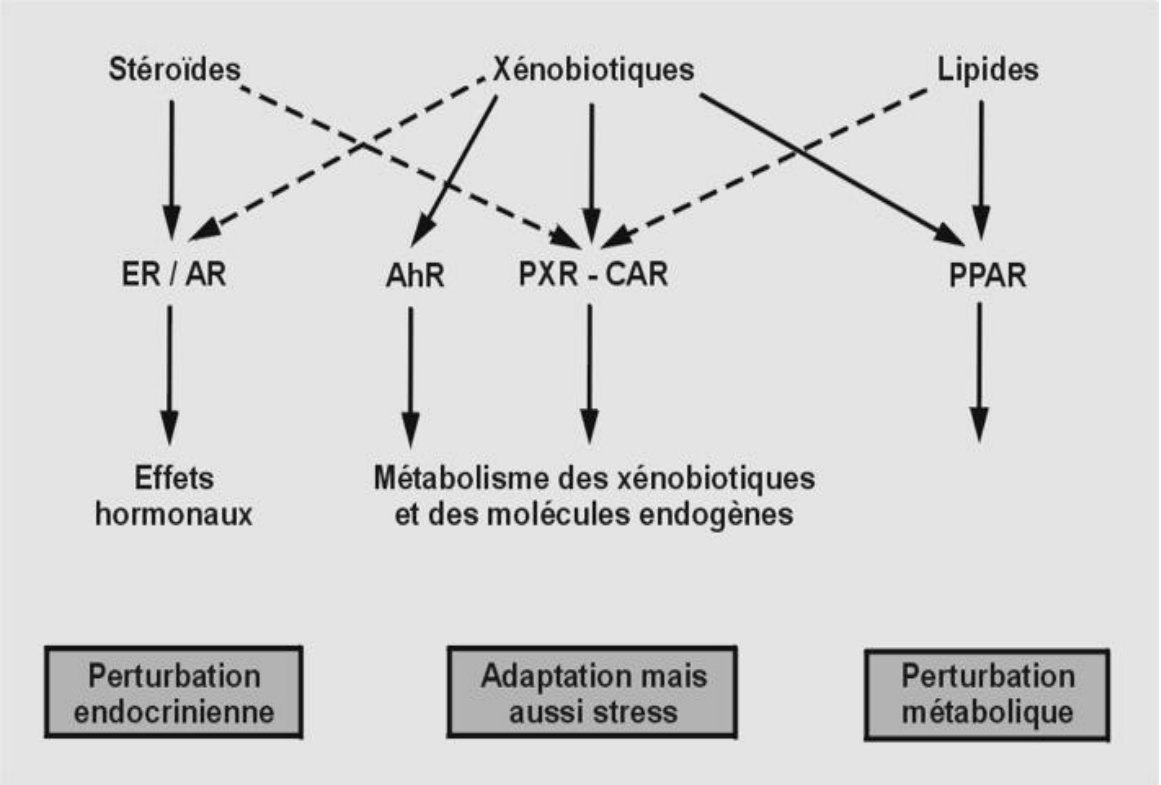

Fig 9. Xenobiotic receptors

Furthermore, xenobiotics can induce the expression of a large number of genes that are not involved in their elimination. It is essential to determine the role of these genes in xenobiotic toxicity.

5.2.2 Biotransformation processes

Xenobiotic metabolism

When a xenobiotic enters a cell, it is quickly taken care of by membrane transporters, efflux pumps that will export it directly outside the cell, or by xenobiotic-metabolizing enzymes (XMEs) (Fig 11).

Xenobiotic-metabolizing enzymes generally modify the compound to make it less active and exportable outside the cell. These xenobiotic-metabolizing enzymes represent a complex system essential for the protection of the organism. Possessing a key role in the metabolism and elimination of potentially toxic compounds, any alteration in their regulation, expression, and/or activity can generate harmful consequences for the organism.

The first step, or functionalization phase, often involves cytochromes P450 (CYPs), particularly those belonging to families 1, 2, and 3. This phase I consists of a metabolic activation that leads to the formation of highly reactive electrophilic intermediates, which will then be taken care of by phase II enzymes (conjugation enzymes or transferases such as glutathione-S-transferase or glucuronosyltransferase), capable of attaching hydrophilic residues and transforming them into an inactive compound easily excreted by the cell.

This excretion of xenobiotics outside the cell involves phase III transport or efflux proteins (P-glycoprotein and Multidrug Resistance-associated Proteins, MRPs).

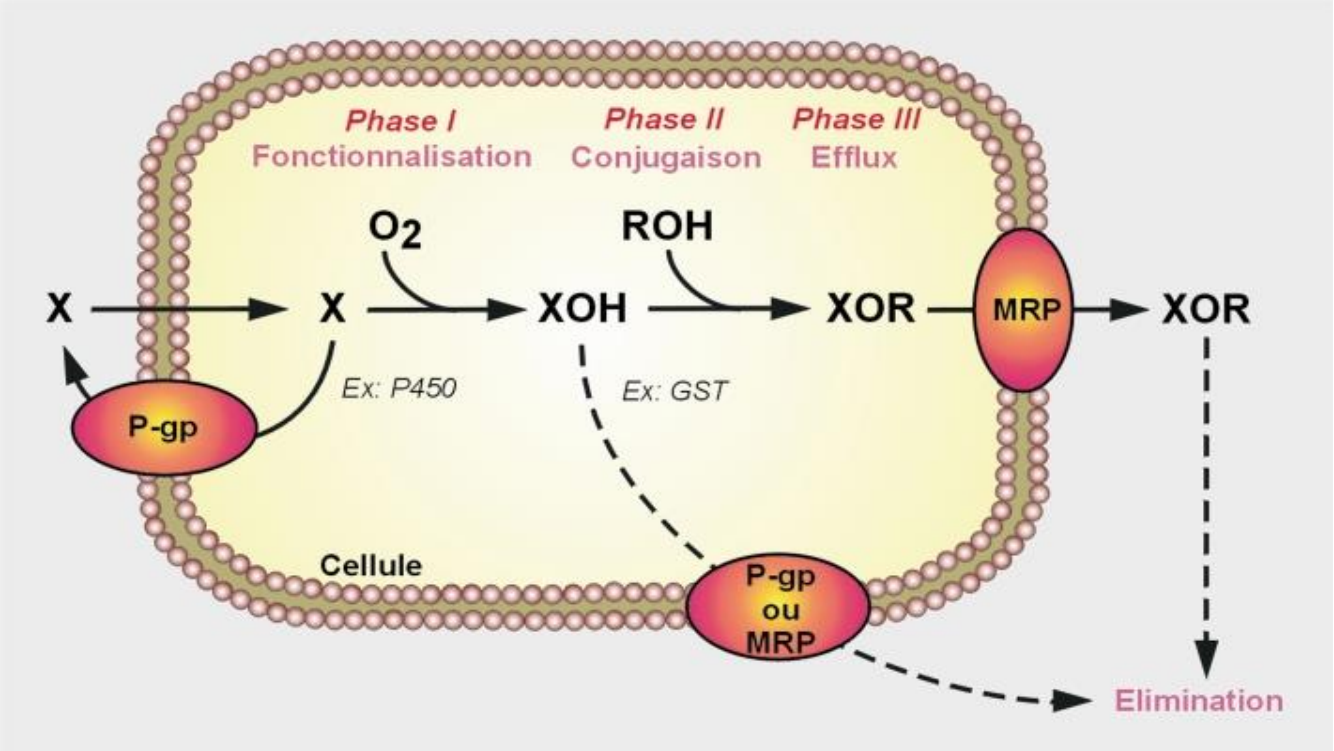

Fig 10. Xenobiotic-metabolize

5.3. Mechanisms of action: toxicodynamic phase

Toxicodynamics more specifically examines the interaction of the xenobiotic with its target and the toxic effect that this produces. The toxic effect will be greater the more the toxic form of a xenobiotic is able to reach the target and the more sensitive this target is to the exogenous agent. Therefore, toxicokinetics is a critical element in the hazard characterization of a chemical substance.

5.3.1 Interaction toxique – récepteur

General mechanisms of toxicity

These mechanisms are undoubtedly multiple. Some are related to adaptive mechanisms. Thus, the formation of reactive intermediate metabolites by phase I enzymes is necessary for the activity of phase II enzymes. However, these same metabolites can also react with cellular macromolecules, particularly DNA, and form adducts, which accounts for their toxicity, and more specifically their genotoxicity. Studies conducted using "knock-out" (KO) animal models have shown that the detoxification function (xenobiotic elimination) appears to predominate over the bioactivation function (production of reactive compounds). Thus, CYP1 KO mice are more sensitive to certain genotoxic agents than wild-type models. Although these studies do not focus on pesticides, they can be used as a reference to support the essential role of XMEs in detoxification processes that would potentially involve pesticides.

The activity of certain cytochromes P450 can lead to the production of reactive oxygen species (ROS), which, depending on their concentration, either play a role in the activation of certain transduction pathways or have a toxic effect (adduct formation with macromolecules) for the cell. This is the case, for example, with cytochromes P450 CYP1A1 and CYP2E1, which are particularly involved in the metabolism of uncoupling agents that promote the production of these ROS.

Other toxicity mechanisms may be linked to the group of genes induced by xenobiotic receptors, which extends far beyond those involved in their metabolism leading to their elimination. This is the case for the dioxin receptor (AhR), for which new gene targets have been identified. Beyond metabolism, nuclear receptors are at the heart of the regulation of numerous gene networks involved in proliferation, cell differentiation, development, and homeostasis. Their dysfunction can lead to various pathologies (hormone-dependent cancers, diabetes, obesity, infertility, etc.).

Finally, toxicity mechanisms may depend on the nature and functions of each tissue. Adipose tissue stores a large quantity of hydrophobic xenobiotics, and the implications of this function are probably not sufficiently appreciated. Similarly, the effects of xenobiotics and their metabolites on the development and functioning of the nervous system as well as on the blood-brain barrier are not well understood.

5.3.2 Effect Classification

When a chemical product is absorbed, various biological effects occur, which can be beneficial (improvement of health after administration of a drug) or harmful (lung damage following inhalation of a corrosive gas).

Toxic effects can be classified in different ways, for example by:

- **Duration**: acute, chronic
- **Type of action**: local, systemic
- **Mechanism of action**: stimulant, inhibitor
- **Route of penetration**: respiratory, cutaneous, digestive
- **Affected tissue or organ**: blood (hematotoxic), liver (hepatotoxic), kidney (nephrotoxic), nervous system (neurotoxic)
- **Nature of the effect**: irritant, sensitizing, asphyxiant, carcinogenic
- **Use**: pesticides, soaps, solvents
- **Labeling**: corrosive substance
- **Chemical family**: aromatic hydrocarbons, alcohols

5.3.3 General Principles of Enzymatic Activity Measurement

The measurement of xenobiotic enzymatic activities is based on determining the rate of enzymatic reaction, by following either the disappearance of the substrate or the appearance of the product, generally by spectrophotometry.

