

6. ENDOCRINE DISRUPTORS AND POTENTIAL COMBINED EFFECTS

Among the potential effects of pesticides on human health, two issues are of particular scientific interest: the ability of some substances to interfere with the hormonal system and the consequences of simultaneous exposure to multiple chemical compounds.

These are different but closely related phenomena. The first concerns substances capable of altering the mechanisms through which hormones regulate bodily functions. The second concerns the possibility that different substances present at the same time may jointly contribute to an overall biological effect.

These phenomena pose particular challenges for toxicology, especially when exposures are repeated over time and involve organisms during development. Scientific knowledge has advanced considerably, but important uncertainties remain.

The fundamental question is not only how toxic an individual substance is, but also when exposure occurs and which other substances may be present at the same time.

6.1 What are endocrine disruptors?

The endocrine system consists of glands and organs that produce substances called hormones. Hormones are chemical messengers that regulate many essential functions: growth, metabolism, reproduction, development of the nervous system, response to stress and energy balance.

The principal endocrine glands include the thyroid, pituitary, adrenal glands, pancreas and gonads, namely the ovaries and testes. Hormones are released into the bloodstream and reach cells and organs that may be far from where they are produced.

To exert their functions, many hormones interact with cellular structures called receptors, which recognise specific chemical messengers and activate particular biological responses. We can imagine the endocrine system as a complex communication network through which organs coordinate their activities.

Some chemicals originating outside the body can interfere with this communication. They are described as endocrine-active substances when they interact with the hormonal system. When this interference causes adverse biological effects through an endocrine mechanism, they are properly called endocrine disruptors.

The distinction matters: not every substance that interacts with hormones necessarily causes harm. Substances capable of interfering with the endocrine system include some pesticides, but also certain industrial contaminants, plastic components and other environmental chemicals.

The concern surrounding endocrine disruptors is that they may alter biological regulatory systems that normally operate through extremely small quantities of hormones.

6.2 How they can alter the hormonal system

Endocrine disruptors can act through different mechanisms. Some substances may mimic the action of a natural hormone, binding to its receptors and triggering a biological response. Others may occupy a receptor without activating it, thereby preventing the natural hormone from exerting its function correctly.

Still others may alter hormone production, transport, metabolism or elimination. A substance can therefore interfere with the endocrine system without chemically resembling a hormone.

One example involves the thyroid, a gland located at the front of the neck. Thyroid hormones are essential for regulating metabolism, growth and nervous-system development. Some chemicals may interfere with the production of thyroid hormones, their transport in the bloodstream, or the processes by which they are transformed and eliminated.

During fetal development, thyroid hormones play a particularly important role in brain maturation. For this reason, significant interference with thyroid function during pregnancy requires specific attention.

The endocrine system has compensatory mechanisms that can correct many hormonal fluctuations. However, these capacities are not unlimited and can depend on age, physiological conditions and the nature of the interference.

A substance does not necessarily need to destroy a cell to cause a biological effect: altering a signal that regulates its functioning may be sufficient.

Hormone mimicry

A chemical activates a hormone receptor



Receptor blockade

A chemical occupies a receptor without activation



Altered regulation

A chemical changes hormone production or clearance



6.3 Potential effects on reproduction and development

Sex hormones regulate numerous processes involved in reproduction and development. Estrogens, androgens and other hormonal messengers contribute to reproductive-organ maturation, germ-cell production and reproductive-system functioning. Some substances with endocrine-disrupting properties may alter these processes.

For certain substances and exposure conditions, experimental studies have documented changes in hormone production, alterations in reproductive development and effects on fertility.

Epidemiological research has also examined possible associations between pesticide exposure and

reproductive-health measures, including semen quality, fertility and pregnancy outcomes.

Results are not uniform across all substances and do not justify attributing the same effects to pesticides as a whole. Evidence assessment must distinguish effects demonstrated experimentally from associations observed in exposed populations.

It is, however, scientifically recognised that significant interference with hormonal systems can impair fundamental processes of development and reproduction. EU legislation therefore establishes specific criteria for identifying substances with endocrine-disrupting properties.

An active substance identified as an endocrine disruptor for human health cannot normally be approved for use in a plant protection product in the European Union, except for exemptions provided by the legislation. The existence of specific regulatory criteria itself illustrates the significance attached to the issue in protecting health.

