Democratic and Popular Republic of Algeria

Ministry of Higher Education and Scientific Research

Université 8 Mai 1945 Guelma

Faculty of Natural and Life Sciences and Earth and Universe Sciences

Department of Ecology and Environmental Engineering

Course for Students:

3rd Year Agri-food Technology and Quality Control

FOOD TOXICOLOGY

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Academic Year 2023/2024

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Food Toxicology

Sofiane BOUDALIA

Food, alongside oxygen and water, ranks among the most essential substances for the survival of living organisms. Food toxicology focuses on substances present in food that, upon consumption, may pose harm to consumers. Hence, the field of food toxicology encompasses the detection of toxic substances in food, the characterization of their properties, the study of their fate within the body (including absorption, distribution, metabolism, and excretion), and the investigation of their adverse health effects. Toxic substances can naturally occur in food, form during food preparation, be directly added to food, or infiltrate food from the surrounding environment, such as through packaging.

Among the various subdisciplines of toxicology, food toxicology has garnered significant public attention in recent years. This increased interest stems from heightened awareness regarding the health impacts of food, instances of foodborne illnesses, and the rapid dissemination of information to consumers, facilitated by the internet.

Food toxicology aims not only to develop a protocol to assess the safety of substances that may be present in foods but also to adopt a biochemical approach to the different phases of toxic interactions with the organism. It involves assessing the safety of food additives, contaminants, pesticides, and other chemicals that may be present in food or introduced during food processing.

Therefore, it seeks to explain the mechanisms of toxicity. Thus, when a diet is unbalanced or contains xenobiotic substances, it is important to explain the dual aspect of toxic interactions with the organism by introducing the concepts of toxicokinetic and toxicodynamic phases of toxic effects.

CHAPTER 1 : TOXICOLOGY CONCEPTS

1. Definitions

Toxicology has long been recognized as the science of poisons. It studies the harmful effects of chemical substances on living organisms. It draws upon a multitude of scientific knowledge and is concerned with several sectors of human activity: agriculture, food, pharmaceuticals, the environment, workplaces, etc. Thus, the toxicity of a substance can be defined as its "*ability to produce harmful effects on a living organism*."

>> A poison or toxicant is a substance capable of disrupting the functioning of a living organism.

The toxicity of food can be classified as:

- **Natural or Intrinsic (coming from within)**

The food contains a toxic substance naturally present or formed during a technological process (such as fermentation, smoking).

- **Extrinsic (coming from outside)**

It results from contamination by a product introduced into the food during its production or manufacturing, either intentionally (additives) or accidentally (washing, materials).

The intensity of the reaction depends on:

- The intrinsic toxicity of the substance: refers to its inherent ability to cause harm to living organisms. It is determined by the chemical properties of the substance itself and its interactions with biological systems.
- The quantity (dose) consumed.
- The duration of consumption.

2. Modes of penetration of toxic substances

The organism must be exposed to a toxic substance for a harmful effect to manifest. In this case, the substance can act at the point of contact (local effect) or penetrate the organism (systemic effect).

The main ways to absorb toxic molecules are inhalation (respiratory route), absorption through the skin (dermal route), and ingestion (digestive route: which can be related to food), and in this case, it is referred to as food toxicology. A substance can be absorbed through multiple routes.

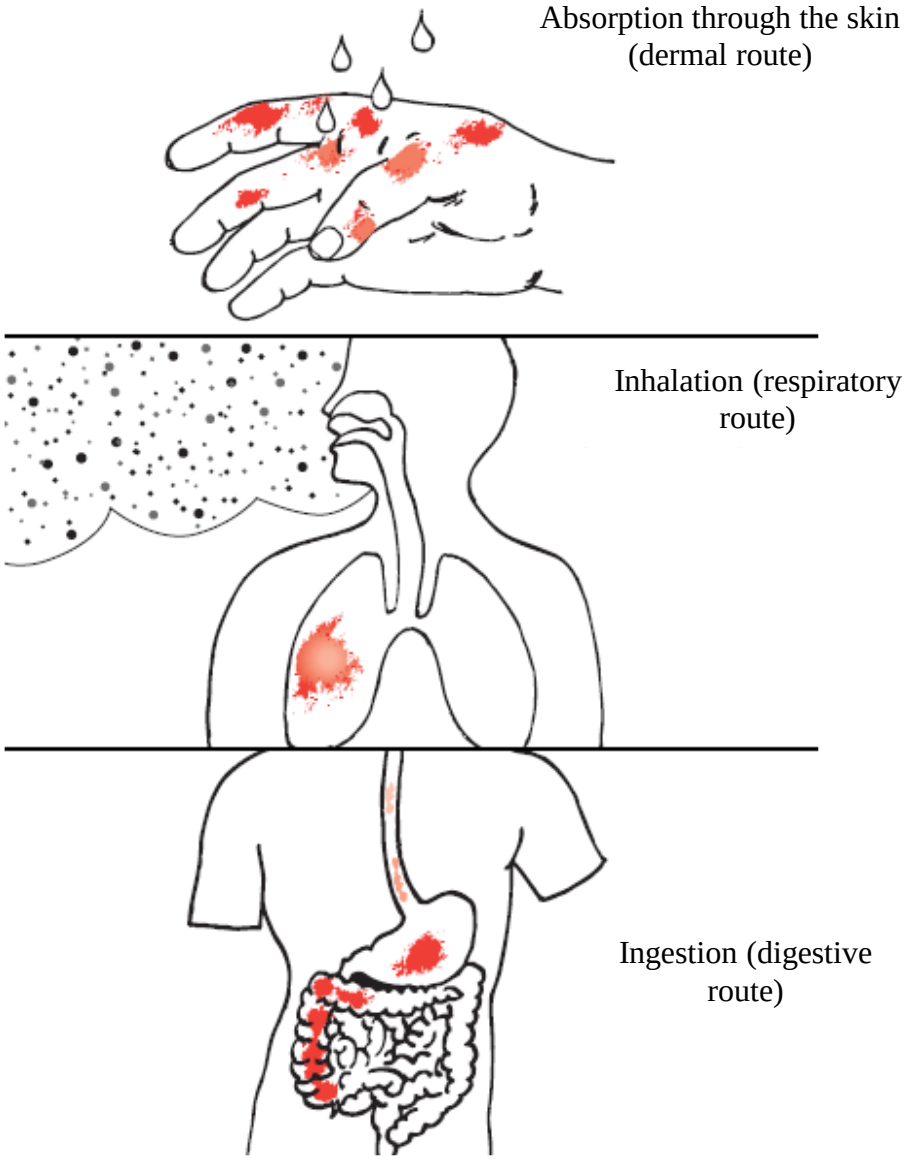


Figure 01. The usual absorption pathways

Table 01. Absorption pathways of certain products

SUBSTANCE	PHYSICAL PROPERTIES	VOIE RESPIRATOIRE	VOIE CUTANÉE	VOIE DIGESTIVE
PHOSPHORIC ACID	SOLID	FAIBLE	WEAK	WEAK
ALCOHOL	LIQUID	YES	WEAK	YES
BERYLLIUM	SOLID	YES	WEAK	WEAK
CHLORPYRIFOS	SOLID	YES	YES	YES
MERCURY	LIQUID	YES	YES	WEAK
MONOXIDE OF CARBON	GAS	YES	NO	NO
TOLUENE	LIQUID	YES	YES	YES

2.1. Respiratory Route (Inhalation)

The lungs are the organs where gas exchange occurs between the air in the alveoli and the blood in the capillary vessels lining the pulmonary alveoli. They are the site of respiration, which allows for the absorption and elimination of gases.

In the majority of workplaces, the respiratory route represents the primary entry route for contaminants. The high possibility that the ambient air may be contaminated by vapors, gases, fumes, dust, etc. explains this situation. Just think, for example, of the inhalation of welding fumes.

2.2. Dermal Route (Skin or Transcutaneous)

The skin is an impermeable barrier that covers the entire surface of the body and protects it. This protective envelope obstructs the penetration of many contaminants. However, this barrier does not offer complete protection because it has weaknesses, including the base of hairs and pores.

This is an important pathway, as several toxins can enter the body by crossing the skin following contact with a liquid, a solid, or vapors (e.g., certain solvents used to clean mechanical parts or diluents or strippers that are used without protection).

2.3. Oral Route (Ingestion or Trophic)

In the workplace, ingestion is generally not considered a significant exposure route. However, it should not be overlooked, as inappropriate work methods can lead to accidental ingestion. Moreover, poor habits can also lead to exposure through ingestion, such as eating, drinking, or smoking in contaminated work areas.

3. Different phases of action of a toxic substance

A substance that enters the body can have beneficial effects (such as food and its ingredients) or harmful effects (e.g., pesticide residues). Conversely, the body can act on this substance; this is what we call metabolism. The organism's response to a toxic substance depends, among other things, on the quantity of the substance present in a tissue or organ. Several factors are involved in the processes of toxic action, including toxicodynamic and toxicokinetic phases.

3.1. Toxicodynamic

Focuses on the influence exerted by a toxic substance on the organism and the factors involved in the toxic response. Toxicodynamic explains how toxic substances interact with biological systems to produce their effects. It encompasses the mechanisms by which toxicants exert their actions at the molecular, cellular, tissue, and organ levels within the body. Toxicodynamic processes involve the absorption, distribution, metabolism, and excretion of toxic substances, as well as their interactions with cellular receptors, enzymes, and other molecular targets.

3.2. Toxicokinetic

Focuses on the influence exerted by the organism on a toxic substance. This influence arises from the processes (absorption, distribution, metabolism, elimination) that govern the pathway of the toxic substance in the organism. When applied to food additives, toxicokinetics examines how these substances are absorbed from the gastrointestinal tract into the bloodstream, how they are distributed to various tissues and organs, how they are metabolized (if at all), and how they are ultimately eliminated from the body.