Enzymatic activity (EA) corresponds to the efficiency of a given amount of enzyme in transforming substrate into product under well-defined optimal conditions (pH, temperature, ionic strength, saturating substrate). The initial velocity is measured at steady state where the enzyme is saturated with substrate, making the maximum velocity (Vmax) independent of substrate concentration and proportional only to enzyme concentration.

The main general approaches for measuring enzymatic activity rely on photometry (UV-visible absorbance), colorimetry (production of a colored compound), fluorimetry (fluorescence emission after excitation), radioactivity (use of radioactive tracers), or acidimetry (monitoring proton production).

Specific Measurement Methods for Xenobiotic Biotransformation Enzymes

In Vitro Approaches for Phase I and II Enzymes

In vitro methods are the most common for characterizing the activity of xenobiotic-metabolizing enzymes (XMEs). Multi-substrate approaches, such as the Xenomix™ cocktail, allow simultaneous measurement of 9 to 12 cytochrome P450 isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5) in human and animal hepatic models (microsomes, hepatocytes). Unlike substrate depletion methods, CYP activity is quantified by the formation of specific metabolites, measured by LC-MS/MS, offering superior precision and sensitivity.

For phase II enzymes, measurement of glutathione S-transferase (GST) activity is performed using spectrophotometric assays with synthetic substrates such as 1-chloro-2,4-dinitrobenzene (CDNB).

Luminogenic Probe and Mass Spectrometry Approaches

The use of chemical probes that, after CYP conversion, produce metabolites quantifiable by mass spectrometry (UPLC-MS) or luminometry constitutes a highly sensitive method. It allows characterization of phase I metabolic competence in 2D cell cultures or 3D primary cultures by direct quantification of probe metabolites by UPLC-MS.

In Vivo Enzymatic Activity

In vivo methods, although less common, are essential when homogenized tissue preparations lead to enzyme degradation or auto-inhibition. The ECOD (7-ethoxycoumarin-O-deethylase) activity assay is a validated example for measuring in vivo CYP activity in invertebrates (annelids), by incubating whole organisms in water containing a fluorescent substrate (7-ethoxycoumarin) and quantifying the formation of the fluorescent product (7-hydroxycoumarin) by spectrofluorimetry.

Enzymatic Activity in Cellular Models

Hepatic cell aggregates constitute a relevant in vitro model for metabolic toxicology studies. They express stable basal activity of phase I (ECOD) and phase II (GST) enzymes, and respond to classic inducers (3-methylcholanthrene, phenobarbital) with a peak of enzymatic activity at 7 days of culture.

Activity-Based Protein Profiling (ABPP)

ABPP uses chemical probes that covalently bind to the active site of enzymes, enabling detection, identification, and characterization of the activity of enzymes such as CYP450 and GST in plant and fungal extracts. This approach allows direct visualization of protein activity rather than just their expression.

Modern Technologies for Measuring Xenobiotic Enzymatic Activities

Fluorogenic probe chemistry (e.g., resorufin) and the use of spectrofluorometers are common for CYP450. UPLC-MS assays are the reference for quantifying multiple metabolites, and automation increases throughput and assay reproducibility (tab3).

Table 3. Summary Table of Methods for Measuring Xenobiotic Enzymatic Activities

Method / Technique	Measurement Principle	Typical Application
UV-visible spectrophotometry / Colorimetry	Light absorbance at a specific wavelength	GST assays (CDNB), monitoring NAD(P)H production or disappearance

Fluorimetry	Fluorescence emission after excitation at an appropriate wavelength	EROD (CYP1A1), ECOD (CYP activity), resorufin assay
Mass spectrometry (LC-MS/MS, UPLC-MS)	Chromatographic separation followed by mass spectrometry detection and quantification	Multi-substrate cocktails (Xenomix™), quantification of specific metabolites (phase I and II)
Radioactivity	Incorporation of a radiotracer atom into the molecule of interest	Historical metabolic studies; less common today for safety reasons
Acidimetry	Monitoring proton (H+) production using a pH meter	Enzymatic reactions generating pH variations

Chapter II: Main types of food poisoning

Food poisoning is a common disease condition that usually results from eating food contaminated with infectious microorganisms (viral, bacterial, parasitic or fungal) or toxins secreted during the different stages of food processing, production or preservation.

Most cases of food poisoning are considered moderate and their symptoms resolve spontaneously within several days without treatment, while severe and chronic cases require hospitalization. Food poisoning can usually be prevented by keeping hands clean and preparing food in proper, hygienic and clean ways.

1. Bacterial food poisoning

Bacteria is one of the main underlying causes of foodborne diseases. Where the bacteria involved in the infection of such diseases in the world, for examples Campylobacter jejuni, Salmonella, and E. coli. It used to be that bacterial infection was more common because only a few places were able to test for norovirus, and passive surveillance for that agent was done. Noting that the symptoms of a bacterial infection are delayed because the bacteria need a period of time to multiply. It is often hidden and not seen until 12-72 hours or more after eating the contaminated food among the most common bacterial pathogens are:

- Campylobacter jejuni, which leads to a secondary form of Guillain-Barré syndrome and periodontitis.
- Salmonella by Eating eggs that have not been cooked enough causes typhimurium infection, or other pathogens that are transmitted between humans and animals.

- Escherichia coli enterohemorrhagic causes hemolytic- uremic syndrome.

Other bacterial pathogens that transmit disease through food include: Bisilis Ceres Escherichia coli, Listeria monocytogenes, Shigella, Staphylococcus aureus, streptococcus bacteria, Vibrio cholerae bacteria, Staphylococcus aureus.

In addition to some diseases caused directly by bacterial infection, there are also some foodborne diseases caused by exotoxins that are secreted by a specific cell during the growth of bacteria. Hence, exotoxins have the potential to cause disease even when the microbes that produce those toxins die or are killed.

Symptoms appear immediately after 1-6 hours, depending on the amount of toxin that was ingested and digested. From here, the infected individuals getting to know each other can identify the outbreak. However, more outbreaks or outbreaks are identified by the public health team's interview with increasing reports of laboratory test results for some strains of bacteria.

Noting that the detection and investigation of disease outbreaks is the responsibility of the local health jurisdictions of the states, making them incompatible from one province to another. It has also been estimated that only about 1-2% of outbreaks are detected (tab4).

Table 4. A summary of common foodborne pathogens and their implications for food safety.

Foodborne Pathogens	Characteristics	Contaminated Food
Listeria monocytogenes	Gram-positive, rod-shaped, facultative anaerobic, non-spore forming	meat (especially beef), eggs, poultry, seafood, vegetable, salad, juice, milk, cheese, dairy, ice-cream
Salmonella enterica	Gram-negative, rod-shaped, facultative anaerobic, flagellate, non-spore forming	eggs, egg products, poultry meat
Staphylococcus aureus	Gram-positive, spherical, facultative anaerobic, flagellate, non-	meat products, dairy products, egg products, poultry, salads, bakery products (especially cream-filled pastries and cakes, and sandwich fillings)

Foodborne Pathogens	Characteristics	Contaminated Food
	spore forming, non-motile	
Pseudomonas aeruginosa	Gram-negative, rod-shaped, obligate aerobic, flagellate, motile	fruits, vegetables, meat, low-acid dairy products
Escherichia coli	Gram-negative, rod-shaped, non-spore forming, metabolically active	fresh meat, fruits, vegetables, raw milk, dairy products
Bacillus cereus	Gram-positive, rod-shaped, facultative aerobic, spore-forming, motile	dairy products, vegetables, meat, rice
Campylobacter jejuni	Gram-negative, rod-shaped, microaerophilic, flagellate, non-spore forming, motile	Animals, poultry, vegetables, fruits, all kinds of cooked food, milk, dairy products

2. Viral foodborne illnesses

Viral foodborne diseases originate from all kinds of viruses that can contaminate food at any level of the supply chain. Viruses are very small infectious microorganisms consisting of a DNA or RNA genome surrounded by a protein capsid. Unlike bacteria, viruses can only reproduce inside the living cells of other organisms. However, many viruses exhibit great resistance when subjected to harsh conditions such as heat, freezing, UV exposure, and others, and are capable of surviving for long periods in food or the environment. Most viral infections are transmitted through human contact, with the risk of contamination via food being a minor risk in the overall context.

the most viruses responsible for food poisoning

The majority of viral foodborne illnesses are often caused by a small number of viruses, including:

- Noroviruses (they cause gastroenteritis, which is the most common viral foodborne infection and is characterized by diarrhea, vomiting, and abdominal pain);
- Hepatitis A and hepatitis E (which cause liver inflammation);
- Rotaviruses (particularly associated with infantile gastroenteritis).
- **The way of contamination**

All foodborne viruses originate from the intestines of humans and animals. Consequently, they are often transmitted via feces or other bodily fluids. Since viruses do not reproduce in food, the spread of viruses via food has three major causes:

- Handling food without observing sufficient hygiene;
- Contact of food with animal waste, human effluent, or sewage water;
- Consuming animals that are themselves contaminated with viruses (e.g., meat, fish, etc.).
- The relative contribution of the different transmission routes of viruses causing foodborne illness has not been determined[1].

The foods most commonly associated with viral foodborne illnesses are:

- Shellfish (such as oysters, mussels, etc.), crustaceans, and their by-products, harvested or farmed in waters near sewage outfalls (near wastewater treatment plants);
- Fruits and vegetables grown on land fertilized with animal waste or irrigated with contaminated water;
- Undercooked meats, especially pork.

Since antibiotics are ineffective against viruses, controlling viral foodborne illnesses relies on preventive measures. These include raising awareness and providing training on hygiene rules such as proper handwashing, correct washing and handling of fruits and vegetables, refrigerated storage of food, and thorough cooking of porkespecially in settings like hospitals where food is prepared for sick or vulnerable individuals.

Additionally, employees normally involved in food service should be reassigned to other duties if they become ill. To further reduce risks, clean water should be used for

irrigating crops (particularly those that will not be processed), animal manure should be avoided as fertilizer for such crops, and shellfish farming should be practiced in clean seawater protected from any sewage contamination.

Many viruses are associated with foodborne illness, but noroviruses and hepatoviruses represent a major risk. To limit the spread of these diseases, increased awareness of the importance of hygiene and training in good food production and handling practices are necessary. Improving detection methods will allow better control of the presence of viruses in food in general, and will particularly reduce the risks for foods commonly associated with viral foodborne illnesses.