6.4 Exposure during pregnancy and childhood

During embryonic and fetal development, many biological processes depend on extremely precise hormonal regulation. Hormones participate in organ formation, tissue differentiation and nervous-system maturation. At these stages, a significant disruption of hormonal signalling may have consequences different from those of the same disruption in an adult organism.

Some chemicals can cross the placenta and reach the fetus. Their ability to do so depends on their chemical properties and the biological mechanisms governing transfer. The presence of a substance in the fetal body does not automatically demonstrate that it has caused harm.

Nevertheless, the possibility of exposure at a particularly delicate stage makes it necessary to study potential developmental effects. After birth, too, the endocrine system continues to play a fundamental role. During childhood and puberty, hormones regulate growth, sexual maturation and many metabolic processes.

Some effects caused during development might not manifest immediately but become recognisable only later in life. This possibility has been documented for certain endocrine disruptors in experimental studies, whereas the relevance of different environmental and dietary exposures in humans requires substance- and context-specific assessment.

The timing of exposure may therefore be as important as the amount of a substance absorbed.

6.5 Low doses and windows of vulnerability

In traditional toxicology, the relationship between dose and effect is a fundamental principle for assessing a substance's hazard. Generally, as the dose of a toxic substance increases, the likelihood or severity of adverse effects also increases.

However, certain substances that interfere with the endocrine system can produce particularly complex biological responses. Natural hormones often act at very low concentrations through regulatory systems sensitive even to small changes.

For some endocrine-active substances, biological responses have been observed that do not increase in simple proportion to dose. Some experimental studies have described non-monotonic dose-response relationships, in which an effect may increase and then decrease, or follow other complex patterns.

This phenomenon has not been demonstrated for all endocrine disruptors and does not mean that every very low dose is necessarily dangerous. It means that, under certain conditions, the behaviour of a substance at low doses cannot always be predicted solely from what happens at high doses.

Another important factor concerns so-called windows of vulnerability: periods of life when particular organs or biological systems undergo especially sensitive stages of development. Nervous-system formation, sexual differentiation and reproductive-organ maturation are examples of processes dependent on coordinated hormonal signalling.

Significant interference during such periods may have consequences different from exposure after development is complete. We cannot therefore regard all exposures as equivalent simply because the same amount of a substance has been absorbed.

Dose remains fundamental, but the timing of exposure and the biological mechanism involved may profoundly alter its toxicological significance.

6.6 Combined effects of multiple pesticides

In reality, chemical exposure rarely involves a single isolated compound. Foods may contain residues of different pesticides, while water, air and other environmental components may contribute to overall exposure. A person may therefore come into contact with different substances from multiple sources and at different times.

A scientific assessment of one substance does not necessarily describe every possible consequence of its simultaneous presence with others. This becomes particularly problematic when several substances act on the same organ or biological system.

Two pesticides, for example, may interfere with different processes that contribute to thyroid function. Even if their mechanisms of action are not identical, they may jointly produce an effect on the same physiological system. Mixture toxicology studies precisely these situations.

A food may contain multiple residues, each below its own legal limit. Yet compliance with individual limits does not automatically amount to a complete assessment of all possible combinations.

This observation does not imply that a mixture is necessarily hazardous. It means that assessment of overall risk requires specific methods that consider which substances are present, their toxicological properties and levels of exposure. To address these challenges, EFSA has developed programmes for cumulative risk assessment.

6.7 Additivity, synergy and antagonism

When two or more chemicals act simultaneously on an organism, their combined effect can follow different patterns.

The first possibility is additivity. When different substances contribute to the same type of toxic effect, their overall effect may be predicted by considering each substance's contribution and its relative potency.

Consider a purely illustrative example: suppose two substances contribute to the same biological effect and, at the doses in question, each provides a contribution equivalent to a certain fraction of the dose needed to produce that effect. Those contributions may add together even when the actual quantities of the two substances differ.