For food additives specifically, toxicokinetic studies help determine the bioavailability of the additive, its potential for accumulation in tissues, its potential to be metabolized into harmful by-products, and the rate at which it is eliminated from the body. This information is crucial for assessing the safety of food additives and establishing regulatory guidelines for their use in food products.

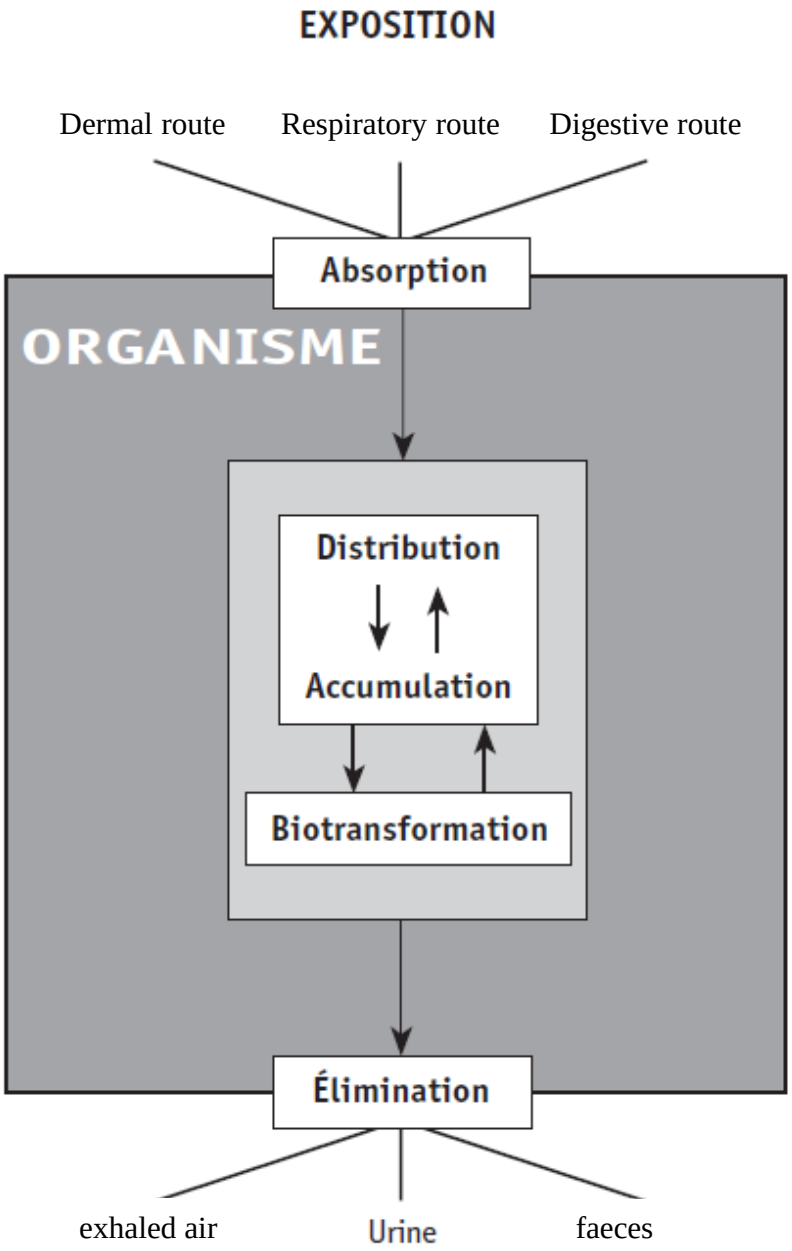


Figure 02. Pathway of a substance in the organism.

4. Biochemical interpretations of the different phases

4.1. Biochemical aspects of the exposure phase

- Also called ENTRY (or ABSORPTION), which refers to the process of penetration of a substance into the organism. This is an important step because until a substance has entered the bloodstream, it cannot cause systemic toxic action, i.e., at locations distant from the initial point of contact.

- Various factors can influence the absorption process of a substance: its nature, solubility, permeability of biological tissues at the point of contact, duration, and frequency of exposure, etc.

- In food toxicology, the exposure phase essentially means absorption at the gastrointestinal level.

- Toxins can be ingested due to accidental ingestion (foods containing physical risk), consumption of contaminated food or beverages (foods containing pesticide residues), or by ingestion of particles eliminated by the respiratory tract. The entire digestive tract, from the esophagus to the anus, has the same basic structure. A mucous layer (epithelium) is underlain by connective tissue and, beyond that, by a network of capillaries and smooth muscle. The surface of the stomach epithelium is highly folded, increasing the surface area for absorption and secretion. The intestinal surface contains numerous folds, capable of absorbing material through "pumping." The active absorption surface in the intestines is about 100 m^2 (first part of the small intestine: the duodenum).

- At the gastrointestinal tract level, all absorption processes are very active: transcellular transport by diffusion through the lipid layer or pores of cell membranes, or by filtration at the pore level; paracellular diffusion through intercellular junctions; facilitated diffusion and active transport; endocytosis and pumping mechanism at the villi level.

- Some ions of toxic metals use specialized transport systems for essential elements: thallium, cobalt, and manganese use the iron transport system, while lead uses the calcium transport system.

- Several factors influence the absorption rate of toxins in various parts of the gastrointestinal tract:

- The physicochemical properties of molecules,
- The amount of food present in the gastrointestinal tract (dilution effect);

- Retention time in each part of the gastrointestinal tract (from a few minutes in the oral cavity to an hour in the stomach and several hours in the intestines);
- Absorption surface and epithelial absorption capacity;
- Peristalsis (muscular movement in the intestines) and local blood flow;
- Gastric and intestinal secretions transform toxins into more or less soluble products; bile is an emulsifying agent producing more soluble complexes (hydrotrophy);
- Combined exposure to other toxins, producing synergistic or antagonistic effects during the absorption processes.

4.2. Biochemical aspects of the toxicokinetic phase

4.2.1. Transport and distribution processes

Once it has entered the bloodstream, the substance can be transported throughout the body. This is called distribution. In addition to oxygen, various nutrients essential for the functioning of the body, and waste, the blood also transports toxins. These toxins can then come into contact with cells and become fixed in certain tissues. For example, organochlorine pesticides like DDT concentrate in adipose tissues. They can remain stored there without causing toxic effects for a longer or shorter period. However, they can cause toxic effects in other tissues or organs where they are present in smaller quantities. The nature, intensity, and location of these disturbances in the body differ from one substance to another and often depend on the dose.

Toxins reach the blood, lymph, or other body fluids. Blood represents the main vehicle for transporting toxins and their metabolites.

Toxins are absorbed in molecular or ionic form. Some of them form colloidal particles at the blood pH, constituting the third form of transport in this fluid. Toxic molecules, ions, and colloids are transported in the blood in various ways: by physical or chemical binding to

blood components, especially erythrocytes; by physical dissolution in the plasma in free form; by binding to one or more types of plasma proteins.

Most blood toxins are either free in the plasma or bound to erythrocytes and plasma constituents. Their distribution depends on their affinity for these constituents. All fractions are in dynamic equilibrium. Globulin molecules (alpha and beta) transport low molecular weight toxins, metal ions (copper, iron, and zinc), and colloidal particles.

Plasma lipoproteins transport lipophilic toxins such as PCBs. Other plasma fractions also play a role in this transport.

Free diffusible ions and certain complexes and free molecules easily pass from the blood to tissues and organs. The free fraction of ions and molecules is in dynamic equilibrium with the bound fraction. The distribution of a toxin from the blood to tissues and organs or, conversely, its mobilization from tissues and organs to the blood, depends on its blood concentration.

The human body can be divided into several compartments: 1) internal organs; 2) skin and muscles; 3) adipose tissue; 4) connective tissue and bone tissue. This classification is primarily based on the degree, in descending order, of vascular (blood) irrigation. Thus, highly irrigated internal organs (including the brain), representing 12% of total body weight, receive approximately 75% of the total blood volume. In contrast, connective and bone tissues (15% of total body weight) receive only 1% of the total blood volume.

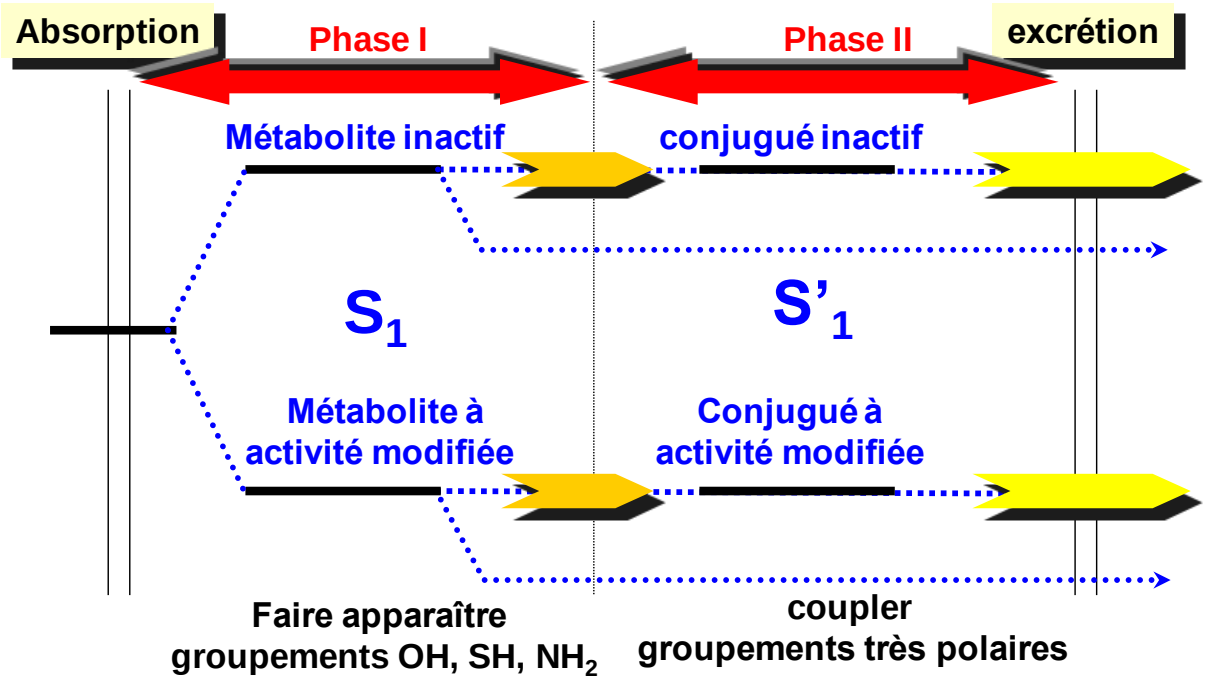
Highly irrigated internal organs generally reach the highest toxic concentration in the shortest time; likewise, equilibrium between these organs and the blood is reached more rapidly. The uptake of toxins by less perfused tissues is slower, but retention is stronger, and the duration of stay longer (accumulation) due to low perfusion.