3. Chemical food poisoning

Worldwide, 80% of corrosive product ingestions (absorption of caustic chemicals) occur in young children. These are generally accidental ingestions of small amounts and are often not very harmful. In adults, ingestion of corrosive substances is frequently intentional, involves large quantities, and is potentially life-threatening

Common sources of caustic products

Its include drain cleaners and liquid or solid toilet bowl cleaners, battery acid, and hydrochloric acid for swimming pools. Industrial products are generally more concentrated than household products and therefore tend to be more harmful. However, certain common household products such as drain cleaners, toilet bowl cleaners, or dishwasher detergents contain harmful corrosive substances, such as sodium hydroxide (lye) and sulfuric acid.

Symptoms of corrosive chemical poisonin

When swallowed, caustic substances can burn the tongue, mouth, esophagus, and stomach. These burns can cause rupture (perforation) of the esophagus or stomach. Food and saliva leaking from the perforation lead to serious, sometimes fatal, infections in the chest (mediastinitis or empyema) or in the abdomen (peritonitis). Non-perforating burns can leave scars on the esophagus and stomach.

Corrosive substances are available in solid or liquid form. The burning sensation caused by a solid particle sticking to a moist surface (such as the lips) may prevent people from ingesting too much of the product. On the other hand, since liquids do not adhere, it is

easier to consume a larger amount of the product, and the entire esophagus may be damaged. Liquids can be inhaled (aspirated) into the respiratory tract, leading to upper airway injury.

Treatment of poisoning by corrosive chemical substances

Treatment is chosen based on the extent of the damage. People with severe burns sometimes require immediate surgical treatment to remove severely damaged tissue.

Corrosive substances can cause as much damage on their way back up as on their way down the esophagus, so vomiting should not be induced after ingestion of a corrosive substance. Ipecac syrup and activated charcoal should not be administered.

If the burns are mild, people may be encouraged to drink liquids, milk, or water early enough to dilute the corrosive liquid in the stomach. Ingestion of liquids may begin at home or while en route to the hospital. As long as people cannot drink on their own, fluids are administered intravenously.

Perforations are treated with antibiotics and surgery, and If a stricture develops, a tube prosthesis (stent) may be placed in the narrowed part of the esophagus to prevent it from closing and to facilitate subsequent dilations. Repeated dilations may be necessary for months or even years. In cases of severe strictures, esophageal reconstruction surgery may be required.

4. Natural Toxin Poisoning

Natural toxins are toxic chemical compounds naturally produced by living organisms. These toxins are harmless to the organisms that produce them but can be toxic to other living beings, including humans, when consumed. Food can contain natural toxins at various stages of the supply chain, either because they are inherently present in certain edible plants and animals, or following contamination by toxin-producing microorganisms or algae. The adverse health effects of natural toxins can range from acute poisoning (allergic reactions, severe stomach pain, diarrhea, or even death) to long-term consequences affecting the immune, reproductive, or nervous systems, and cancer. Unlike bacteria, these toxins are generally not destroyed by heat (cooking or freezing).

4.1. Main Types of Natural Toxins

- **Aquatic Biotoxins**

Certain microscopic algae in the ocean and fresh water produce toxins called algal toxins during blooms. Bivalve mollusks (mussels, scallops, oysters) are particularly likely to accumulate these toxins. Algal toxins can cause diarrhea, vomiting, tingling, paralysis, and other effects in humans. Ciguatera fish poisoning is caused by consuming fish contaminated with dinoflagellates that produce ciguatoxins. Some fish known to harbor these toxins include barracuda, black grouper, dog snapper, and king mackerel.

- **Cyanogenic Glycosides**

These phytotoxins occur in at least 2000 plant species, several of which are used as food: cassava, sorghum, stone fruits, bamboo roots, and almonds. Their potential toxicity depends on their ability to release a concentration of cyanide that is toxic to humans. Acute cyanide intoxication can cause rapid breathing, drop in blood pressure, dizziness, headache, stomach pains, vomiting, diarrhea, mental confusion, convulsions, coma, and death.

- **Furocoumarins**

These stress toxins are present in many plants such as parsnips, celery roots, citrus plants (lemon, lime, grapefruit, bergamot), and some medicinal plants. Some of these toxins can cause gastrointestinal problems in susceptible people. Furocoumarins are phototoxic: they can cause severe skin reactions under sunlight (UVA exposure).

- **Lectins**

Many types of beans contain toxins called lectins. Red kidney beans have the highest concentrations. As few as 4 or 5 raw beans can cause severe stomach pain, vomiting, and diarrhea. Lectins are destroyed when dried beans are soaked for at least 12 hours and then boiled vigorously for at least 10 minutes.

- **Mycotoxins**

Mycotoxins are toxic compounds naturally produced by certain molds (fungi) that grow on many foods such as cereals, dried fruits, nuts, spices, apples, and coffee beans, often under warm and humid conditions. Several hundred different mycotoxins have been identified, but the most concerning to human health include aflatoxins, ochratoxin A, patulin, fumonisins, zearalenone, and deoxynivalenol. Most mycotoxins are chemically stable and survive food processing. Aflatoxins are among the most poisonous: large doses can lead to acute poisoning

(aflatoxicosis), which can be life-threatening, usually through liver damage. They have also been shown to be genotoxic and can cause liver cancer in humans. Ochratoxin A, produced by several species of *Aspergillus* and *Penicillium*, is a common contaminant of cereals, coffee beans, dried vine fruits, wine, grape juice, spices, and licorice.

4.2. Natural Toxin Poisoning Prevention

Since natural toxins are generally not destroyed by cooking or freezing, prevention relies on a series of dietary precautions. One should avoid consuming wild plants, especially mushrooms, unless their safety has been verified by an expert. Beans must be thoroughly cooked after prolonged soaking typically 5 to 12 hours of soaking followed by vigorous boiling to destroy lectins. Green, sprouted, damaged, or rotting potatoes should not be eaten, as glycoalkaloids are not eliminated by cooking. Cyanogenic plants such as cassava, bamboo shoots, and bitter apricot seeds require proper processing: cutting them into small pieces and cooking in boiling water eliminates over 90% of cyanide compounds, whereas dry heat is ineffective.

To prevent mycotoxin-producing molds, cereals, nuts, spices, and dried fruits should be stored in cool, dry conditions. Ackee fruit should only be consumed when fully ripe and properly prepared, discarding the rinds and seeds which contain high levels of hypoglycin A. In regions where toxic plants like rhododendrons and mountain laurel are common, honey from unknown or unreliable sources should be avoided. Finally, to reduce the risk of ciguatera poisoning for which there is currently no specific treatment one should limit the consumption of large carnivorous reef fish such as barracuda, grouper, and snapper in tropical regions.

5. Foodborne Parasitic Diseases

The parasites affect the health of millions of people every year, infecting muscle tissues and organs, causing epilepsy, anaphylactic shock, amoebic dysentery and other problems. Some can live on in our bodies for decades (fig12). The main parasites are:

1. Protozoa : Toxoplasma gondii, Cryptosporidium spp.
2. Nematodes: Trichinella spiralis
3. Cestodes: Taenia solium
4. Trematodes (Flukes)

Various foods can serve as vehicles for parasitic infections. Raw or undercooked meats may harbor parasites such as *Trichinella*, *Taenia solium*, *Taenia saginata*, and *Toxoplasma*

gondii. Raw or undercooked freshwater or marine fish, squid, and crustaceans can carry *Anisakis*, *Opisthorchis*, *Clonorchis*, and *Paragonimus*. Fresh produce such as leafy greens, berries, root vegetables, and herbs may be contaminated with *Cyclospora*, *Cryptosporidium*, *Giardia*, *Toxoplasma*, *Ascaris*, or *Echinococcus* eggs.

Contaminated water (including ice and unpasteurized juices) is a known source of *Giardia*, *Cryptosporidium*, *Cyclospora*, *Fasciola* metacercariae, and *Echinococcus* eggs. Finally, aquatic plants like watercress and wild water spinach can transmit *Fasciola hepatica* (fig12).

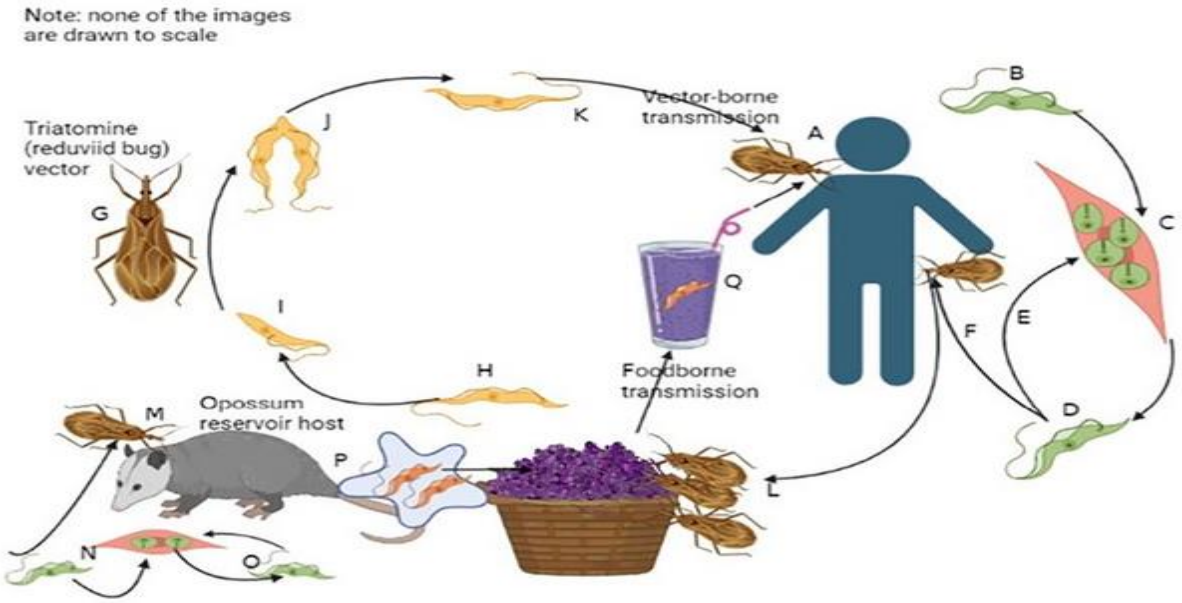

Fig 11. Foodborne Parasitic Diseases

Chapter III: Manifestation and Assessment of Food Toxicity

Food poisoning also called foodbome illness, or illness caused by eating contaminated food is a term used to cover an unpleasant range of illnesses.

Food poisoning symptoms vary with the source of contamination. Most types of food poisoning cause one or more of the following signs and symptoms: nausea, vomiting, watery diarrhea, abdominal pain and cramps and fever Signs and symptoms may start within hours after eating the contaminated food, or they may begin days or even weeks later. Sickness caused by food poisoning generally lasts from a few hours to several days.