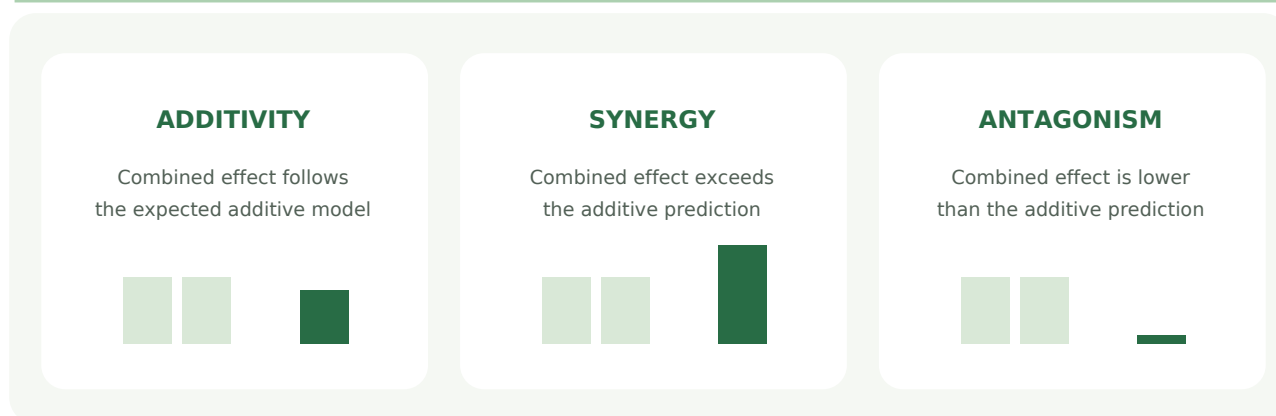
This does not necessarily mean adding the milligrams found in the food: the biological potency of each substance must also be considered.

A second possibility is synergy. Synergy occurs when the effect of the mixture is greater than predicted by the appropriate additivity model. This may happen, for example, if one substance changes the metabolism of another, slowing its elimination or increasing formation of a toxic metabolite.

A third possibility is antagonism. In this case, the combined effect is lower than predicted, for example because one substance reduces the absorption of another or alters its biological action.

These phenomena have been studied experimentally, but their occurrence and importance depend on the substances, doses and exposure conditions. Not every pesticide mixture causes synergistic effects. Nor can we assume that every substance always behaves as though it were present alone.

The scientific challenge is to predict which pattern may occur under actual conditions of human exposure.



6.8 How EFSA assesses cumulative risk

The European Food Safety Authority has developed specific methods for assessing the risk arising from simultaneous exposure to multiple pesticide residues. One principal tool is to group substances that share particular toxicological effects.

These are called Cumulative Assessment Groups (CAGs). The aim is to assess together substances capable of contributing to the same adverse effect on an organ or biological system.

EFSA's first major cumulative assessments concerned effects on the nervous system and the thyroid. They used data on residues actually detected in food, information on food consumption and toxicological data on the substances assessed.

Taking scientific uncertainties into account, those initial assessments concluded that the estimated cumulative risk for consumers, in the scenarios examined, remained below the threshold identified for possible regulatory action. This is an important result and should be accurately reported.

However, those assessments did not cover every possible substance, target organ or existing combination. The programme has therefore gradually been extended.

In 2025 EFSA published work on cumulative assessment of liver effects and initiated further research concerning reproductive function. In 2026 the first stages of cumulative assessment of pesticide effects on the kidneys were completed. The European programme aims to complete by 2030 the cumulative assessments considered necessary for pesticide residues.

Thus, scientific assessment of mixtures is already a reality, but it is not yet a comprehensive system capable of describing every potential consequence of combined exposure. This distinction matters.

It would be incorrect to claim that mixture or “cocktail” effects have never been studied. It would be equally incorrect to treat a question as definitively resolved while significant research and assessment programmes remain under way.

6.9 What we know and what we do not yet know

Current knowledge allows us to draw several scientifically robust conclusions. We know that certain chemicals can interfere with the endocrine system and cause adverse effects through such interference.

We know that some developmental stages may be particularly vulnerable to disruption of hormonal signalling. We also know that simultaneous exposure to multiple substances can produce combined effects, sometimes predictable through additivity models and sometimes influenced by more complex interactions.

But important questions remain for which science does not yet have complete answers. We do not know precisely the health effects of every possible combination of pesticides found in the environment and in food.

For not all substances do we have sufficient information to predict every potential effect of chronic low-dose exposure. We cannot always distinguish the contributions of individual pesticides from those of other environmental contaminants acting on the same biological systems.