Retention of a toxin in a given compartment is usually temporary and ends with redistribution to other tissues. During distribution and retention in organs and tissues, various biotransformation processes occur, producing more polar and hydrophilic metabolites that are easier to eliminate. A low rate of biotransformation of a lipophilic toxin generally results in its accumulation in a compartment.

4.2.2. Biotransformation (or Metabolism) of toxins in the organism

During or after its transport in the blood, the toxin can come into contact with different cells of the organism that have the ability to transform it. The set of reactions of metabolic transformation is called biotransformation, while the products of biotransformation are called metabolites. This process can result in a less toxic product (detoxification) or a more toxic one (activation), as well as accumulation or elimination of the product and its metabolites.

Toxic transformation is primarily carried out by the liver, which contains a multitude of enzymes (protein substances that catalyze chemical reactions in the organism). It enriches the blood with nutrients and purifies it by concentrating and eliminating many substances. Other organs such as the lungs and kidneys can also transform toxins.



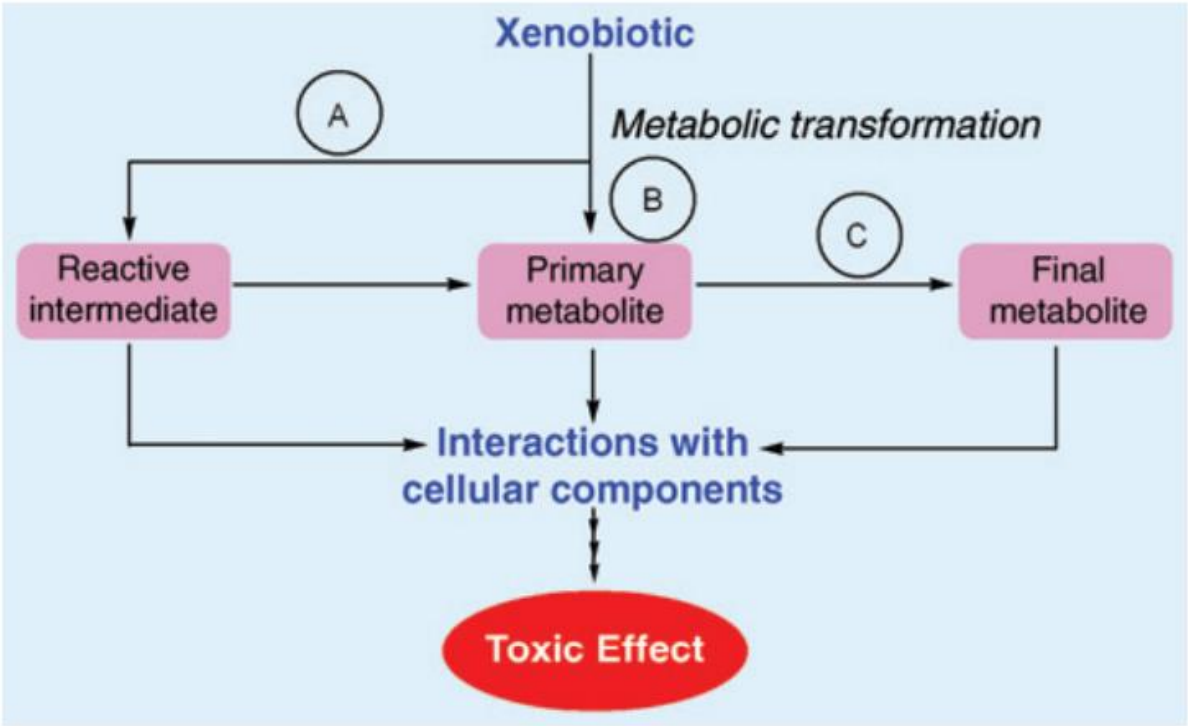


Figure 03. Biotransformation pathways

During their retention in the cells of various tissues and organs, toxins are exposed to enzymes that can biotransform them (metabolize) and convert them into metabolites (through Phase I and Phase II enzymes). The elimination of toxins or their metabolites can occur in multiple ways: through exhaled air, urine, bile, sweat, saliva, and milk.

Elimination depends on the entry route. At the pulmonary level, the absorption/desorption process begins immediately, with toxins being partially eliminated through exhaled air. Longer elimination occurs for toxins absorbed through other routes, starting after blood transport and only completing after distribution and biotransformation.

Two groups of compartments can be distinguished: 1) the rapid exchange system in which the tissue concentration of the toxin is similar to that of the blood; 2) the slow exchange system, where this concentration is higher than in the blood due to binding and accumulation in adipose tissue, the skeleton, and the kidneys, resulting in temporary retention of certain

toxins, such as arsenic and zinc, for example. A toxin can be eliminated simultaneously by two or more excretion pathways. However, one pathway is generally predominant.

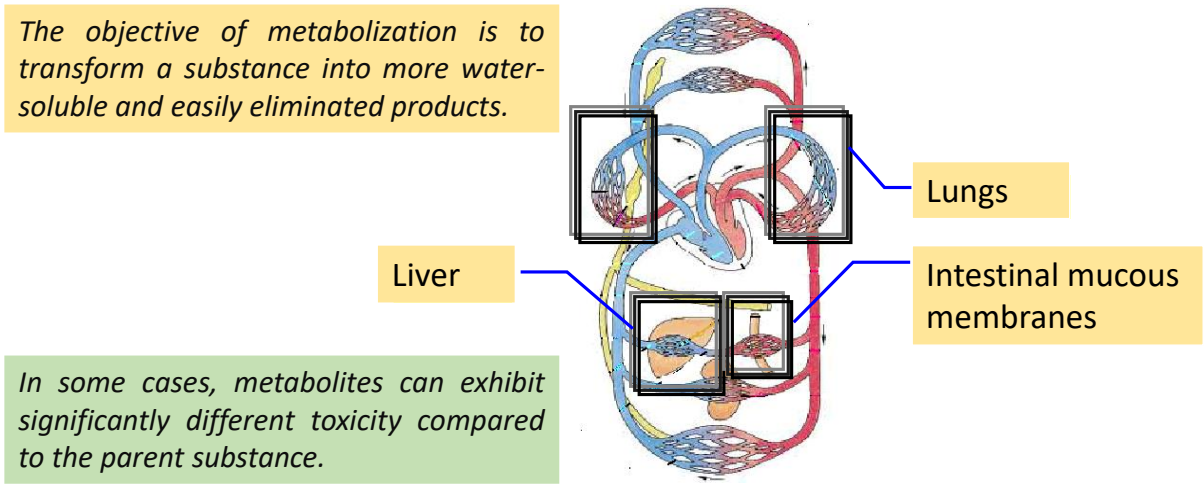


Figure 04. Metabolism sites

- ***Excretion:*** This process involves expelling the unchanged product or its metabolites outside the organism. Excretion can occur through renal (urine), gastrointestinal (feces), pulmonary (expired air), cutaneous (sweat), or lacteal (milk) pathways. For example, the blood transports many products to the kidneys, including several metabolic waste products. The kidneys filter the blood, thereby fulfilling a crucial function in maintaining the balance of blood components, and ensure the elimination of many products.

4.3. Biochemical aspects of the toxicodynamic phase

The action of toxins is linked to their physicochemical properties. From circulation, xenobiotics will pass to their target organ, where they will bind to the active site to exert their effect. The intensity of the effect depends on the strength of binding, the quantity of sites saturated by the toxin, and also the toxin's affinity (acute or chronic intoxication).

4.4. Analysis of the effects of compounds on the organism

Toxins do not produce effects of the same intensity on all organs (e.g., the kidney) or tissues (e.g., blood). They target specific organs, known as target organs, for reasons that are not always understood. Several reasons may contribute to this, including a greater sensitivity of these organs, a higher concentration of the toxin and/or its metabolites, etc. Among the effects are:

- ***Irritation:*** a reversible reaction (recovery after a certain time following the cessation of exposure) of the skin or mucous membranes to products. This reaction can vary in severity depending on the affected tissues or organs (skin, eyes, respiratory tract, digestive tract).
- ***Corrosion:*** involves irreversible damage to tissues following contact with a product (e.g., hydrofluoric acid). Products that can cause destruction of living tissues and materials such as metals and wood are referred to as corrosive.
- ***Carcinogenicity (carcinogenic effect):*** there exists an interaction between the cells of the organism that ensures each tissue has a size and organization adapted to the needs of the organism. In certain situations, cells no longer respond to signals from other cells and only obey themselves. These are cancer cells. Several causes are related to cancer, including diet (exposure to food additives, packaging migrants), tobacco, prolonged exposure to sunlight, certain viruses, and certain chemicals.
- ***Mutagenicity (mutagenic effect):*** a mutation is a change that occurs in the genetic material of the cell, namely DNA (deoxyribonucleic acid). DNA is located inside the cell nucleus and constitutes the material support for heredity. Its role is essential for the transmission of genetic information from one cell to the next generation. The consequences of modifications will depend on the type of cells modified. There are two types of cells that can be affected: somatic cells and germ cells. Somatic cells include all cells of the body (e.g., liver cells, neurons), except germ cells. Germ cells are sperm and eggs.