Foodborne toxic-infections most often manifest as mild gastrointestinal symptoms, such as vomiting, abdominal cramps, or diarrhea. However, more severe forms can occur, leading to septicaemia, hepatitis, or neurological symptoms.

1. Clinical Manifestations of Food Toxicity

After the intoxication, symptoms usually appear between a few hours and several days after consumption of the contaminated food. They typically include: Abdominal pain or cramps, Diarrhea, sometimes bloody depending on the causative agent, Nausea and vomiting, Fever and chills, Headache, intense fatigue. However, some pathogens also cause specific symptoms, such as neurological disorders (botulism) (tab5).

Thus, the clinical manifestations of food toxicity are mainly:

1.1. Gastrointestinal Symptoms

In general, food poisoning lasts from a few hours to three days. It follows the consumption of contaminated food. Symptoms of food poisoning appear rapidly, at most a few hours after ingestion of the contaminated food.

Symptoms of food poisoning include:

- Nausea, Vomiting, and Diarrhea.
- Cramps, Fever, and Headache.

Symptoms of gastroenteritis last longer and are slightly more persistent. Gastroenteritis is generally linked to a viral infection and is not the result of food consumption. Generally, symptoms disappear completely after a few days. However, complications may arise, especially in at-risk individuals such as children, pregnant women, or the elderly. If complications occur, consult a doctor as soon as possible.

1.2. Neurological Symptoms

The neuroparalytic illness characterized by symmetric, descending flaccid paralysis of motor and autonomic nerves, always beginning with the cranial nerves. Signs and symptoms may include; Dysphagia, Muscle weakness, Diplopia, Ptosis, Blurry vision, Slurred speech, Respiratory distress or failure, and Ocular palsy.

An example of neurotoxicity: Botulinum toxins are neurotoxic and therefore affect the nervous system. Foodborne botulism is characterized by descending, flaccid paralysis that can cause respiratory failure.

Early symptoms include marked fatigue, weakness and vertigo, usually followed by blurred vision, dry mouth and difficulty in swallowing and speaking. Vomiting, diarrhea, constipation and abdominal swelling may also occur. The disease can progress to weakness in the neck and arms, after which the respiratory muscles and muscles of the lower body are affected. There is no fever and no loss of consciousness.

1.3. Systemic Manifestations

The systemic manifestations of food toxicity reflect the spread of the pathogen or its toxins throughout the body. Fever, dehydration, renal impairment, liver damage, or septicemia are all signs that require rapid, often hospital-based, management.

1.4. Allergic Reactions

Food allergy is an adverse immune response to food proteins. Most reactions are from peanut, tree nuts, milk, egg, fish, shellfish, wheat, and soya. Symptoms usually appear within 20 minutes of ingestion and nearly always within 2 hours. Symptoms and signs may vary from pruritus and mild cutaneous eruption to severe anaphylactic respiratory, gastrointestinal, or cardiovascular like hypotensive manifestations.

Table 5. Symptoms by Organ System

System	Key Symptoms
Cutaneous	Urticaria (transient pruritic papules), angioedema (deep swelling), flushing, erythema, eczema flare
Respiratory	Nasal congestion, rhinorrhea, sneezing, cough, wheezing, dyspnea, stridor (laryngeal edema), ocular pruritus, lacrimation
Cardiovascular	Hypotension, tachycardia (sometimes bradycardia), syncope, dizziness, pallor, cyanosis

The duration of food poisoning varies depending on the infectious agent responsible for the poisoning and also on the person's state of health.

- **For mild forms:** symptoms may disappear within 24 to 72 hours.
- **For moderate forms:** improvement in health status occurs after 3 to 7 days.
- **For severe forms:** the course of the poisoning is longer, sometimes requiring hospitalization (severe dehydration, renal complications, neurological complications, septicemia).

As soon as these signs appear, it is important to consult a doctor promptly. This allows for confirmation of the diagnosis (with possible prescription of a stool culture to look for germs), to avoid potential health complications, and above all to notify the authorities if several people who shared the same meal or the same food become ill. This may indeed be a collective foodborne illness outbreak.

2. Assessment of Food Toxicity

The assessment of food toxicity aims to identify, characterize, and quantify the adverse effects linked to the ingestion of toxic substances present in foods (bacteria, toxins, heavy metals, pesticides, additives, natural contaminants). It is based on a multidisciplinary approach combining clinical, biological, epidemiological, and toxicological methods.

2.1. Clinical Diagnosis

The clinical diagnosis of food toxicity is primarily based on:

- patient interview
- a precise analysis of ingested foods
- Symptoms and their chronology, as well as a careful clinical examination to look for signs of severity (dehydration, neurological signs, sepsis).
- Complete clinical examination: looking for signs of dehydration, neurological involvement, fever, abdominal, cutaneous, and cardiovascular signs.

2.2. Additional Examinations

Additional examinations are reserved for severe forms, at-risk patients, or in cases of suspected outbreak, such as stool culture, PCR, and biological workup.

Biological Examinations

Most cases of mild foodborne illness, which resolve spontaneously within 24–72 hours, do not require any additional examinations. Examinations are indicated in the presence of signs of severity (high fever, bloody diarrhea, severe dehydration, altered general condition) or for at-risk patients (extremes of age, immunocompromised individuals) (tab6).

Table 6. Biological Examinations

Examination	Main Indications
Stool culture	Fever, bloody or mucoid diarrhea, severe abdominal pain, signs of septicemia; testing for *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, STEC, *C. difficile*.
***C. difficile* toxin testing (PCR, EIA)**	History of antibiotic use within the previous 8–12 weeks, persistent diarrhea. A single sample is sufficient.
Blood cultures	Infants <3 months, suspected typhoid fever, signs of septicemia, immunocompromised patients.
Multiplex PCR	Simultaneous detection of numerous agents (bacteria, viruses, parasites); very sensitive. Note: may detect asymptomatic carriage (interpret based on clinical presentation).
Botulinum toxin testing	Clinical suspicion of botulism (on serum, stool, or food).

Renal panel (creatinine, blood urea nitrogen, electrolytes)	Monitoring of renal involvement (HUS, severe dehydration).
Complete blood count (CBC)	Thrombocytopenia (HUS), hyperleukocytosis (invasive infection).

Microbiological analyses

Microbiological analysis in a case of food poisoning aims to identify the responsible pathogen and, if possible, link it to the incriminated food. It relies on early sampling: patient stool (before any antibiotic therapy), vomit (search for preformed toxins), blood in case of fever, as well as leftover food and environmental samples (surfaces, water). Depending on the clinical presentation and incubation period, the laboratory directs the search toward frequent targets such as *Salmonella*, *Listeria*, *Campylobacter*, Shiga toxin-producing *E. coli*, *Clostridium perfringens*, *Bacillus cereus*, *Staphylococcus aureus* (toxin), norovirus, or *Clostridium botulinum*.

Methods include direct examination, culture on selective media (aerobic and anaerobic), biochemical tests (MALDI-TOF), toxin detection by ELISA or PCR, and molecular typing (PFGE, sequencing) to confirm identity between human and food strains. Formal incrimination requires isolation of the same serotype or pulsotype in at least two patients and in the suspect food. Main pitfalls are late sampling (beyond 48 hours), prior antibiotic therapy, heat destruction of certain toxins, or asymptomatic carriage. In France, analyses follow ISO standards (e.g., NF EN ISO 6579-1 for *Salmonella*) and are integrated into the mandatory reporting of collective foodborne toxinfections (TIAC) to the Regional Health Agency (ARS). A rigorous approach enables not only individual diagnosis but also rapid withdrawal of a contaminated batch and prevention of new cases.

Toxicological assays

Toxicological assay (quantitative determination of a xenobiotic in a biological fluid) is not systematic. It is indicated in specific situations to guide symptomatic and/or specific management.

And as a mains Objectives of toxicological assay are:

- Confirm a suspected poisoning (etiological diagnosis)

- Assess severity (dose-effect relationship)

Biochemical tests

2.3. Severity assessment

Severity assessment of poisoning helps guide management (simple monitoring, hospitalization, intensive care) and decide on specific treatments (antidotes, extracorporeal purification). It is based on a combination of clinical, paraclinical, and toxicological evidence.

2.4. Epidemiological investigation

The roles of the epidemiological investigation in the context of collective foodborne illness are mainly to **Detect and define of a suspected outbreak** By Identify at least two cases of similar gastrointestinal symptoms (diarrhea, vomiting) in people who shared the same meal.

Secondly, to treat any suspicion as a health emergency to quickly identify the contamination source, stop its spread, and limit public health impact. Finely, to immediately stop the outbreak: recall contaminated products, enforce corrective hygiene measures, and temporarily close establishments if necessary and put long-term preventive actions in place.

2.5. Therapeutic management

Symptomatic measures

Symptomatic measures vary according to the symptoms to be treated. However, in general, symptomatic measures in therapy include:

- pain management by analgesics (paracetamol, NSAIDs, opioids depending on intensity). Fever management: antipyretics (paracetamol, ibuprofen). Nausea/vomiting management: antiemetics (domperidone, metoclopramide, ondansetron).
- Dyspnea management: oxygen therapy, bronchodilators, semi-sitting position, diuretics in case of pulmonary edema. Correction of hydroelectrolyte disorders: oral or IV rehydration, electrolytes.
- Sedation or anxiety: benzodiazepines if indicated.

Specific treatments

Treatment of food poisoning

The treatment of these poisonings varies depending on toxic agent or toxin involved and also on the health status of the affected individual. Indeed, children, the elderly, pregnant women, and immunocompromised individuals should consult a physician as soon as they suffer from symptoms of gastroenteritis.

Treatment of poisonings caused by microorganisms consists of preventing dehydration of the patient. In most cases, symptoms disappear within a few days and medication is not necessary. However, in severe cases, antibiotics and antidiarrheals are sometimes useful. Staphylococcal and *Bacillus aureus* poisonings are treated with supportive care: fluid replacement and symptom relief. However, botulism is treated with specific serotherapy to counteract the toxin responsible for the disease. Polyvalent antitoxins A, B, and E can slow toxin binding.

- **Molds** There is no treatment for mold poisoning.
- **Algae** Treatment of paralytic poisoning consists of gastric lavage and artificial respiration if necessary. However, it is necessary to consult a physician as soon as possible if mollusk poisoning is suspected.

Treatment of poisonings caused by animal toxins is no antidote for tetrodotoxin poisoning. Symptoms due to histamine poisoning resolve after a few hours but may sometimes last several days.

Treatment of poisonings caused by plant toxins

There is no universal treatment for all types of poisoning caused by plant toxins, but some require an antidote.