It also remains difficult to reconstruct the consequences of exposures that can begin during fetal life and continue through different sources over many years.

These uncertainties do not justify concluding that exposures normally encountered in food are necessarily harmful. Equally, they do not justify considering the absence of every possible effect from all mixtures scientifically demonstrated.

The safety of a single substance assessed under defined conditions does not automatically provide complete knowledge of the effects of all combinations in which it may be present.

The difference between what we know and what remains to be understood is one of the central challenges of contemporary toxicology.

6.10 The precautionary principle and reducing exposure

The precautionary principle is one of the tools used by the European Union to address situations in which scientifically grounded reasons for concern exist but uncertainty remains about the nature or magnitude of potential risks.

It does not mean treating every substance whose effects are not fully understood as dangerous. It means recognising that, in certain circumstances, scientific uncertainty does not necessarily prevent proportionate protective measures.

For pesticides, this principle is particularly relevant to substances capable of interfering with the endocrine system and to exposure involving vulnerable population groups.

Exposure can be reduced through several measures: improved farming practices, prevention of pest infestations, alternative crop-protection methods, residue monitoring and development of less hazardous substances and technologies.

Progress in analytical techniques also plays an important role, enabling laboratories to detect increasingly small quantities of many substances. This capability, however, must be interpreted correctly.

The ability to detect a substance at a very low concentration does not automatically mean that the substance causes harm at that concentration. At the same time, knowing whether a residue is actually present makes it possible to distinguish food in which a substance has been detected from food in which it has not been quantified within the method's analytical limits.

Analytical information does not replace risk assessment, but gives consumers information that regulatory compliance alone cannot provide.

Where knowledge of the effects of particular combinations is still incomplete, choosing foods selected for the lowest possible presence of residues is a legitimate and informed criterion.

This is not because every residue is necessarily harmful, but because reducing avoidable exposures may be a prudent choice, without confusing that preference with proof of a specific health benefit.

Conclusion to Chapter 6

Endocrine disruptors and the combined effects of chemicals represent two of the most complex issues in food-safety assessment.

Research has demonstrated that some substances can alter hormonal mechanisms and that multiple compounds can contribute to overall biological effects. It has also highlighted the importance of developmental stages, duration of exposure and individual characteristics.

Risk-assessment methodologies continue to evolve, and European scientific authorities are gradually expanding the evidence on cumulative pesticide effects. Assessments already completed have yielded generally reassuring findings for the specific dietary scenarios examined, but scientific questions remain open.

The fact that a food complies with the limits established for each pesticide does not necessarily mean that every effect of every possible combination present has been assessed. This is not an accusation against the regulatory framework, but a description of a current limitation of available scientific knowledge and tools.

For consumers, knowing which substances are actually present in food therefore provides additional information. Food choices can be based on regulatory compliance, production methods, nutritional and sensory qualities, but also on the desire to understand and reduce the presence of chemical residues.

Science does not allow us to claim that every trace of pesticide is a danger. But it also teaches us that something not fully understood cannot be declared harmless merely because all its potential effects have not yet been demonstrated.

Knowledge does not mean fear. It means being able to make more informed choices.

Scientific and institutional sources

EFSA – Endocrine disruptors. Page updated 1 October 2026.
<https://www.efsa.europa.eu/en/topics/endocrine-disruptors>

EFSA – Chemical mixtures. Page updated in 2026; describes methods for assessing combined effects and the status of the European programme. <https://www.efsa.europa.eu/it/topics/topic/chemical-mixtures>

EFSA – Cumulative risk assessment of pesticides: frequently asked questions. Results of the first cumulative assessments concerning the thyroid and nervous system.
<https://www.efsa.europa.eu/it/news/cumulative-risk-assessment-pesticides-faq>

European Commission – Scientific criteria for identifying endocrine disruptors.
https://health.ec.europa.eu/endocrine-disruptors/process-set-scientific-criteria_it

Commission Regulation (EU) 2018/605: scientific criteria for determining endocrine-disrupting properties of active substances used in plant protection products.

EFSA/ECHA – Guidance for the identification of endocrine disruptors. Technical document on criteria and methods for identifying substances with endocrine-disrupting properties.

EFSA – Scientific reports on cumulative risk to the liver, kidneys and reproductive function, published in 2025 and 2026 and available through the chemical-mixtures topic pages.