- ***Allergy (sensitization):*** The human body possesses various defense systems that allow it to recognize substances favorable to its proper functioning. When the body responds excessively or exaggeratedly to foreign chemicals that usually do not provoke an immunological reaction, it is called an allergy. Allergy is an adverse reaction of the organism to chemicals, physical agents, or biological agents generally harmless to most people. Allergic reaction occurs when the individual's immune system mistakenly recognizes a substance as foreign, called an allergen.

- ***Reproductive toxicology:*** concerns disorders of reproduction, non-heritable effects on the embryo and fetus, as well as those that can affect the child from birth to puberty. The range of effects observed can be summarized as follows: effects on fertility; effects on development (prenatal and postnatal); and effects during lactation.

Toxic effects can affect fertility in both men and women. Impairments in libido, sexual behavior, spermatogenesis, oogenesis, or fertilization capacity are among the possible adverse effects that may occur (e.g., sperm abnormalities caused by exposure to dibromo-1,2-chloro-3-propane or DBCP).

Lactation is an important stage during the postnatal period. Indeed, breastfeeding provides significant nutritional benefits for the baby, as breast milk is a natural food containing essential nutrients for its development (fatty acids, vitamins, minerals, etc.). It is therefore important that it is a healthy food. Although there is much data on the effects of drugs on milk and breastfeeding, there are few studies on contamination of breast milk by chemicals present in the workplace. Several substances are excreted in breast milk (e.g., aldrin, perchloroethylene, lead, toluene), but the consequences for the breastfed baby and breastfeeding are still poorly documented.

4.5. Identifying target organs

- ***The liver:*** It is a vital organ, like the heart and lungs. It performs multiple functions, and its role is crucial in maintaining overall balance. It participates in digestion, food storage, detoxification by helping the body get rid of poisons, and elimination. It plays an important role in transforming substances circulating in the blood, including toxic substances, which can often be neutralized there. It is a target for many toxins due to its significant blood flow and its position relative to the bloodstream (e.g., carbon tetrachloride, dimethylformamide, chronic excessive alcohol ingestion). Hepatotoxicity is referred to when the liver is affected.

- ***The kidney:*** It is the elimination organ responsible for urine secretion. It plays a role in regulating the body's fluid balance and helps rid the blood of impurities, including certain toxins (e.g., cadmium, chloroform). Nephrotoxicity is referred to when the kidney is affected.

- ***The nervous system:*** It consists of specialized or non-specialized cells, with the fundamental unit being the neuron. Neurons transfer information (nerve impulses) from one part of the body to another to ensure the internal functioning of the organism and its interactions with the external environment. The nervous system consists of two sets, the central nervous system (commonly abbreviated as CNS) and the peripheral nervous system (PNS). There are various categories of neurotoxic effects, including depression of the central nervous system, with symptoms such as headaches, nausea, vomiting, dizziness, etc., which occur following exposure to solvents such as toluene and xylene.

- ***The skin:*** The overall toxic effects of substances on the skin (dermatosis, skin sensitization) are known as dermatoxicity. The term "occupational dermatoses" is generally used for skin conditions (dermatoses) where a link has been established between the cause and the workplace. These include dermatoses exclusively arising from the workplace, as a result of skin contact with irritant and corrosive products, or subsequent to systemic

intoxication, as in the case of chloracne caused by dioxins (found as contaminants in certain products containing polychlorinated biphenyls or PCBs).

4.5.1. Mechanisms of action: toxicodynamic phase

4.5.1.1. Toxic receptor interaction

Similarly, to how organisms have the ability to respond on an immune level to original agents, there are defense mechanisms against damage caused by exposure to potentially toxic substances (such as certain food packaging migrants). These are metabolic pathways stimulated by the cellular detection of compounds defined as foreign to the body (xenobiotics).

There is no single mechanism, and we cannot definitively state that those known have been selected to respond to these aggressions (exposure to xenobiotics). Nevertheless, it is possible to define basic rules that help place the activation of cellular mechanisms in the broader context of cell defenses against this type of aggression.

The interaction of xenobiotics with specific receptors implies high-affinity binding, thus occurring at low doses. A good understanding of the biological processes affected by the association of the ligand (the xenobiotics) with its receptor will allow us to better define the toxicological consequences.

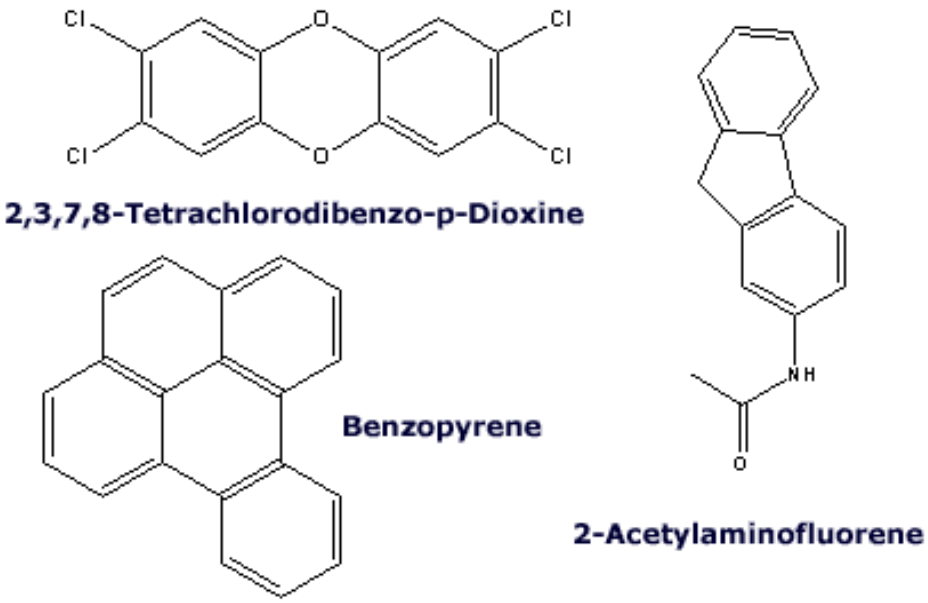


Figure 05: Some xenobiotics from the family of polycyclic aromatic hydrocarbons (PAHs)

- ***Nuclear receptors***

They constitute a superfamily of proteins that act as transcription factors, activated by ligand binding. They exhibit structural analogies (transcriptional regulatory domains, ligand-binding domains, DNA interaction domains) and all bind small lipophilic ligands (passive diffusion through membranes). There are 48 nuclear receptors in the human genome, belonging to two groups:

- Those with unique ligands (a definition for hormonal receptors) such as estrogen receptors, androgen receptors, glucocorticoid receptors, thyroid hormone receptors, for example.

- The others, long considered orphan receptors, have a broader specificity spectrum (fatty acids, bile acids, and other lipophilic substances).

The particular forms of ligand-binding pockets confer some tolerance towards recognized molecules and thus potentially trigger transcriptional activation, generally involving phase I or II enzymes. Thus, many foreign substances bind to this site, hence the term xeno-receptors attributed to some of these molecules.

It is possible to classify the receptors of interest based on their specificity for various types of substrates:

- The PXR receptor (or pregnane X receptor) binds certain steroids and various substances.

- The CAR receptor (constitutive androstane receptor) also binds some steroids and many drugs.

- The PPAR family (peroxisome proliferator-activated receptors) primarily binds lipids but also, for example, phthalates (food packaging migrants).

- LXR and FXR respectively bind cholesterol metabolites and bile acids.

Two essential points to remember:

- The consequence of receptor activation is increased transcription (and thus enzymatic activity) of phase I (xenobiotic and drug activation) and phase II (conjugation) enzymes, with all the unpredictable consequences on the balance between increased toxicity or detoxification.