Preventing food poisoning

Preventing food poisoning relies on four essential measures. **First, strict personal and kitchen hygiene** is crucial: insufficient hand washing and lack of disinfection of surfaces and utensils allow dangerous microorganisms to spread from raw foods or handlers to ready-to-eat meals.

Second, ensuring safe water and proper handling of raw ingredients is vital—consuming untreated water, insufficiently washed fruits and vegetables, raw meat or poultry, raw fish or oysters, or

undercooked eggs introduces pathogens such as *Salmonella, E. coli*, *Vibrio,* and *Anisakis* directly into the body.

Third, rigorous temperature control prevents bacterial proliferation: improper food storage, leaving dairy products or mayonnaise-based preparations at room temperature, breaking the cold chain, or inadequate reheating all allow toxins and microorganisms to multiply. **Fourth, avoiding high-risk untreated or underprocessed foods** such as unpasteurized dairy products (which may carry *Listeria* or *Salmonella*) and undercooked eggs eliminates pathogens that would otherwise survive and cause severe illness.

Chapter IV: Modulation of Toxic Actions

The modulation of toxic actions is the study of how and why two people exposed to the same toxic substance may not develop the same reaction. It is a key concept in risk assessment for estimating actual dangers and defining acceptable daily intakes of potentially harmful substances.

In addition, modulation of toxic actions, in the context of food poisoning, refers to all the mechanisms, factors, and processes capable of mitigating or aggravating the effects of a harmful substance. The most important are:

➢ **Interaction phenomena**: When several chemical substances are present like additives, pesticide residues, or heavy metals in contaminated food as:

1. **Potentiation or synergy**: One substance increases the toxicity of another in the case of drugs, but accidental in poisoning). Or,

2. **Antagonism**: One substance reduces or cancels the toxicity of another, and it is the key phenomenon for the development of antidotes or therapeutic approaches).

➢ **Individual intrinsic factors** like the age, health status, genetic, or medication use can modulate how a toxin is absorbed, metabolized, or eliminated, thus altering its danger.

➢ **Internal detoxification processes**: The body possesses biotransformation systems that, through chemical reactions, can render a substance less harmful and easier to eliminate. Conversely, these same processes can sometimes activate a substance, making it even more toxic.

1. Restrictive groupings

Modulation is particularly governed by restrictive groupings, regulatory or chemical classifications that impose exposure limits and specific usage conditions depending on the toxic product.

1.1. Case of food additives

Among additives, modulation by restrictive groupings often relies on prohibiting certain associations or imposing protective co-formulations. For example, sodium nitrite (E250), sulfites (E220–E228), and aspartame (E951).

- **Sodium nitrite (E250)**

Sodium nitrite is a preservative widely used in processed meats (mainly cured meats). During digestion, nitrite ions react with amino acids from proteins to form nitrosamines. Four of these substances are classified as probable carcinogens (increased risk of colon cancer). Their intentional use is therefore strongly restricted. Nitrite ions can also react with iron to form nitrosylated iron, which is also a promoter of colon cancer (fig13).

The French Agency for Food, Environmental and Occupational Health & Safety confirms that there is indeed an association between the risk of colorectal cancer and exposure to nitrites and/or nitrates through the consumption of cured meats.

In addition, high nitrite consumption also increases methemoglobinemia, and vigilance is required, particularly in heavy-consuming children.

More recently, a French cohort study showed that higher consumption of preservative food additives, including nitrites, is associated with an increased risk of cancer. Sodium nitrite has also been individually associated with a higher incidence of type 2 diabetes.

Finally, the existence of experimental data suggesting the endocrine-disrupting nature of this substance.

It specifies that the intentional addition of nitrites and nitrates to food must be kept as low as reasonably achievable.

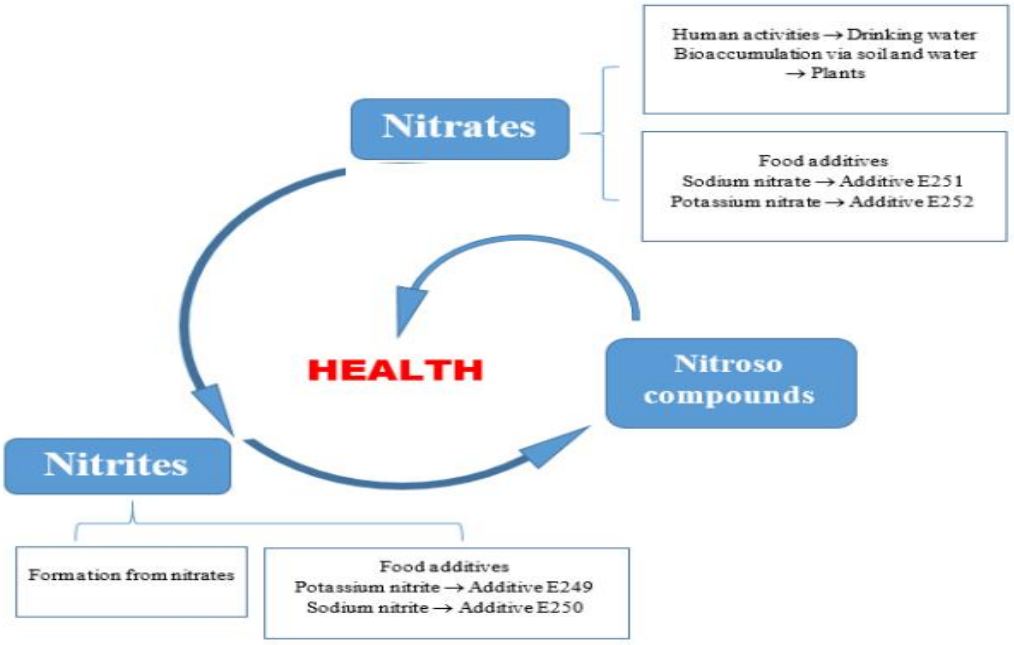

Fig 12. Sodium nitrite.

➢ **Aspartame** (E951).

Aspartame (E951), an artificial sweetener omnipresent in our diet, is now at the heart of a lively scientific and health controversy. Present in more than 2,500 products across Europe, it is used particularly in "light" sodas, low-fat desserts, chewing gums, and yogurts. Yet, despite European regulations that prohibit the placing on the market of dangerous substances, this additive continues to be widely consumed.

The safety of aspartame is regularly reassessed by international scientific bodies. The key concept for measuring its safety is the Acceptable Daily Intake (ADI). This indicator has been set at 40 mg per kilogram of body weight per day. For a 70 kg adult, this represents approximately 2,800 mg of aspartame per day.

European Food Safety Authority or Joint FAO/WHO Expert Committee on Food Additives consider that this ADI is protective for the general population, including children and pregnant women. EFSA, for example, concluded in 2013 that aspartame, at current exposure levels, does not present a risk to the brain, nervous system, or fetal development, except for women suffering from phenylketonuria (PKU).

The major restrictive group: phenylketonuria

There is a clear and mandatory restrictive group concerning aspartame, linked to a rare genetic disease.

- **Phenylketonuria (PKU)**:

This is an inherited disorder in which affected individuals cannot properly metabolize an amino acid called phenylalanine.

- **aspartame dangerous**

In the body, aspartame naturally breaks down into phenylalanine, aspartic acid, and a small amount of methanol.

- **Protective measure**

For people with PKU, an accumulation of phenylalanine can lead to severe brain damage. This is why European regulations require that any food or drink containing aspartame must bear the statement: "Contains a source of phenylalanine" on its label. This measure effectively informs and protects this specific population group.

1.2. Case of phytosanitary products (residues)

The modulation of the toxic actions of plant protection product residues relies on several restrictive groupings, whether regulatory, chemical (metabolic), or physiological. From a regulatory standpoint, Maximum Residue Limits (MRLs) constitute a major modulation tool. Set by Regulation (EC) No 396/2005 of the European Parliament and of the Council, they define the maximum authorized concentration of a pesticide residue in a foodstuff, expressed in milligrams per kilogram.

An MRL is not an acute toxicity limit but a regulatory value whose compliance guarantees, according to EFSA assessments, that consumer exposure to this residue is below the dose considered to have no harmful effect on health.

From a chemical standpoint, pesticides undergo biotransformation phenomena in the body, mainly through the action of cytochrome P450 (CYP) enzymes, which play a major role

in modulating their toxicity. The toxicity of a pesticide can thus be modified by the activity of CYP enzymes.

Certain organophosphorus insecticides (chlorpyrifos, diazinon) are inactive prodrugs (phosphorothioates) that require hepatic CYP-mediated desulfuration to become toxic oxon metabolites. Oxons potently inhibit acetylcholinesterase (AChE), an enzyme essential for nerve transmission. Conversely, other enzymatic reactions (hydrolyses, conjugations) detoxify the substance. Thus, depending on the pesticide and metabolic pathway, toxicity can be amplified (bioactivation) or attenuated (detoxication).

1.3. Case of drugs

In the context of accidental or criminal food poisoning, the modulation of the toxic actions of drugs (cocaine, amphetamines, MDMA, THC, opiates) relies on metabolic, dietary, and regulatory restrictive groupings.

On a metabolic level, toxicity is modulated by cytochrome P450 (CYP). Cocaine is partially transformed by CYP3A4 into norcocaine, itself metabolized into a hepatotoxic derivative (nitroxide). In the presence of ethanol, transesterification produces cocaethylene, which is more cardiotoxic and has a half-life five times longer than that of cocaine (3.5 h vs. 0.7 h) an illustration of potentiation by combination. Amphetamines (MDMA) are mainly degraded by CYP2D6; slow metabolizers (5–10% of Caucasians) have an increased risk of malignant hyperthermia and hepatotoxicity.

On a dietary level, certain foods modulate absorption and toxicity. Fatty foods delay gastric emptying, attenuating the plasma peak but prolonging exposure. Grapefruit juice irreversibly inhibits intestinal CYP3A4, reducing the first-pass metabolism of many opiates (methadone, fentanyl) and increasing their bioavailability and toxicity. Chronic alcohol induces CYP2E1, modifying the metabolism of other drugs.

2. Bio-activation and inactivation phenomena (Case study of insecticides)

The mechanism of action of organophosphorus insecticides is mainly based on the irreversible inhibition of acetylcholinesterase, an enzyme essential for proper nervous system function. However, for most of them, this toxic action occurs only after a crucial prior step: their bio activation in the body.

Main mechanism: inhibition of acetylcholinesterase

Acetylcholinesterase (AChE) is an enzyme whose role is to degrade acetylcholine (ACh), a neurotransmitter, after it has transmitted a nerve signal. Organophosphates act by blocking this enzyme. This blockage prevents the degradation of ACh, which then accumulates in the synapses, causing excessive and uncontrolled stimulation of neurons and muscles, leading to paralysis, convulsions, and in severe cases, death.

