

## 5. HEALTH EFFECTS OF PESTICIDES: ACUTE AND CHRONIC TOXICITY

Pesticides are substances designed to interfere with specific biological processes in organisms considered harmful to agricultural crops. They may act on insects' nervous systems, interfere with the growth of weeds, block important metabolic processes in fungi, or alter other functions essential to the survival of target organisms.

However, living organisms share many fundamental biological mechanisms. For this reason, some substances developed to act on insects, fungi, or plants may also produce undesirable effects in humans.

Not all pesticides present the same hazard. Differences may be enormous, both in the nature of their toxic effects and in the quantities required to cause them. Some pesticides can cause very severe acute poisoning. For others, scientific attention focuses mainly on the potential consequences of repeated or prolonged exposure.

Research has documented effects on several organs and systems, including the nervous system, liver, kidneys, and reproductive system. For certain substances, associations with particular types of cancer have also been identified.

It is nevertheless essential to distinguish effects observed in experimental studies, those found in occupationally exposed populations, and the risks actually associated with the quantities of residues present in food.

The scientifically appropriate question is not merely whether a pesticide can be toxic, but under what conditions, at what doses, and through which mechanisms it can cause harm to health.

### 5.1 How pesticides interact with the human body

When a pesticide enters the human body, its behaviour depends on the chemical characteristics of the substance and the route of exposure. Toxicology distinguishes four fundamental stages to describe this process.

**Absorption.** The passage of the substance from the external environment into the body. It can occur through the digestive tract, respiratory tract, or skin.

**Distribution.** Once absorbed, the substance may enter the bloodstream and reach different organs and tissues.

**Metabolism.** The body may transform the substance through chemical reactions, mainly in the liver. These transformations may make it easier to eliminate, but in some cases they produce metabolites with their own toxicity, sometimes greater than that of the original molecule.

**Elimination.** Depending on their characteristics, the substance and its metabolites may be excreted mainly in urine and faeces.



Toxicokinetics: the four main stages of the fate of a pesticide in the human body.

Together, these processes are called **toxicokinetics**. In parallel, **toxicodynamics** studies how a substance interacts with cells, enzymes, receptors, and other biological components to produce its effects.

Some pesticides, for example, inhibit enzymes essential to the functioning of the nervous system. Others may interfere with cellular energy metabolism or alter oxidative processes.

The term **oxidative stress** describes a condition in which the production of reactive molecules exceeds the body's capacity to neutralise them. Under certain circumstances, these molecules may damage cell membranes, proteins, and DNA.

Metabolites are particularly important. The fact that our body transforms a pesticide does not necessarily mean that it has rendered the substance harmless. Metabolic transformation may be a detoxification process, but it may also be a stage of toxic activation. For this reason, scientific pesticide assessments examine not only the parent compounds but also the main products of their metabolism.

## 5.2 Routes of exposure: ingestion, inhalation, and skin contact

People can come into contact with pesticides through different routes. Exposure through **ingestion** occurs mainly through food or water containing residues. **Inhalation** exposure may occur when pesticide-containing particles, aerosols, or vapours are breathed in. **Dermal contact** occurs when substances come into contact with the skin, from which some may be absorbed to varying degrees.

These routes of exposure are not equivalent. The quantity actually absorbed can vary substantially according to the compound, its concentration, and the characteristics of the tissues through which contact occurs.

A farmer preparing a concentrated mixture or carrying out a treatment may be exposed to quantities and routes of exposure very different from those of a person consuming food containing residues. For this reason, findings from studies of agricultural workers cannot automatically be applied to consumers.

Nevertheless, these studies provide important information about the potential biological effects of substances, particularly when they identify relationships between exposure and health outcomes.

The difference between occupational and dietary exposure lies primarily in the conditions and magnitude of exposure, not necessarily in the nature of the toxic mechanism. Risk assessment must therefore take both types of information into account.

### 5.3 Acute toxicity: the effects of high exposure

Acute toxicity concerns effects that may arise after a single exposure or repeated exposures over a relatively short period. Acute pesticide poisoning is a documented public-health problem, especially in settings where highly hazardous substances are used and protective measures are inadequate.

Symptoms depend on the substance involved and the amount absorbed. They may include nausea, vomiting, abdominal pain, dizziness, headache, skin and eye irritation, breathing difficulties, and neurological disturbances. In the most severe cases, seizures, respiratory failure, loss of consciousness, and death may occur.

A particularly significant example is provided by **organophosphate insecticides**. Many of these compounds inhibit **acetylcholinesterase**, an enzyme essential for normal nervous-system function.