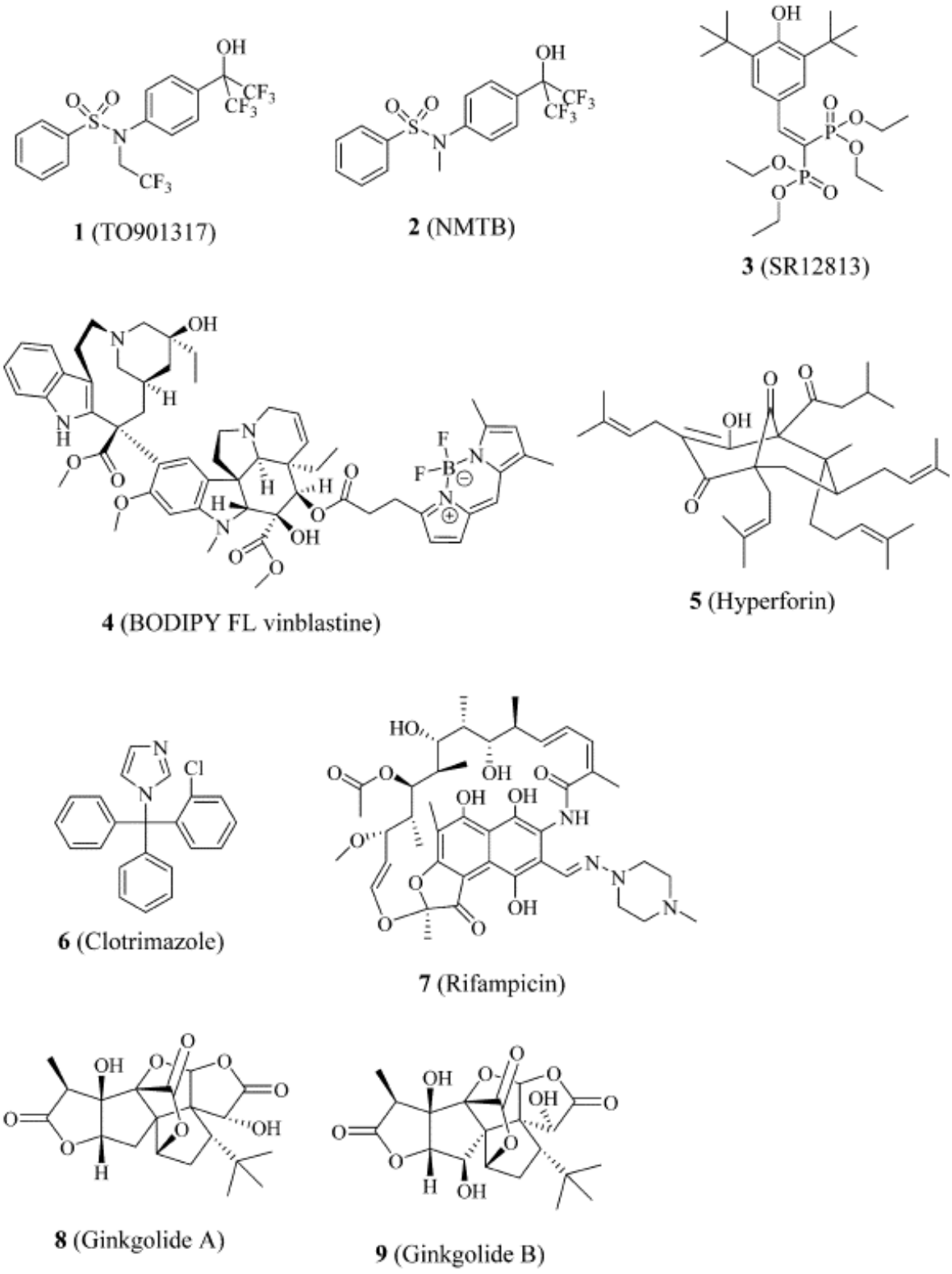


Figure 06. Structures of a panel of PXR ligands.

4.5.1.2. Measurement of enzymatic activities

Enzymology (the study of enzymatic activities) is primarily used to determine the quantity of an enzyme present in a biological environment. It is not common to directly measure the enzyme as a protein; rather, its biological function (catalytic activity) is typically measured.

Enzymatic activity is measured by the rate of the reaction transforming the substrate S into product P: **S → P**

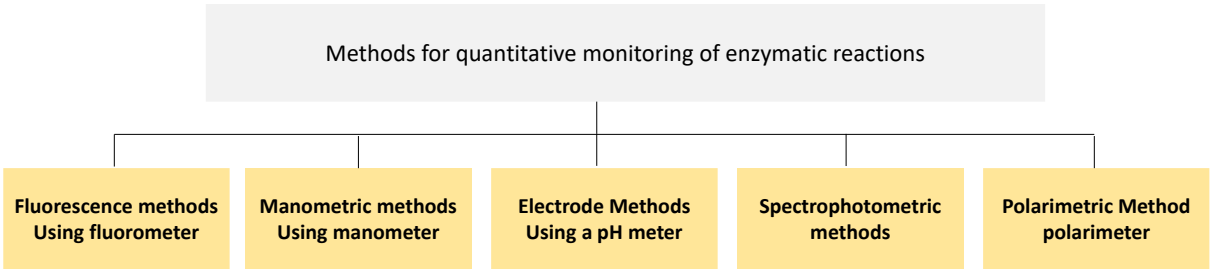


Figure 07. Different methods for determining enzyme activity

CHAPTER 2: MANIFESTATION AND EVALUATION OF TOXICITY

1. Different types of toxicity

1.1. Acute toxicity (short-term)

A practical way to characterize the toxicity of a substance is to determine its median lethal dose (LD50). This dose helps identify symptoms of intoxication and compare substances with each other regarding their toxic potential. It often serves as the starting point for toxicity studies because it provides a minimum level of understanding.

The LD50 is the dose of a substance that can cause the death of 50% of an animal population under specific experimental conditions. The substance is generally administered to rats or mice divided into several groups at increasing doses sufficient to achieve a mortality rate ranging from 0% to 100%. When dealing with an inhaled toxicant, the term used is median lethal concentration (LC50), which expresses the concentration of the toxicant in the inhaled air that causes the death of 50% of the animals.

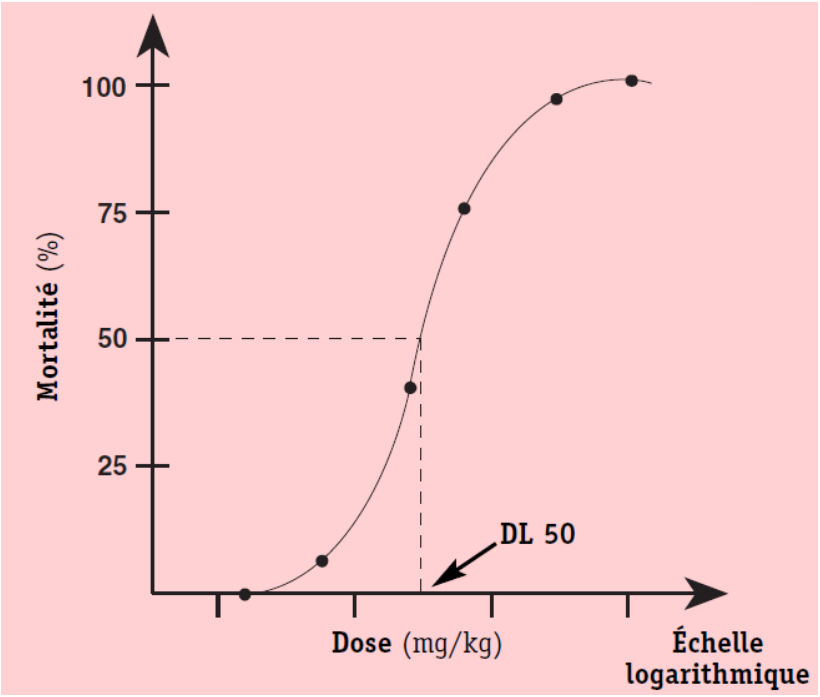


Figure 08. Determination of lethal dose 50 (LD50)

1.2. Chronic toxicity (long-term)

Some adverse effects may take several weeks or many years to be diagnosed and may eventually prove to be irreversible (e.g., neurotoxicity of hexane). The assessment of acute toxicity does not predict this type of toxicity from a substance. Studies aimed at evaluating chronic toxicity must therefore be conducted. These studies last for several months or years and involve the administration of more than one dose at intervals depending on the method used.

We can also divide toxicity into:

1.3. Direct toxicity

These are highly chemically reactive substances. They act directly on the organism (target organs) without undergoing any transformation: such as the case with highly reactive alkylating agents (dimethyl sulfate $C_2H_6O_4S$, diazomethane CH_2N_2, formaldehyde or methanal CH_2O). Alkylating agents are capable of introducing an alkyl hydrocarbon group onto a given molecule (derived from alkanes by the loss of a hydrogen atom).

At the cellular level, alkylating agents attack proteins and nucleic acids, transforming these cellular constituents into substituted derivatives that are altered and can no longer perform their functions.

1.4. Indirect toxicity

The substance itself is not inherently toxic but necessitates prior enzymatic metabolism within the body for a toxic effect to occur. Enzymatic metabolization mechanisms also operate in other organs such as the kidneys, brain, placenta, lungs, skin, nasal cavity, etc. This accounts for the selective toxicity of certain compounds. Their interaction with proteins may result in necrosis and immune damage of varying repairability, while interaction with nucleic acids (DNA) could potentially induce mutations followed by a tumorigenic process.

2. Toxicity evaluation

The toxicity of a substance depends on:

- ✓ *His nature*
- ✓ *The quantity ingested = dose*
- ✓ *The duration or frequency of consumption*
- ✓ *The sensitivity of the individual*

Foods and Toxicity

2.1. Intrinsic toxicity

Toxic elements are naturally present in food:

- o *Poisoning from plant foods*
- o *Poisoning from mushrooms and mold*
- o *Poisoning from marine biotoxins*
- o *Toxic byproducts from certain culinary techniques*

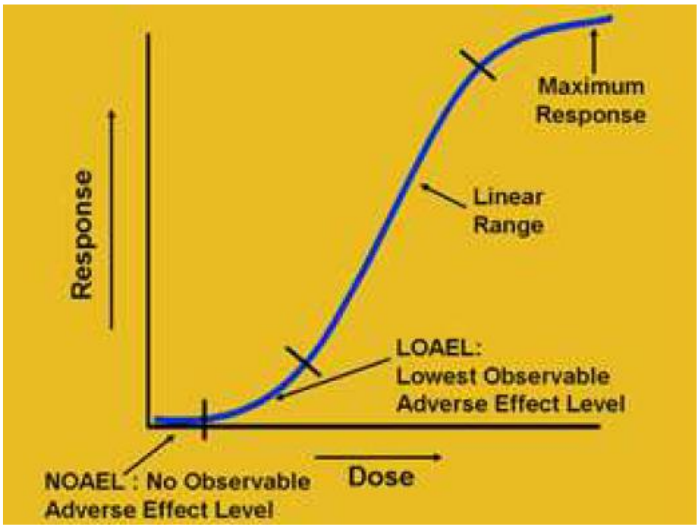
2.2. Extrinsic toxicity

It is acquired through contact or the accidental or intentional addition of contaminants or technological substances.