Unlike other substances, inhibition by organophosphates is most often irreversible because the pesticide binds extremely stably to the enzyme's active site. Restoration of normal enzymatic activity then requires the synthesis of new AChE molecules by the body.

bioactivation in the liver

A large number of organophosphorus insecticides or phosphorothionates are marketed in a relatively inactive chemical form ("thion" form, with a sulfur atom). To become toxic, they must be transformed in the liver by a family of enzymes called cytochrome P450 (CYP450).

This reaction, called oxidative desulfuration, replaces the sulfur atom with an oxygen atom, giving rise to an active metabolite called oxon, which is a much more potent inhibitor of acetylcholinesterase. For example, malathion (inactive) is transformed into malaoxon (toxic).

- **Specific CYPs are involved in**

A single type of CYP does not carry out bio activation. Studies have shown that isoenzymes such as CYP2B6, CYP2C19, and CYP1A2 are mainly responsible for the activation of methyl-parathion and diazinon. This specificity may explain why sensitivity to pesticides varies among individuals and species.

Variability and consequences (toxicity)

This dependence on bioactivation by CYP450 is a major source of variability in toxicity between species and between individuals. The presence and activity of these enzymes differ, for example, between target insects and mammals, or from one person to another due to genetic factors (polymorphisms).

Once AChE is inhibited, the excess of acetylcholine (ACh) in the body causes various symptoms, classified according to the type of nerve receptor stimulated:

- **Muscarinic effects (overreaction of the parasympathetic system)**: Excessive salivation, lacrimation, sweating, urinary and fecal incontinence, breathing difficulties (bronchospasm), and slowing of the heart rate (bradycardia).
- **Nicotinic effects (involvement of muscles and the sympathetic system)**: Muscle weakness, fasciculations (involuntary contractions), paralysis, and acceleration of the heart rate (tachycardia).
- **Central effects**: Anxiety, confusion, ataxia (loss of coordination), convulsions, coma, and respiratory depression.

Delayed neuropathy may also appear several weeks after exposure and manifest as muscle weakness and sensory disturbances in the lower limbs.

3. Compartmental models and hydrophobic interactions

The basis of the distribution and interaction of xenobiotics (molecules foreign to the body, such as drugs or toxic substances) with biological media lies in thermodynamic principles. The key concept is chemical potential (μ), which determines the tendency of a molecule to move from one phase (or compartment) to another to reach equilibrium.

The hydrophobic interaction between an apolar (lipophilic) molecule and water is a thermodynamically unfavorable process. The formation of structured water "cages" around a hydrophobic xenobiotic (hydrophobic effect) is accompanied by a decrease in the entropy of the system ($\Delta S < 0$). To minimize this state of disorder, the system tends to exclude the apolar molecule from the aqueous phase. Thus, the Gibbs free energy (ΔG) for transferring a hydrophobic molecule from an aqueous phase to an apolar medium (such as a lipid membrane or organic solvent) is negative ($\Delta G < 0$), making the process spontaneous.

This spontaneous transfer is the driving force behind compartmental distribution. The passage of a xenobiotic from the central compartment (aqueous, vascularized) to a peripheral compartment (lipid-rich, poorly vascularized) is governed by this thermodynamics. The lipid compartment acts as a favorable energy sink.

3.1. Partition coefficient

The partition coefficient (P) is the direct quantitative measure of hydrophobic interaction. It quantifies the tendency of a xenobiotic to distribute between two immiscible phases: an aqueous phase and a lipophilic phase.

- **Definition and value**: It is defined as the ratio of the concentrations of the xenobiotic in the organic phase (often octanol) and in the aqueous phase (water), at equilibrium. Its logarithmic form, log P (or log Kow for octanol-water), is the standard measurement used. It is a thermodynamic measure of the hydrophilic/lipophilic balance (HLB) of a molecule.
- **Scale and interpretation**:
    - log P < 0 (very negative): Very hydrophilic molecule. Remains mainly in the aqueous compartment (e.g., metformin).
    - 0 < log P < 3: Moderately lipophilic molecule. Has the ability to cross lipid membranes.
    - log P > 4 (very positive): Very lipophilic molecule. Has a strong tendency to accumulate in peripheral lipid compartments (fats, membranes).
- **Importance**: This parameter is fundamental in pharmacokinetics and toxicology. It allows prediction of the Volume of Distribution (Vd). A very lipophilic xenobiotic (high log P) will have a very large Vd, as it will leave the blood compartment to concentrate in adipose tissues, potentially reaching several hundred liters, well beyond the total body water volume.

3.2. Compartmental model: water-lipid type

The compartmental model is a mathematical representation that simplifies the body into a finite number of compartments to describe the evolution of xenobiotic concentrations over time. The two-compartment model is the most relevant for describing water-lipid interaction.

- **Central Compartment**: Represents blood, plasma, and highly perfused organs (heart, liver, kidneys). It is the main aqueous medium for distribution.
- **Peripheral Compartment**: Represents less perfused tissues, mainly fats (adipose tissue), but also muscles and skin. This compartment acts as a lipid reservoir.

The transfer of the xenobiotic between these two compartments is not instantaneous. It is governed by rate constants, k12 (from central to peripheral) and k21 (from peripheral to central). For a highly lipophilic xenobiotic, k12 will be large (rapid entry into the lipid reservoir), while k21 will be very small (very slow exit). This model explains a long terminal half-life.

3.2.1 Dispersion

In this context, "dispersion" does not refer to the optical phenomenon, but to the process of distribution and diffusion of the xenobiotic within the body. After absorption, the xenobiotic is dispersed by the bloodstream (central compartment) before passively diffusing into the various peripheral compartments.

- The alpha phase (distribution) of a concentration-time curve corresponds to this period of rapid dispersion into well-perfused tissues and initial transfer to fats.
- The beta phase (elimination) reflects the slow release of the xenobiotic from the peripheral reservoirs where it has been dispersed.

The dispersion model is essential for understanding redistribution. Anesthetics like thiopental (high log P) are rapidly dispersed to the brain (immediate effect), then to adipose tissues, which terminates the initial anesthetic effect.

3.2.2 Passive or active absorption (stomach, intestine)

Absorption is the first step of the ADME process. In the gastrointestinal tract (stomach and intestine), a xenobiotic can enter the body by two main mechanisms.

- **Passive absorption (most common)** :
  - **Mechanism**: Simple diffusion across the lipid bilayer of enterocytes. It occurs without energy consumption and down the concentration gradient (from the intestinal lumen, rich, to the blood, poor).
  - **Determining factor**: This pathway is directly proportional to the lipophilicity of the xenobiotic and its non-ionized form. A xenobiotic with a high log P will have rapid and almost complete passive absorption.
  - **Ion trapping**: pH influences ionization. Weak acids will be better absorbed in the acidic stomach (pH ~2), where they are non-ionized, while weak bases will be better absorbed in the alkaline small intestine (pH ~8).

- **Active absorption (specialized pathway)** :
  - **Mechanism**: Involves specific membrane transporter proteins. This process can be active (ATP-consuming) and allow transport against the concentration gradient.

- **Role**: Although a minority, this mechanism is crucial for the absorption of essential nutrients (e.g., vitamin B12), but also for certain xenobiotics. Many xenobiotics are recognized as substrates by these transporters.

The absorption of many xenobiotics results from a combination of these two phenomena. A lipophilic molecule will be mainly absorbed passively, while a hydrophilic molecule may be absorbed by an active mechanism.

3.2.3 Transport et affinity with blood proteins

Once absorbed and dispersed in the central compartment (blood), the xenobiotic interacts directly with plasma components. Binding to plasma proteins is a key step in this transport.

- **Main proteins**:
  - **Albumin**: The most abundant (60%). It preferentially binds to acidic xenobiotics and some neutral ones.
  - **α1-acid glycoprotein (AGP, orosomucoid)**: An inflammation protein. It mainly binds to basic xenobiotics and neutral agents.
  - **Lipoproteins**: Involved in the transport of highly lipophilic xenobiotics.
- **Pharmacokinetic consequences**:
  - **Dynamic equilibrium**: In the blood, there is an equilibrium between the free xenobiotic (dissolved in plasma) and its protein-bound form.
  - **Free fraction**: Only the free fraction is biologically active, can diffuse into tissues (peripheral compartment), and can be metabolized or eliminated. The bound form constitutes a circulating reservoir that maintains the concentration of the free fraction.
  - **Volume of distribution (Vd)**: Strong binding to proteins (mainly albumin for acids) tends to keep the xenobiotic in the vascular bed, resulting in a low Vd (e.g., warfarin, 99% bound).
- **Drug interactions**: Saturation of these binding sites by a first drug can lead to a sudden increase in the free fraction of a second drug, potentiating its effects and toxicity.

4. Action in the liver (activation/bioinactivation by enzymatic systems)

The liver has many functions that can be grouped into three main functions:

Metabolic function: maintaining blood glucose through gluconeogenesis (particularly important in ruminants), synthesis of many proteins, fatty acid metabolism and ketogenesis. Detoxification and clearance function: capture and transformation of ammonia. Excreto-biliary function: transformation of water-insoluble compounds into water-soluble compounds for excretion in bile, excretion of toxic substances.

Adverse drug reactions (ADRs) that are unpredictable and not easily reproduced in animals are a major therapeutic complication. Investigating their mechanisms is necessary to

- identify structural features causing toxicity
- Detect sensitive individuals. Toxicity may arise directly, via genotoxicity, or immune-mediated, often involving chemically reactive metabolites.

The balance between bioactivation and bioinactivation is critical.

Metabolism of drugs in the liver

Drug metabolizing enzymes are broadly classified into phase I enzymes, which are mostly oxidative, reductive or hydrolytic, and phase II enzymes, which are conjugative (Tab 7, fig 14)

Table 7. Examples of metabolic enzymes in liver.