**Acetylcholine** transmits signals between nerve cells and between nerves and muscles. After performing its function, it must be broken down rapidly by acetylcholinesterase. If this enzyme is inhibited, acetylcholine accumulates and causes excessive stimulation of nerve and muscle structures.

This can cause involuntary muscle contractions, excessive salivation, sweating, cardiac disturbances, and serious respiratory problems. The mechanism is well understood and demonstrates how a substance developed to interfere with the nervous system of insects can also act on the human nervous system.

The World Health Organization considers exposure to highly hazardous pesticides a major public-health concern, especially in occupational and accidental poisoning.

These effects are not the usual consequences of consuming food containing residues that comply with legal limits. Rather, they demonstrate the toxic capacity of certain substances when exposure is sufficiently high.

### 5.4 Chronic toxicity: the consequences of prolonged exposure

Chronic toxicity concerns effects that may arise following repeated or prolonged exposure over time. Unlike acute poisoning, chronic effects can develop slowly and may only become recognisable after many years.

Studying them is particularly complex. In everyday life, people are exposed to many chemicals through food, water, air, the home environment, and occupational activities. It can be difficult to separate the contribution of a single pesticide from that of other environmental, genetic, and behavioural factors.

Knowledge therefore comes from different research approaches: animal toxicology studies, cell experiments, investigations of biological mechanisms, and epidemiological studies in exposed populations.

Epidemiological studies seek to determine whether certain diseases are more frequent among people exposed to a substance than among those who are not exposed. However, a statistical association does not automatically demonstrate a cause-and-effect relationship. Conclusions become more robust when findings from different studies are consistent and supported by plausible biological

mechanisms.

Chronic effects under investigation include neurological changes, liver and kidney damage, reproductive effects, developmental disorders, and certain cancers. Research into chronic low-dose exposure, particularly through food, still faces important difficulties.

The absence of immediately observable harm does not necessarily demonstrate that repeated exposure is free from long-term consequences. At the same time, the mere presence of a substance in the body does not in itself prove that health damage has occurred. This distinction makes thorough scientific assessment indispensable.

## 5.5 Effects on the nervous system

The nervous system is one of the principal toxicological targets of several pesticide families. This is unsurprising, since many insecticides were developed specifically to interfere with the transmission of nerve impulses in target organisms.

Organophosphates and certain carbamates act on acetylcholinesterase. **Pyrethroids**, on the other hand, modify the functioning of **sodium channels**, structures in cell membranes that are essential for transmitting nerve signals. Other pesticides may interfere with different cellular mechanisms involved in neuron function and survival.

### Pesticides and Parkinson's disease

One important field of research concerns possible links between pesticide exposure and neurodegenerative diseases. Parkinson's disease is characterised by the progressive loss of certain neurons that produce **dopamine**, a substance essential to movement control.

Numerous epidemiological studies have identified associations between exposure to some pesticides and an increased risk of developing this disease. The US **National Institute of Environmental Health Sciences (NIEHS)** reports particularly significant evidence relating to substances such as **paraquat**, **rotenone**, and other pesticides.

In one epidemiological study, occupational use of rotenone or paraquat was associated with a frequency of Parkinson's disease approximately **2.5 times higher** than among non-users. It is important to clarify that this result was observed under specific exposure conditions and is not an estimate of the risk associated with food residues.

Research has also identified plausible biological mechanisms. Some substances may interfere with the functioning of **mitochondria**, cellular structures that produce the energy cells need. Others may promote oxidative stress or alter processes that protect neurons.

The relationship between pesticides and Parkinson's disease is therefore an area in which epidemiological and experimental evidence reinforce each other, while still not making it possible to attribute every individual case to a particular exposure.

### The case of acetamiprid

Another important example is **acetamiprid**, an insecticide belonging to the neonicotinoid family. In 2024, **EFSA** reviewed available information on possible **developmental neurotoxicity**: the capacity of a substance to interfere with maturation of the nervous system.

The assessment highlighted important scientific uncertainties that were considered sufficient to warrant a more precautionary approach. EFSA therefore proposed reducing both the daily and acute reference values from **0.025 to 0.005 milligrams per kilogram of body weight**—a fivefold reduction.

This review does not demonstrate that previous dietary exposures necessarily caused neurological damage. It does, however, show that advances in scientific knowledge can lead to substantial revisions of pesticide quantities considered acceptable in risk assessments.

This example illustrates why authorisations and toxicological reference values need to be reviewed periodically in light of new evidence.