- o *Food additives*
- o *Toxicity of metals and arsenic*
- o *Toxicity of pesticides*
- o *Materials in contact with food*
- o *Detergents and disinfectants.*

Question: *how are the maximum acceptable limits set?*

Setting maximum acceptable limits



- Determine the no-effect doses (NoEL, LoAEL, and NoAEL) in µg/kg/d.
- Assign a safety factor of **100** or more.
- Estimate the acceptable daily intake (ADI) in µg/d.
- Set maximum residue limits (MRL) in parts per billion (ppb) = µg/kg of food.
- For medications, establish a withdrawal period before slaughter.

- **Determination of the no-effect level (No-observed-adverse-effect level)**

= the maximum amount of a toxic substance that an animal can ingest daily, throughout its life, without causing physiological disorders (in mg/kg of body weight).

- **Establishment of Acceptable Daily Intake (ADI)**

It is calculated from the No-observed-adverse-effect level:

Human ADI = No-observed-adverse-effect level / 100 (in mg/kg body weight)

- A factor of 10× = specific factor: it is assumed that the human species is 10 times more sensitive than the most sensitive animal species tested.

- A factor of 10× = individual safety factor: within a human population, individuals may vary in sensitivity; some may be 10 times more sensitive than average (children, pregnant women, elderly people, etc.).

3. Influence of individual state

The human population is a heterogeneous group in which there is great variability among individuals. They may be affected differently by the same toxic dose, and a person may react differently to it over time (dose-response relationship). Two main categories of factors contribute to explaining the nature and intensity of toxic effects.

3.1. Genetic Factors

Genetic differences can affect individuals' ability to metabolize toxins (e.g., the level of expression of a gene in a tissue: hepatic dehydrogenase).

3.2. Physio-pathological factors

- Age: Sensitivity to toxic effects is usually greater in children and the elderly.

- Sex: There are differences between men and women, especially regarding the metabolism of toxins.

- Nutritional status: Toxicity can be influenced by factors such as adipose tissue mass, dehydration, etc.

- Health status: Individuals in good health are more resistant because they metabolize and eliminate toxins more easily than those with liver or kidney diseases.

4. Extrinsic factors

4.1. Bioactivation of toxic substances

During Phase I of the metabolism of a xenobiotic (mostly oxidative), detoxification may occur (production of less active compounds). However, a phenomenon called bioactivation may also occur, where instead of decreasing biological activity, there is an increase in biological activity and thus an increase in the toxicity of the product.

4.2. Synergistic and antagonistic action and other interactions

- **Additive Effect:** For example: **2 + 3 = 5**. An effect is additive when the combined effect of at least two chemicals is equal to the sum of the effects of each chemical taken individually (no direct interaction).

- **Potentiation:** For example: **0 + 3 > 3**. Potentiation occurs when a substance that usually has no toxic effect is combined with a chemical, making the latter much more toxic.

- **Synergy:** For example: **2 + 3 > 5**. Synergy is a phenomenon whereby multiple factors or influences acting together create an effect greater than the sum of the effects expected if they had operated independently, or create an effect that each of them would not have created alone.

- **Antagonism:** For example: **2 + 3 < 5**. Antagonism is the opposite of synergy. It occurs when the combined effect of at least two compounds is less toxic than the individual effects of the substances.

- **Coalitive Action:** For example: **0 + 0 = 4.** Coalitive action is observed when each of the substances taken individually does not produce toxic effects, but their combination is toxic.

Chapter 3: Modulation of Toxic Actions

1. Introduction: principle of Modulation

There are two main categories of factors (intrinsic and extrinsic) that contribute to the modulation of toxic effects, and consequently can explain the nature and intensity of toxic effects.

2. Introduction of restrictive groups

2.1. Case of food additives

Definitions of food additives (direct food additives, ingredients added to foods for a specific purpose) vary among government agencies and organizations and include the following:

- ***US Food and Drug Administration (FDA):*** The term 'food additive' means any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including any source of radiation intended for any such use), if such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case as a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use; except that such term does not include: (1) a pesticide chemical in or on a raw agricultural commodity; or processed food; or (2) a pesticide chemical; or (3) a color additive; or (4) any substance used in accordance with a sanction or approval granted prior to the enactment of this paragraph1 (footnote 2) pursuant to this Act, the Poultry Products Inspection Act (21 U.S.C. 451 and the following) or the Meat Inspection Act of March 4, 1907 (34 Stat 1260) as amended and

extended (21 U.S.C. 71 and the following); (5) a new animal drug; or (6) an ingredient described in paragraph (ff) in, or intended for use in, a dietary supplement (US FFDCA §201 (s)).1

- ***European Economic Community (EEC):*** A food additive is any substance not normally consumed as a food in itself and not normally used as a characteristic ingredient of food whether or not it has nutritive value, the intentional addition of which to food for a technological purpose in the manufacture, processing, preparation, treatment, packaging, transport or storage of food results, or may be reasonably expected to result, in it or its by-products becoming directly or indirectly a component of such foods. 89/107/EEC.

- ***World Health Organization (WHO):*** Food additive means any substance not normally consumed as a food by itself and not normally used as a typical ingredient of the food, whether or not it has nutritive value, the intentional addition of which to food for a technological (including organoleptic) purpose in the manufacture, processing, preparation, treatment, packing, packaging, transport or holding of such food results, or may be reasonably expected to result (directly or indirectly), in it or its by-products becoming a component of or otherwise affecting the characteristics of such foods. The term does not include contaminants or substances added to food for maintaining or improving nutritional qualities Codex Alimentarius, second edition (revised 1995), volume 1A (General Requirements), p. 11.

- ***According to the Codex Alimentarius:*** A food additive is any substance that is not typically consumed as a food, nor used as a characteristic ingredient of a food, whether or not it has nutritional value. It is intentionally added to a foodstuff for a technological purpose (including organoleptic), at any stage of its manufacture, processing, preparation, treatment, packaging, transportation, or storage. The addition of such substance may directly or indirectly lead to its incorporation or that of its derivatives into the food, or otherwise affect

its characteristics. This definition does not encompass contaminants or substances added to foodstuffs to maintain or enhance their nutritional properties.

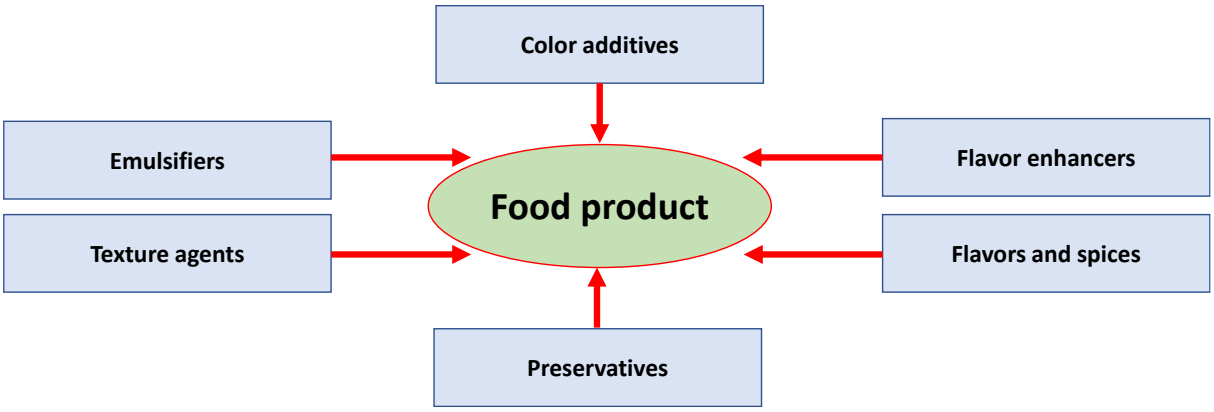


Figure 09. Food additives

Arrêtent :

Article 1er. — En application des dispositions de l'article 7 du décret exécutif n° 92-25 du 8 Rajab 1412 correspondant au 13 janvier 1992 susvisé, le présent arrêté a pour objet de fixer la liste des additifs qui peuvent être incorporés dans les denrées alimentaires.

Art. 2. — Les additifs, dont la liste est annexée au présent arrêté, sont classés par catégorie d'emploi comme suit :

* Colorants ;
* Conservateurs ;
* Antioxygènes ;
* Epaississants et gélifiants ;
* Acidifiants et correcteurs d'acidité ;
* Emulsifiants ;
* Stabilisants ;
* Antiagglomérants ;
* Exhausteurs de goût ;
* Agents d'enrobage ;
* Sels de fonte ;
* Poudres à lever
* Edulcorants.

Art. 3. — Les additifs, cités à l'article 2 ci-dessus, doivent répondre aux spécifications d'identité et de pureté fixées par les normes algériennes.