Enzymes	Substrates	Inhibitors	Inducers
Phase I			
CYP1A2	Alosetron, caffeine, duloxetine, melatonin, ramelteon, tacrine, tizanidine	Ciprofloxacin, enoxacin, fluvoxamine, oral contraceptives, phenylpropanolamine	Montelukast, phenytoin, smoking components of cigarettes
CYP2B6	Artemisinin, bupropion, cyclophosphamide, efavirenz, ifosphamide, ketamine, meperidine,	Clopidogrel, ticlopidine, voriconazole	Artemisinin, carbamazepine, efavirenz, nevirapine, phenobarbital, phenytoin, rifampicin

CYP2C8	Repaglinide, paclitaxel, sorafenib	Gemfibrozil, fluvoxamine, ketoconazole, trimethoprim	Rifampicin
CYP2C9	Fluvastatin, rosuvastatin (also CYP2C19, minor)	Amiodarone, capecitabine, etravirine, fluconazole, fluvoxamine, fluvastatin, ketoconazole,	Carbamazepine, phenobarbital, phenytoin, rifampicin
CYP2C19	Omeprazole, diazepam, phenobarbitone, clopidogrel, progesterone,	Cimetidine, lansoprazole, omeprazole,	Carbamazepine, efavirenz, enzalutamide, rifampicin, ritonavir, St John's Wort
CYP2D6	Tamoxifen, carvedilol, fluoxetine, risperidone, donepezil, lidocaine, fluvoxamine,	Cimetidine, celecoxib, citalopram, cocaine, escitalopram,	Dexamethasone, rifampicin
CYP2E1	methoxyflurane, sevoflurane, ethanol, benzene, N,N-dimethylformamide	Diethyl-dithiocarbamate, disulfiram	Ethanol, isoniazid
CYP3A	cyclosporine, indinavir, nelfinavir, ritonavir, saquinavir, oestradiol, progesterone, testosterone, caffeine,	bicalutamide, cilostazol, cimetidine, ciprofloxacin, clarithromycin, ,	corticosteroids, efavirenz, modafinil, nafcillin, nevirapine, phenytoin, pioglitazone,
Phase II			
UGTs	Bilirubin, phenols, oestradiols, opiates and carboxylic acids	Paclitaxel, midazolam, cyclosporine A, ketoconazole,	Bilirubin, phenobarbitone, rifampicin
SULTs	Phenols, alcohols and amines	Flavonoids, mefenamic acids, salicylic acids, clomiphene and danazol	Retinoic acid, methotrexate
NATs	Para-aminobenzoic acid, para-aminosalicylic acids, paraaminoglutamate,	Caffeic acid, esculetin, qurcetin, genitin, scopoletin and coumarin	Androgens, aminophylline
GSTs	Epoxides, quinone, sulfoxides, ester	Phenols, quinone, vitamin C derivatives, dopamine and	Extracts of broccoli

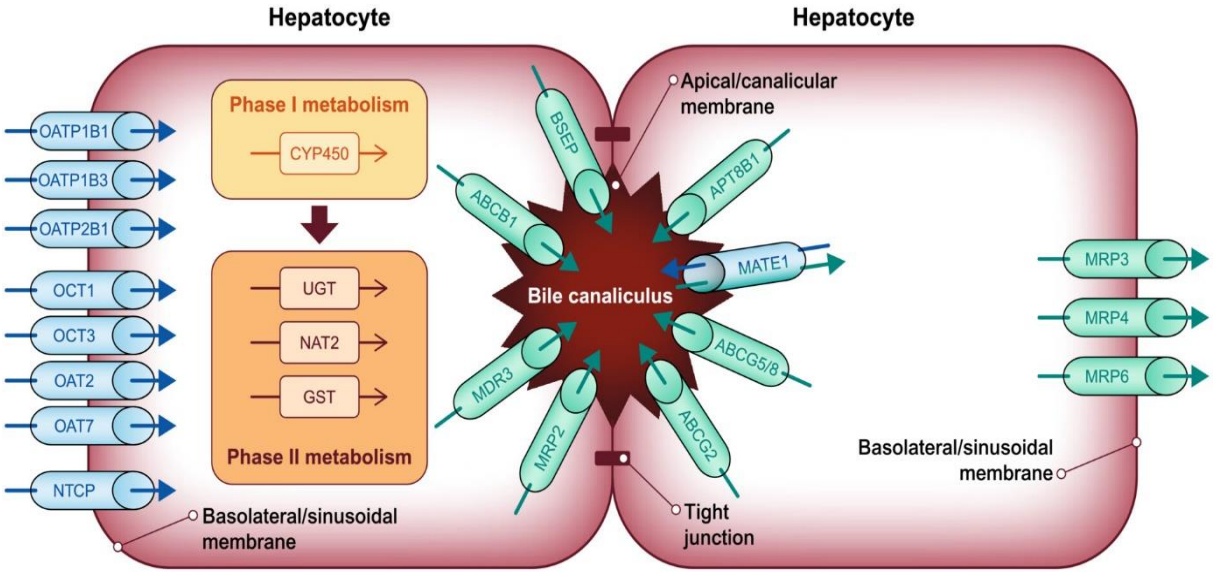

Fig 13. Key protein enzyme classes involved in phase I and phase II metabolism, and main intake and efflux transporters, in hepatocytes.

2.1 Phase I metabolism

Oxidation/reduction and hydrolysis reactions mediated by phase I are most often catalysed by membrane-bound enzymes of the cytochrome P450 (CYP) enzyme group. This superfamily of enzymes are monooxygenases containing haem as a cofactor, absorbing at 450 nm in the visible spectrum in the reduced state.

The CYP enzymes often catalyse substrate oxidation in the context of membrane-bound electron transfer chains located either in the inner membrane of mitochondria or in the smooth endoplasmic reticulum of cells. Oxidation of the substrate makes it more water-soluble, facilitating excretion by the kidneys. In other cases, metabolism of a pro-drug transforms it into a pharmacologically active form.

Many isoenzymes of the CYP superfamily can be induced upon exposure to specific chemicals, providing a protective mechanism against a wide variety of toxic compounds. Drugs and other xenobiotics that stimulate smooth endoplasmic reticulum production also induce CYP enzymes (Tab 8). It is estimated that approximately 70–80% of all commercially available drugs are metabolized by enzymes of the CYP superfamily.

The inhibition and induction of the CYP enzymes are 2 principal mechanisms causing PK drug–drug interactions. Genetic variations resulting from single-nucleotide polymorphisms contribute to the interindividual variability in the activity of CYP variants.

Table 8. Enzymes involved in endoplasmic reticulum stress (ER, endoplasmic reticulum; GI, gastrointestinal; SERCA, sarcoplasmic/endoplasmic reticulum calcium ATPase).

Drug	Mechanism of ER stress	Effects
Paracetamol	Unknown	Hepatotoxicity and nephrotoxicity
Amiodarone	Unknown	Hypotension, cutaneous reactions, thyroid toxicity, liver injury and pulmonary toxicity
Arsenic trioxide	Oxidative stress and impairment of protein folding	GI disorders, rash, hematologic toxicity, infections, cardiac toxicity renal toxicity, myopathy, neuropathy and hepatotoxicity
Bleomycin	Unknown	GI disorders, cutaneous reactions, myelosuppression and life-threatening pulmonary toxicity
Bortezomib	Proteasome inhibition	GI symptoms, fatigue, peripheral neuropathy and thrombocytopenia
Cisplatin	Unknown	GI disorders, kidney injury, neurotoxicity, hepatotoxicity and cardiotoxicity
Clozapine and olanzapine	Unknown	GI disorders, drowsiness, extrapyramidal symptoms, elevation in liver enzymes and obesity (with related metabolic disorders such as insulin resistance and fatty liver)
Cyclosporin	Unknown	Infections, hypertension, neurotoxicity, nephrotoxicity and hepatotoxicity (including cholestasis and cytolysis)
Diclofenac	Unknown	GI complications (including gastric injury and intestinal damage), hypersensitivity reactions, hepatotoxicity and kidney injury
Efavirenz	Possibly secondary consequence of mitochondrial dysfunction and release of mitochondrial calcium into the cytosol	Rash, neuropsychological symptoms, lipodystrophy and hepatotoxicity (in particular cytolysis and cholestasis)
Erlotinib	Unknown	Rash and GI manifestations (in particular severe diarrhoea)
Furosemide	Unknown	Dehydration, hypotension, hyponatraemia and hypokalaemia
Indomethacin	Unknown	GI complications (including gastric injury and intestinal damage), hypersensitivity reactions, hepatotoxicity and kidney injury
Paclitaxel	Unknown	GI disorders, cardiac and skeletal muscle toxicity, myelosuppression, neurotoxicity and acute liver injury (mostly hepatic cytolysis)
Protease inhibitors (e.g. indinavir and ritonavir)	Possible proteasome inhibition and oxidative stress	GI toxicity, rash, kidney injury, hepatotoxicity (including cytolysis, cholestasis and steatosis), dyslipidaemia, lipodystrophy, insulin resistance and type 2 diabetes
Sertraline	Unknown	Somnolence, GI disorders, tremor, sexual dysfunction, weight gain and liver injury
Thapsigargin	Inhibition of SERCA, thus leading to severe calcium depletion in the ER	Severe skin irritation, salivary hypersecretion, gastroenteritis, nervous disorders and death

2.2 Phase II metabolism

Conjugation reactions in the liver are carried out by uridine diphosphate-glucuronosyltransferases (UGTs), sulfotransferases (SULTs), N-acetyltransferases, glutathione S-transferases (GSTs), amino acid conjugation enzymes and methyltransferases.

- UGTs are smooth ER glycoproteins that interact with CYPs and catalyseglucuronidation, adding glucuronic acid to drugs to increase polarity and renal excretion. They exhibit latency (underestimated activity in microsomes). PBPK modeling helps predict pharmacokinetics of drugs cleared by glucuronidation, though this pathway plays a minor role. UGTs are linked to drug-induced liver injury, as reactive acyl glucuronides can covalently bind proteins..

- **SULTs**

  SULTs catalyze sulfation of drugs and endogenous compounds. SULT1A1 substrates include paracetamol and minoxidil; SULT1A3 substrates include dopamine and serotonin. NSAIDs can inhibit SULTs, affecting drug interactions. SULT polymorphisms contribute to variability in drug response and toxicity.

- **NATs**

  N-acetyltransferases are cytosolic enzymes that transfer acetyl groups to arylamines. Acetylation rate determines slow, intermediate, or rapid phenotypes. They metabolize drugs such as isoniazid, hydralazine, and sulfonamides.

- **GSTs**

  GSTs conjugate glutathione to drugs and protect against oxidative stress. GST polymorphisms (e.g., GSTM1 null, GSTT1 null, GSTP1-Val) may increase susceptibility to type 2 diabetes, MASLD, hepatitis, cirrhosis, and HCC.

- **TPMT**

  Thiopurine methyltransferase methylates thiopurine drugs (mercaptopurine, thioguanine, azathioprine). TPMT deficiency can cause severe bone marrow toxicity; screening is recommended, especially in patients with advanced fibrosis or cirrhosis.

2.3.Hepatic transport proteins

Transmembrane transport proteins from the solute carrier (SLC) superfamily generally mediate the secondary active uptake of endogenous compounds and xenobiotics into the hepatocyte, and transport proteins of the ABC family mediate their primary active, ATP-dependent, elimination from liver cells into bile.