## 5.6 Possible effects on the liver, kidneys, and other organs

The liver plays a central role in the metabolism of substances foreign to the body. Through numerous enzyme systems, it contributes to the transformation of pesticides and their metabolites, often facilitating their elimination.

For this reason, the liver may be one of the organs affected by the toxic effects of certain substances. In experimental studies, some pesticides have caused changes in liver enzymes, oxidative stress, cellular alterations, and, under certain conditions, tissue damage.

The kidneys may also be target organs. Their functions include filtering blood, regulating the composition of body fluids, and eliminating many substances through urine. During these processes, some pesticides or metabolites can reach significant concentrations in kidney tissue.

For certain substances and exposure conditions, toxicological studies have documented changes in kidney function and cellular damage. However, the consequences depend on the compound, dose, and duration of exposure.

It would be incorrect to claim that all pesticides generally damage the liver and kidneys. It is correct, instead, to state that liver and kidney toxicity are among the effects that must be carefully assessed for individual active substances.

Scientific assessments also consider possible effects on the immune system, blood, and other organs. Particular attention is paid to metabolic transformation products, which may have toxicological properties different from those of the parent substance.

## 5.7 Pesticides and cancer: what scientific research tells us

The possible relationship between pesticide exposure and cancer is one of the most extensively studied and debated topics. Research draws on epidemiological studies, animal experiments, and investigations into the mechanisms by which a substance may interfere with cellular processes.

These mechanisms include DNA damage, oxidative stress, alterations of cellular regulation, and other biological processes involved in **carcinogenesis**—the process by which a normal cell may progressively become a cancer cell.

Not all pesticides have carcinogenic properties, and the available evidence varies considerably from one substance to another.

## The IARC classification

The **International Agency for Research on Cancer (IARC)**, a specialised agency of the World Health Organization, evaluates whether substances and other agents can cause cancer. Its classification distinguishes categories according to the strength of scientific evidence.

**Group 1:** carcinogenic to humans.

**Group 2A:** probably carcinogenic to humans.

**Group 2B:** possibly carcinogenic to humans.

**Group 3:** not classifiable as to its carcinogenicity to humans because the available evidence is insufficient for a more specific classification.

These categories concern the strength of evidence for carcinogenicity, **not** the probability that a person will develop cancer at a given dose.

## The case of glyphosate

In 2015, IARC classified **glyphosate** in **Group 2A**, as probably carcinogenic to humans. The assessment was based on limited evidence of carcinogenicity in humans, sufficient evidence in experimental animals, and important findings concerning mechanisms of **genotoxicity**, the ability of a substance to damage the genetic material of cells.

IARC's conclusion generated extensive scientific and regulatory debate. In 2022, the **European Chemicals Agency (ECHA)** concluded that glyphosate did not meet the criteria for classification as a carcinogen under the European system for classifying chemical substances.

In 2023, **EFSA**, also using ECHA's assessment, identified no critical areas of concern in its review of glyphosate risk for the representative uses assessed, although it noted several data gaps and unresolved questions.

These differing conclusions also reflect differences in methodology, criteria, and assessment objectives. IARC's classification identifies a potential carcinogenic hazard, whereas the European assessment also examines risks associated with the conditions of use and exposure under consideration.

The glyphosate case demonstrates the importance of distinguishing the potential to cause harm from the probability of that harm occurring under real exposure conditions.

## Other pesticides examined by IARC

In the same 2015 evaluation, IARC also classified the insecticides **malathion** and **diazinon** as probably carcinogenic to humans. **Parathion** and **tetrachlorvinphos** were classified as possibly carcinogenic.

These findings show that carcinogenicity concerns are not limited to a single substance. However, these classifications should not automatically be interpreted as evidence that traces of these pesticides in food create a significant cancer risk.

Establishing dietary risk requires further information about residue concentrations, quantities ingested, and the toxicological characteristics of the substances. The distinction between

occupational and dietary exposure is particularly important when interpreting cancer studies.

## 5.8 Pregnancy, childhood, and other conditions of particular vulnerability

The effects of a toxic substance depend not only on the dose but also on the characteristics of the exposed organism. Age, physiological status, health conditions, and genetic characteristics may affect the ability to absorb, metabolise, and eliminate chemicals.

During pregnancy, for example, the fetal organism goes through particularly complex stages of development. Formation of the nervous system, organs, and biological regulatory mechanisms depends on coordinated processes that, under certain conditions, may be sensitive to toxic substances.

Some pesticides can cross the placenta and reach the developing organism. Not all substances cross the placenta equally readily, and transfer does not necessarily mean that a harmful effect will occur. Nevertheless, this possibility makes assessment of reproductive and developmental toxicity particularly important.