Art. 4. — Outre les mentions prévues par l'article 6 du décret exécutif n° 92-25 du 8 Rajab 1412 correspondant au 13 janvier 1992 susvisé, l'étiquetage des

ANNEXE

LISTE DES ADDITIFS AUTORISES DANS LES DENREES ALIMENTAIRES

Tableau I

Colorants

NUMERO DU SYSTEME DE COORDINATION INTERNATIONALE	DENOMINATION
JAUNE	
100	Curcumine
101 i	Lactoflavine (ou Riboflavine)
101 ii	Riboflavine - 5' - phosphate sodique
102	Tartrazine
104	Jaune de quinoléine
ORANGE	
110	Jaune orangé sunset ou jaune soleil FCF
ROUGE	
120	Cochenille
122	Azorubine

Figure 10. List of additives authorized in the foodstuffs in Algeria

2.2. Toxicity of food additives

2.2.1. Case study: coloring materials

While natural color additives are generally believed to rarely cause adverse reactions, recent research has unveiled various physiological dysfunctions associated with their consumption. For example, individuals with angioedema and urticaria have displayed allergic reactions to carotene and canthaxanthin. Annatto, derived from carotene, has been linked to cases of anaphylactic shock, with the presence of Annatto-specific IgE antibodies confirmed.

Furthermore, specific IgE antibodies have been associated with other dyes like saffron, carmine, curcumin, and enocianina. In 1959, tartrazine, an artificial coloring material, was reported to induce asthma, urticaria, and hypersensitivity.

Moreover, studies have suggested that these coloring substances may provoke migraines, blurred vision, itching, rhinitis, suffocation, weakness, heat sensation, palpitation, pruritus, and urticaria.

Brilliant blue FCF, once used in dairy products, sweets, and drinks, has been banned in most European countries due to its carcinogenic effects observed in rat tumor studies induced by tar. Similarly, Fast green FCF, which imparts green color to various foods, has shown chromosomal aberrations in mice and inhibition of neurotransmitter release in rats after intestinal absorption.

Indigotine, utilized as a coloring material in tablets, capsules, coatings, ice creams, confectionery, cookies, sweets, and baked goods, has been linked to allergic reactions such as occupational asthma.

Table 2. Toxicity of some food additives

S. No.	Functional Class	Use	Example	Toxic Effect Reported	Reference
1.	Acidifiers	Acidity, sour taste	Ammonium hydroxide, calcium sulfate, citric acid, water, sodium diacetate	Weight gain, acidity	Shibata et al. (1992)
2.	Acidity regulators	pH regulator	Sorbic acid, acetic acid, benzoic acid, propionic acid, citric acid	Chromosomal aberration, mutation, dental cell toxicity	Carocho et al. (2014)
3.	Anticaking agents	Lowers molecules adherence	Sodium ferrocyanide and ferric ferrocyanide, calcium silicate, sodium aluminosilicate	Neuronal toxicity	Dorazio and Bruckner (2015)
4.	Antifoaming agents	Foaming prevention	Silicone fluids	neurotoxic, focal lesions, pulmonary collapse, hemorrhage	Harington (1961)
5.	Antioxidants	Deterioration protection	Oregano, basil, rosemary, pepper, nutmeg, cinnamon and thyme, BHA, BHT, and propyl gallate	Asthma, joint pain, dermatitis, stomach and eye problems	Anbudhasan et al. (2014)
6.	Colorants	Coloration of food	Erythrosine, Tartrazine, Quinoline Yellow, Carmosine	Cancer, hyperactivity, asthma, migraine, headaches, DNA damage	Pandey and Upadhyay (2012)
7.	Color retentioners	Color stabilization	Ascorbic acid	Aging, cancer	Eylar et al. (1996)
8.	Emulsifiers	Uniformity of mixtures	Polysorbate-80 and carboxy methyl cellulose	Disruption of gut bacteria, obesity, and irritable bowel syndrome	Aponso et al. (2017)
9.	Flavor enhancers	Enhancement of taste and color	Monosodium glutamate, aspartame, acesulfame K, saccharine,	Cancer, DNA damage, fetal abnormalities, lung tumors	Pandey and Upadhyay (2012)

2.2.1.1. Bio-kinetics of food colorants

Like any food substance, colorants end up in the gastrointestinal tract where they undergo the action of digestive juices and intestinal flora.

- They are absorbed according to their physicochemical properties (hydro/liposolubility, molecule size).

- Water-soluble food colorants are eliminated without being degraded. This is what gives stools and urine an atypical coloration.

- It is possible for urine to take on a reddish hue. Absolutely harmless to health, this phenomenon occurs when beet pigments (betalains) are absorbed by the intestine instead of being degraded.

- Several factors influence this coloring: the acidity of the stomach, the speed of digestion, and the variety of beet consumed.

- Food colorants, in particular, have been studied concerning the intestinal flora because the bacterial flora possesses azo-reductase activity, which is responsible for a fundamental transformation: the N=N bond is broken, resulting in the appearance of cyclic amines that can then have different absorption kinetics or absorption pathways.

- The polarity of molecules is a key factor in enterocytic passage; highly polar compounds are therefore poorly absorbed. However, this is not the case for products resulting from bacterial azo-reduction. For instance, it is suggested that 95% of the oral dose of Tartrazine is absorbed through this pathway in rats, with 1% of Tartrazine, 22% of p-acetamido-benzenesulfonic acid, and 74% of sulfonic acid found in the urine after 48 hours.

- If the colorant is absorbed by the intestinal mucosa, it will be transported through the bloodstream and quickly reach the liver. Degradation may occur primarily at the microsomal level (reductions, N-dealkylations, hydroxylations, conjugations, etc.). In the case of azo dyes, reduction leads to two amines, one primary and the other substituted. Dealkylation leads to demethylated compounds. Conjugation with glucuronic acid promotes water solubility and therefore excretion.

- The degradation rate is quite rapid, as 41% of Tartrazine and 90% of Methyl Orange (banned in France) are reported to be degraded in the digestive tract.

- Bile can serve as an excretion route for approximately 5% of the ingested dose, while the majority of excretion occurs through urine.

- In urine, either the original compound or conjugated derivatives are found. These conjugated derivatives can be hydrolyzed by glucuronidase; the hydrolysis products may be reabsorbed, establishing an enterohepatic circulation.

2.2.2. Case study: packaging additives (Bisphenol A)

2.2.2.1. Chemical nature and source of exposure

Bisphenol A [(2,2-(4,4'-Dihydroxydiphenyl) propane] (BPA, Figure 20) was first synthesized in 1891. This molecule is used in the synthesis of polycarbonate plastics used in food packaging (film, plastic bottles), internal coatings, canned foods, medical products, as well as halogenated derivatives used as flame retardants. Incomplete polymerization or poor resistance to autoclave sterilization can lead to contamination of foodstuffs.

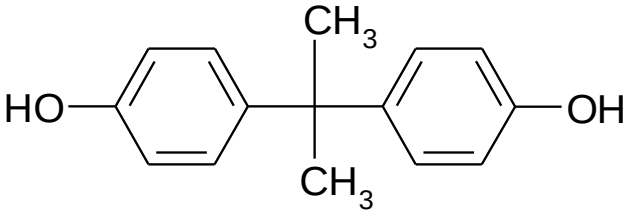


Figure 10. Chemical structure of bisphenol A

Human exposure to BPA varies depending on diet and age, with estimates suggesting it is less than 1 µg/kg body weight per day. According to the U.S. Environmental Protection Agency (EPA), the Lowest-Observed Adverse-Effect Level (LOAEL) is 50 mg/kg body weight per day. However, several studies indicate that BPA at low doses has unpredictable effects, challenging the notion that "the dose makes the poison."

BPA binds to both types of ER receptors, exhibiting a 10 times higher affinity for ERβ but remaining 1000 to 10000 times lower than that of estradiol. It can also moderately bind to other receptors, such as androgen receptors (AR), progesterone receptors (PR), and corticoid receptors.

Several human studies have demonstrated correlations between blood and urine levels of BPA and the onset of adult pathologies such as obesity, diabetes, and cardiovascular diseases. Additionally, research in rats supports the hypotheses generated by epidemiological studies.

2.2.2.2. Endocrine Effects of Bisphenol A

- *Reprotoxicity*

In vivo studies conducted in rodents have shown that in utero exposure decreases fertility and fecundity at very low doses, on the order of nanograms (ng) administered to the animal via mini-pumps. Similarly, in males, the same type of exposure, at a low dose on the order of micrograms (µg) but orally, affects the number and mobility of spermatozoa, which is associated with a decrease in the steroid receptor expression profile. Transgenerational effect (F2, F3) of BPA at a low dose introduced orally on the expression profile of co-activators of steroid receptors such as SRC-1 (Steroid Receptor Coactivator-1), which play a key role in spermatogenesis was also reported.

- *Neurotoxicity and Behavior*

In both humans and animals, the ability of BPA to cross the placental barrier is established: the passage of BPA through the placenta in CD1 mice and was evaluated to be 4% of the dose administered subcutaneously. In humans, the presence of unconjugated BPA in the umbilical cords of 152 baby boys was reported.

The passage of BPA through the placenta indicates exposure of the brain during embryogenesis, which may explain the alterations observed in adulthood. This hypothesis was reinforced during autopsies conducted at Antwerp Hospital (Belgium), where BPA levels was measured in the brain (n=8, concentration= 0.91 ng/g). Alterations in maternal behavior in mice after peri- and postnatal exposures to BPA at 10 µg/kg body weight per day, which were more pronounced than those obtained after continuous exposure was also reported. These

changes may be due to a local effect of BPA on neuroendocrine secretions that govern maternal behavior.

Similarly, maternal behavior, assessed on various parameters such as nursing, nest building, or pup licking, is altered after in utero exposure of 40 µg/kg body weight in Sprague-Dawley rats. Additionally, subcutaneous injections of 20 µg/kg body weight of BPA over a period of six weeks (3 weeks of gestation + 3 weeks of lactation) disrupt behavior in Open Field Tests designed to evaluate locomotor activity and exploration ability in mice.

BPA can also alter sexual dimorphism by masculinizing the social and emotional behavior of females. A significant loss of dimorphism in male and female mice exposed to BPA during the postnatal period (PND 32 - PND 87) at a dose of 40 µg/kg body weight per day suggests that BPA may act as an estrogen or anti-estrogen in certain brain regions.