Transport proteins have been associated with toxicity of drugs in the liver, as altered transporter expression and function due to liver disease, or functional impairment due to transporter gene polymorphisms, can increase the risk for drug-induced liver injury (Tab 8).

Table 9. Transporters in liver disease (some exemples).

Transporter	Substrates	Inhibitors	Changes in liver disease
OATP1B1	Atorvastatin, pitavastatin,	Carbamazepine, clarithromycin, cyclosporine,	- Reduction in expression in MASLD
OATP1B3	Fluvastatin, pravastatin, rosuvastatin,	Clarithromycin, cyclosporine, erythromycin	- Reduction in expression in MASLD, HCC, MASH
OATP2B1[73]	Angiotensin II receptor blockers, coproporphyrin III, balsalazide, olsalzine, gavestinel,	Rifampin, cyclosporine, naringin, hesperidin, streptomycin, linezolid,	- Reduction in expression in MASLD - Increased protein levels in cirrhosis
P-gp	Atorvastatin, lovastatin, pitavastatin, simvastatin, digoxin, fexofenadine,	Amiodarone, atorvastatin, azithromycin, captopril, carvedilol, cimetidine.	- Increased protein levels in HCC, MASH, cirrhosis
BCRP	2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine, methotrexate, oestradiol-17-β-glucuronide	Elacridar (GF120918), fumitremorgin C, ko143, novobiocin, curcumin,	- Increased levels in HCC, MASH, cirrhosis
OAT1	Adefovir, p-aminohippurate, cidofovir, tenofovir	Benzylpenicillin, probenecid	
OAT2	Bumetadine, bendamustine, irinotecan,	Indomethacine, bromsulphthalein, probenecid, irinotecan,	- Reduction in expression in MASLD
OAT3	Benzylpenicillin, estrone-3-sulfate, methotrexate, pravastatin	Benzylpenicillin, probenecid	
OAT7	Pravastatin	Glutaric acid, BSP, ketoprofen	- Reduction in expression in MASLD
MATE1, MATE2K	Creatinine, metformin, 1-methyl-4-phenylpyridinium, tetraethylammonium	Cimetidine, pyrimethamine, ranolazine, trilaciclib, vandetanib	
ABCA1, ABCG1	Cholesterol		- Downregulation in MASLD
ABCB11 (BSEP)	Pravastatin	Cyclosporine A, rifampicin, glibenclamide, glyburide	- Decreased expression in cholestasis, HCC, MASH
OCT1	Metformin, oxaliplatin, acyclovir, ganciclovir, ranitidine	Quinine, quinidine, disopyramide, atropine	- Decreased expression in HCC

2.3.1 Influx transport

The SLC superfamily of drug transporters comprises several key members, including organic anion-transporting polypeptides (OATPs), organic anion transporters (OATs), organic cation transporters (OCTs), organic cation/carnitine transporters, peptide transporters, as well as multidrug and toxin extrusion proteins.

In liver disease, the expression of these uptake transporters may change, potentially resulting in the plasma accumulation of toxic metabolites. Such alterations can arise from structural causes, such as hepatocyte loss in fibrotic areas, changes in hepatocyte distribution or bypass in cirrhosis, or reduced transporter protein levels per cell in tumors.

During acute-on-chronic injury, inflammatory signaling pathways drive a widespread downregulation of transporter expression, primarily at the transcriptional level, as part of a coordinated negative acute-phase response in the liver.

5. Excretion

Excretion, or elimination, is the final step in the fate of a xenobiotic. It allows the compound to pass from the blood compartment to the outside of the body, often after transformation into more water-soluble metabolites by the liver. The goal is the definitive elimination of the substance and its derivatives.

Main excretion pathways

Renal pathway: the major elimination route

The kidneys are the main organs for the excretion of water-soluble xenobiotics, whether unchanged or as polar metabolites. The renal process combines several mechanisms.

- **Glomerular filtration (passive)**: The fraction of xenobiotic not bound to plasma proteins is passively filtered at the glomeruli. Only small molecules (approximately one-fifth of the plasma reaching the glomeruli) are filtered.
- **Active tubular secretion (predominant)**: This active, saturable mechanism occurs mainly in the proximal tubule. It is ensured by membrane transporter systems. Organic anion transporters (OAT1, OAT3) excrete substances such as penicillins, while organic cation transporters (OCT2) excrete weak bases such as morphine or metformin. These

transporters, located on the basolateral (OAT, OCT) and apical (MRP2, MATE) membranes of tubular cells, are crucial for the rapid elimination of many drugs.

- **Tubular reabsorption**: This is a passive diffusion process that mainly concerns liposoluble and non-ionized xenobiotics that have been filtered. This phenomenon can be modulated by urinary pH (influencing the degree of ionization) and by urine flow rate.
- **Impact of urinary pH**: Urinary pH (varying from 4.5 to 8.0) affects the reabsorption of weak acids and bases. Weak acid drugs (salicylates) are better excreted by urine alkalinization, while weak bases (amphetamines) are better excreted by acidification.

Biliary pathway and enterohepatic cycle

- **Biliary excretion**: This pathway mainly concerns high molecular weight molecules (>300-500 Da) or their conjugated metabolites, actively secreted into the bile by hepatocytes via transporters such as MRP2 and P-gp.
- **Enterohepatic cycle**: After biliary secretion, the substance reaches the intestine, where conjugates can be hydrolyzed by the intestinal flora. The thus regenerated active lipophilic form can be reabsorbed into the blood, cross the liver again, and undergo biliary excretion once more. This cycle has major consequences: prolongation of half-life, appearance of secondary peaks in plasma concentration, and increased exposure to the active substance. Erythromycin, digoxin, and certain estrogens are concerned.

Pharmacokinetic parameters of excretion

- **Clearance (Cl)**: Volume of plasma cleared of a xenobiotic per unit time (mL/min). Total clearance is calculated as the sum of renal, hepatic, and other clearances.
- **Elimination half-life (t½)**: Time required for the plasma concentration to decrease by 50%. It depends directly on the volume of distribution and inversely on clearance.
- **Elimination kinetics**: For most drugs, the kinetics are first-order (rate proportional to concentration). They can become zero-order (constant rate, saturable) for certain substances like ethanol at high doses.
- **Impact of renal excretion on total clearance**: The relative contribution of the renal pathway and other pathways determines whether dosage adjustment is necessary in case of renal or hepatic insufficiency. Renal clearance results from the interaction between glomerular filtration, tubular secretion, and tubular reabsorption (tab 9).

Table 10. Factors influencing excretion

Factor	Effect on excretion
Urinary pH	Alkalinization increases excretion of weak acids (barbiturates); acidification increases that of weak bases (amphetamines).
Age	At 80 years, renal clearance is only half of that at 30 years. Dosage adjustment is often necessary.
Renal failure	Accumulation of renally excreted drugs, requiring dose reduction based on estimated glomerular filtration rate (notably the Cockcroft-Gault formula).
Hepatic failure	Decreased biliary excretion and altered enterohepatic cycle, potentially disrupting pharmacokinetics.
Transporter interactions	Competition for OAT between certain drugs (e.g., probenecid + penicillin) or for OCT2 (e.g., cimetidine + metformin) alters renal excretion and risks drug interactions.

6. Particular affinity (accumulation in adipose tissue, bone tissue)

Certain xenobiotics (drugs, environmental toxicants, heavy metals) have a particular affinity for specific tissues, leading to prolonged accumulation. This retention can constitute an internal reservoir, responsible for a very long elimination half-life and sometimes chronic toxicity.

Accumulation in adipose tissue

Adipose tissue is highly lipophilic. Non-ionized hydrophobic xenobiotics (with a high octanol/water partition coefficient) passively dissolve there. This accumulation is not an active phenomenon but simple partitioning. Adipose mass represents 15 to 30% of body weight, constituting a true reservoir (table 10). It **Characterise by :**

Kinetics: Rapid initial distribution (alpha phase), then slow redistribution from blood to fat (beta phase). The terminal half-life can reach several weeks, months, or years.

Consequences: Prolongation of systemic exposure, possibility of progressive release during weight loss or stress (risk of re-intoxication).

Table 11. Examples of xenobiotics accumulating in adipose tissue

Xenobiotic	Characteristic	Half-life in fat
Dichlorodiphenyltrichloroethane (DDT) (organochlorine insecticide)	Highly lipophilic (log P ~ 6)	Several years
Polychlorinated biphenyls (PCBs) (industrial pollutants)	Liposoluble, resistant to degradation	> 10 years
Liposoluble benzodiazepines (diazepam, midazolam)	Accumulation after repeated administration	Days to weeks
Tetrahydrocannabinol (THC) (cannabis)	Highly lipophilic	> 7 days (detectable for several weeks)
Volatile anesthetics (halothane, isoflurane)	Dissolution in fat during anesthesia	Post-operative release
Dioxins (TCDD)	Ultra-lipophilic pollutants	5 to 10 years in humans

Pharmaco-toxicological consequences

- **Enzyme induction**: Accumulation of DDT and PCBs induces cytochrome P450, modifying the metabolism of other xenobiotics.
- **Delayed toxicity**: During fasting, lipolysis releases accumulated toxicants → exacerbation of effects.
- **Screening**: Positive detection in adipose tissue attests to past exposure (e.g., fat biopsy for PCBs).

Accumulation in bone tissue

Bone is a dynamic tissue, composed of a mineral matrix (calcium hydroxyapatite) and an organic matrix (collagen). Accumulation occurs by two main mechanisms:

Adsorption/ion exchange at the crystal surface: Certain metal ions (lead, strontium, radium) mimic calcium and bind to hydroxyapatite. This process is reversible: ions can be remobilized during bone remodeling.

Chelation or incorporation: Tetracyclines bind to newly deposited calcium during osteogenesis, incorporating into the bone matrix where they remain chemically active (tab 11).

Table 12. Examples of xenobiotics accumulating in bone

Xenobiotic	Mechanism	Consequence
Lead (Pb^{2+})	Replaces calcium in hydroxyapatite	Bone half-life: 20-30 years. Release during pregnancy or osteoporosis. Toxic to fetal CNS.
Strontium (radioactive Sr-90)	Calcium analog, incorporated into the mineral matrix	Risk of bone cancers and leukemias (internal radioactivity).
Radium (Ra-226)	Same mechanism	Historically used for luminous watches → jaw osteonecrosis ("radium girls").
Tetracyclines	Chelation with calcium in growing bone (children, skeletal bone)	Yellow-brown tooth discoloration and temporary inhibition of bone growth.
Bisphosphonates (drugs)	High affinity for hydroxyapatite, used therapeutically	Selective binding in bone, bone half-life of several years.
Fluoride (excess)	Replaces the hydroxyl group of hydroxyapatite (fluoroapatite)	Skeletal fluorosis: osteosclerosis, fragility, exostoses.

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