Children may also have different vulnerabilities from adults. Their bodies are growing, some metabolic systems are still maturing, and for the same ingested quantity, the dose relative to body weight may be higher.

A simple example illustrates this point. If a **15 kg child** and a **75 kg adult** ingest the same amount of a substance, expressed in milligrams, the child receives a dose per kilogram of body weight **five times higher**.

This does not automatically mean that the harm is five times greater; it shows why exposure assessment must account for body weight and the characteristics of different population groups.

For certain substances, there may also be developmental periods during which a biological function is especially sensitive. These are known as **windows of vulnerability**.

A substance capable of interfering with a biological process during development may have consequences different from those of the same exposure in an adult organism.

Effects on the endocrine system—the system of glands and hormones that regulates many bodily functions—will be examined in the next chapter.

The safety of a substance cannot be assessed by considering only a healthy adult; it must also take account of more vulnerable individuals and the most delicate stages of development.

## 5.9 The difference between a substance's hazard and its actual health risk

One of the most common errors in scientific communication is to confuse a substance's **hazard** with the **actual risk** associated with its presence.

Hazard is the intrinsic capacity of a substance to cause harm. Risk, by contrast, depends on the probability and severity of harm under the exposure conditions considered.

A substance may have important toxic properties but pose no significant risk when exposure is sufficiently limited. Conversely, a substance with relatively modest toxicity may cause harmful effects when absorbed in large quantities.

To assess dietary risk, scientific authorities consider the substance's toxicological characteristics and the quantity a person may ingest through the diet.

Two important parameters are:

**ADI — Acceptable Daily Intake.** The amount of a substance that, according to available knowledge and including appropriate safety margins, may be ingested every day throughout life without an appreciable health risk.

**ARfD — Acute Reference Dose.** The estimated amount that may be ingested over a short period, generally not exceeding 24 hours, without an appreciable health risk.

Both values are generally expressed in milligrams of substance per kilogram of body weight. They do not necessarily represent doses at which harm begins. They are reference parameters obtained from toxicological assessments and safety factors, used to protect consumers' health.

Their determination nevertheless depends on the scientific knowledge available at the time of assessment. As the acetamiprid case demonstrates, new evidence or new uncertainties can lead to substantial revisions of these parameters.

Scientific risk assessment is not an immutable truth, but a process that must evolve with knowledge. This does not mean that the established values are arbitrary or lack scientific foundations. It means that they reflect the best assessment possible on the basis of available data and methods.

Another important distinction concerns **maximum residue levels (MRLs)** established by food legislation. These limits do not necessarily coincide with toxicological reference values and are set taking account of good agricultural practices and assessments of consumer exposure.

Food that complies with legal limits is not therefore necessarily free of residues. At the same time, the presence of a residue does not automatically demonstrate a health risk.

To understand a food product properly, three pieces of information must be distinguished: **which substances it contains, the quantities present, and the toxicological significance of their presence.**

Legislation establishes the conditions under which a food may be marketed. Chemical analysis, by contrast, makes it possible to identify which substances are actually present in the product, within the capabilities and limitations of the analytical method used. These are two different tools, both important, but not equivalent.

## Conclusion to Chapter 5

Scientific knowledge demonstrates that some pesticides can cause important toxic effects on human health. For certain substances, the mechanisms responsible for acute poisoning are well documented, while experimental and epidemiological studies have identified effects and associations involving the nervous system, several organs, and some cancers.

However, the evidence is not uniform across all substances, and not all exposure conditions entail the same risks. In particular, effects observed in occupationally exposed populations cannot automatically be attributed to pesticide concentrations that may be present in food.

Assessment of dietary exposure requires specific data on substances, quantities ingested, consumption frequency, and individual characteristics.

It also remains essential to continue studying the effects of chronic exposure, potential consequences during the most vulnerable stages of life, and possible interactions among different substances.

The presence of a pesticide does not mean that harm has occurred; equally, failure to demonstrate harm is not automatically proof that the substance is harmless. This distinction must guide accurate scientific communication.

Food safety is based on risk assessment, whereas analytical knowledge makes it possible to determine which substances are actually present in food. For those who wish to reduce exposure to unwanted residues even further, detailed analytical information therefore provides an additional basis for choice.

The next chapter will explore one of the most complex issues in modern toxicology: endocrine disruptors and the possible combined effects of exposure to several pesticides.

## Scientific and institutional sources

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## **National Institute of Environmental Health Sciences (NIEHS)**

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