- *Metabolic Disturbance*

In the literature, studies contradict each other regarding the effects of BPA; however, the majority conclude the existence of effects at very low doses on energy balance and overall homeostasis. An epidemiological study conducted by The National Health and Nutritional Examination Survey (NHANES) 2003-2008 in the United States shows a correlation between increased BPA concentrations in urine and the onset of diabetes in 3967 participants (51.7% women).

In animal models, exposure *in utero* from the 6th day of gestation until weaning through drinking water at low doses (0.1 mg/kg BW/day and 1.2 mg/kg BW/day) shows increased body weight in adulthood in both sexes, with a more pronounced effect in females. The effect is also dose-dependent, as the low dose has the greatest effect. These effects are more pronounced in females, suggesting the involvement of sex hormones.

In adult male mice, exposure to BPA via subcutaneous injections (for 8 days) at relatively low doses (100 µg/kg BW/day) decreases energy metabolism, resulting in impaired insulin

signaling in the periphery (especially in muscle tissue). Body weight was not affected, but there was a decrease in food intake, body temperature, and locomotor activity, indicating that BPA may be considered a risk factor in the development of diabetes. In adult ovariectomized female Sprague-Dawley rats, exposure to BPA at doses of 4 mg/day or 5 mg/day via mini pumps implanted dorsally for 15 days shows a decrease in weight gain, with preferential accumulation in brown adipose tissue.

Despite the effects of BPA on energy balance, the mechanisms remain poorly understood. A change in preference for sweet foods (saccharin and sucrose) after in utero exposure to low doses of BPA (0.1 mg/kg BW/day, 1 mg/kg BW/day) was reported. This increased consumption of sweet foods signifies increased energy intake, resulting in weight gain. Interactions at the neuroendocrine system level that control energy balance on one hand and reproduction on the other hand may be targeted by endocrine disruptors, which can explain these effects.

In vitro, BPA affects the expression of adipocyte differentiation genes in 3T3-L1 cells without altering triglyceride accumulation. BPA at a low dose (1 nM) decreases potassium channel activity, increases insulin secretion in mouse or human pancreatic β cells, with a more pronounced effect on human pancreatic cells. This means that BPA at very low doses can alter glucose homeostasis.

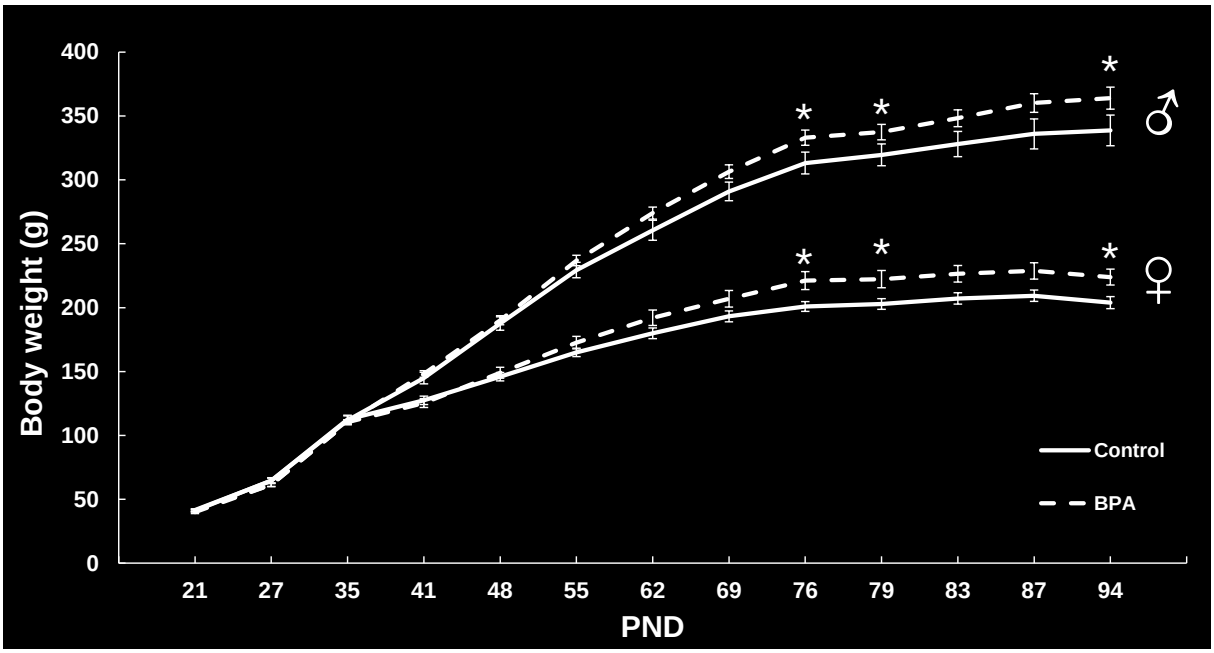


Figure 11. Effects of bisphenol A on body weight

Table 3. Packaging additives and their toxicity

S. No.	Packaging Additive	Examples/Metabolite	Toxicity Reported	Reference
1.	Plasticizer	Butyl stearate, acetyl tributyl citrate, alkyl sebacates, adipates	Phthalate: carcinogenic, estrogenic	NTP (1982), USDHHS (1982)
2.	Thermal stabilizers	Poly(vinyl chloride), poly (vinylidene) chloride, and polystryrene	Cellular toxicity	Hine et al. (1958), CEC (1990)
3.	Slip additives	Polyolefins, polystyrene, and polyvinyl chloride	Residue migration calculated	Cooper and Tice (1995)
4.	Light stabilizers	Tinuvin770 and Chimasorb 944	Cardiac myocytes	Sotonyi et al. (2001)
5.	Antioxidants	Aryl substituted phosphites, triphenyl phosphate	Highly toxic	Lefaux and Technica (1968)
6.	Styrene	Phenyloxirane	Mutagenic	Bond (1989), ECETOC (1993)
7.	Polyvinyl chloride	Venyl chloride	Highly toxic	WHO (1974, 1975)
8.	Epoxy resins	Bisphenol A diglycidyl ether	Cytotoxic	Lau and Wong (2000)
9.	Polyurethane polymers and adhesives	Isocyanate	Toxic compound	Lau and Wong (2000)
10.	Polyamides	Caprolactam	Bitter taste	Stepek et al. (1987)
11.	Polyethylene terephthalate	Migrants: Formaldehyde, acetaldehyde, antimony	Endocrine disorder	Castle et al. (1989)
12.	Polyethylene bags	Heavy metals	Abdominal pain, anemia, ataxia, and memory loss	Musoke et al. (2015)

2.2.2.3. Bio-kinetics of Bisphenol A

The absorption of BPA is rapid and significant after oral and cutaneous exposure. It is distributed in tissues, crosses the placental barrier, and passes into maternal milk. The metabolites are mostly eliminated in feces; less than 10% is eliminated unchanged.

In animals

2.2.2.3.1. Absorption

After oral exposure, absorption in the gastrointestinal tract is rapid and significant; however, no quantification has been performed. The peak of radio-labeled molecules in the blood is reached 5 minutes after oral exposure to [C]-bisphenol A for low doses (10 mg/kg) and after 15 minutes for higher doses (100 mg/kg); the maximum concentration increases linearly with the dose. Bisphenol A levels then decrease, with a rebound at 3 hours (100 mg/kg) or 6 hours (10 mg/kg), likely related to an enterohepatic cycle.

2.2.2.3.2. Distribution

The distribution of BPA in the body has not been specifically studied. In rats exposed 14 days after giving birth, 8 hours after exposure, 77% of the administered dose is found in milk, blood, plasma, tissues, and carcasses, with the remainder in the liver, kidneys, and lungs; transfer to offspring through milk is limited (less than 0.01% in offspring carcasses after 2 to 24 hours). 10 minutes after exposure of pregnant rats, BPA is detected in the liver and kidneys of fetuses, reaching its maximum concentration in 20 minutes, then decreasing over 6 hours to 5% of its maximum following the decrease in concentration in maternal blood.

2.2.2.3.3. Metabolism

In vitro, rat hepatocytes in culture, when incubated with BPA for 2 hours, produce a major metabolite identified as BPA glucuronide, and two minor metabolites, 5-hydroxybisphenol A and BPA sulfate, formed only at high doses, suggesting metabolic saturation.

In vivo, the blood level of BPA glucuronide is inversely proportional to the dose (96% to 76% for oral doses of 10 to 100 mg/kg) in the first 10 minutes following exposure; the parent compound represents 2% to 8%. After a longer period (45 minutes for males and 18 hours for females), 100% of the BPA is in glucuronide form for the low dose in both sexes compared to 68% (males) and 98% (females) for the high dose. The parent compound represents 11% (males) and 2% (females); its presence in the blood long after exposure may be due either to enterohepatic circulation or intestinal cleavage of the conjugate (after subcutaneous exposure, the parent compound is not detected).

2.2.2.3.4. Elimination

After oral exposure in rats, BPA is primarily eliminated in the form of glucurono-conjugates (single or double), mostly in feces (61-63% and 71-75% of the dose, respectively), and to a lesser extent in urine, more so in females than in males (19-20% and 8-10% of the dose, respectively). The parent compound eliminated in urine represents 2 to 10% of the dose depending on the rat strain. A minor metabolite, BPA sulfate, has been detected in feces (4-5% of the dose in males and 2-4% in females). Elimination via maternal milk of BPA and/or its metabolites has also been demonstrated. Elimination is rapid, with the majority of the absorbed dose being excreted within 72 hours. The elimination half-life is 9.7 hours after oral exposure. In carcasses, between 0.03% and 0.35% of the oral dose is found after 7 days; in tissues (liver and kidneys), less than 0.02% remains.

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