

5. HEALTH EFFECTS: TOXICITY, THE THYROID AND ENDOCRINE DISRUPTION

WHEN A SUBSTANCE INTERFERES WITH BIOLOGY

Imagine a chemical substance designed to prevent a fungus from growing on the surface of a leaf.

The substance works because it interferes with certain processes that are essential to the microorganism's survival.

Yet fungi, plants and animals, although profoundly different organisms, share many biological mechanisms.

They all have cells, use enzymes and depend on complex chemical reactions to remain alive.

It is therefore reasonable to ask: could a substance capable of disrupting the functioning of fungal cells also affect the human body?

The answer is yes, under certain conditions.

This does not mean that every fungicide necessarily causes harm to health, or that the presence of a trace of it in food automatically represents a danger.

It means that the biological effectiveness of a substance must be accompanied by a careful assessment of its possible effects on organisms that are not the intended targets of treatment.

In the case of dithiocarbamates, this assessment has produced particularly important findings.

NOT ALL DITHIOCARBAMATES ARE THE SAME

We have already learnt that dithiocarbamates are not a single substance, but a family of chemical compounds.

Some, such as mancozeb, maneb and metiram, belong to the ethylenebisdithiocarbamate group.

Others, such as thiram and ziram, have different structures.

This distinction is fundamental from a toxicological perspective.

Substances belonging to the same family may differ in how they are absorbed by the body, converted into metabolites, reach particular organs and exert biological effects.

For this reason, it would not be scientifically correct to attribute the same toxicological properties to all dithiocarbamates.

In this discussion we will focus mainly on mancozeb and metiram, two substances widely used in the past and extensively assessed by the European Food Safety Authority (EFSA).

An important part of the findings concerns the thyroid gland.

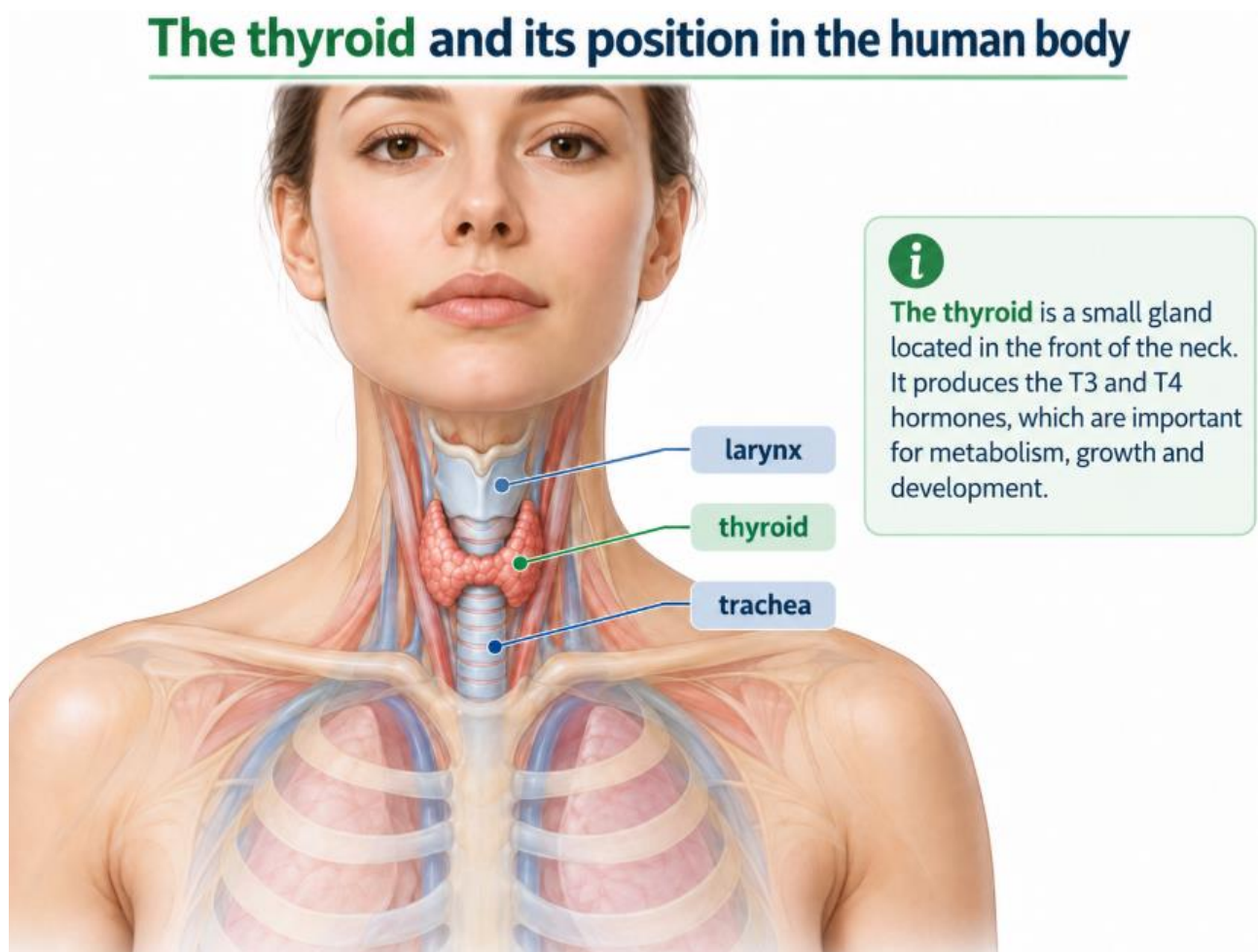
THE THYROID: A SMALL REGULATORY CENTRE

The thyroid is a gland located at the front of the neck.

It is relatively small, but performs essential functions.

It mainly produces two hormones, known as T3 and T4, which help regulate metabolism, body temperature, energy expenditure and numerous growth and development processes.

We can think of thyroid hormones as chemical messages sent to cells to regulate the speed at which they carry out certain activities.



During pregnancy and the early stages of life, these hormones are particularly important for the proper development of the nervous system.

The thyroid uses several biochemical mechanisms to produce them.

One involves an enzyme called thyroid peroxidase, or TPO, which is needed to incorporate iodine into the molecules that will become thyroid hormones.

And this is precisely where a substance we have already encountered comes into play: ethylenethiourea, or ETU.

ETU AND THYROID FUNCTION

ETU is one of the main transformation products of certain ethylenebisdithiocarbamates.

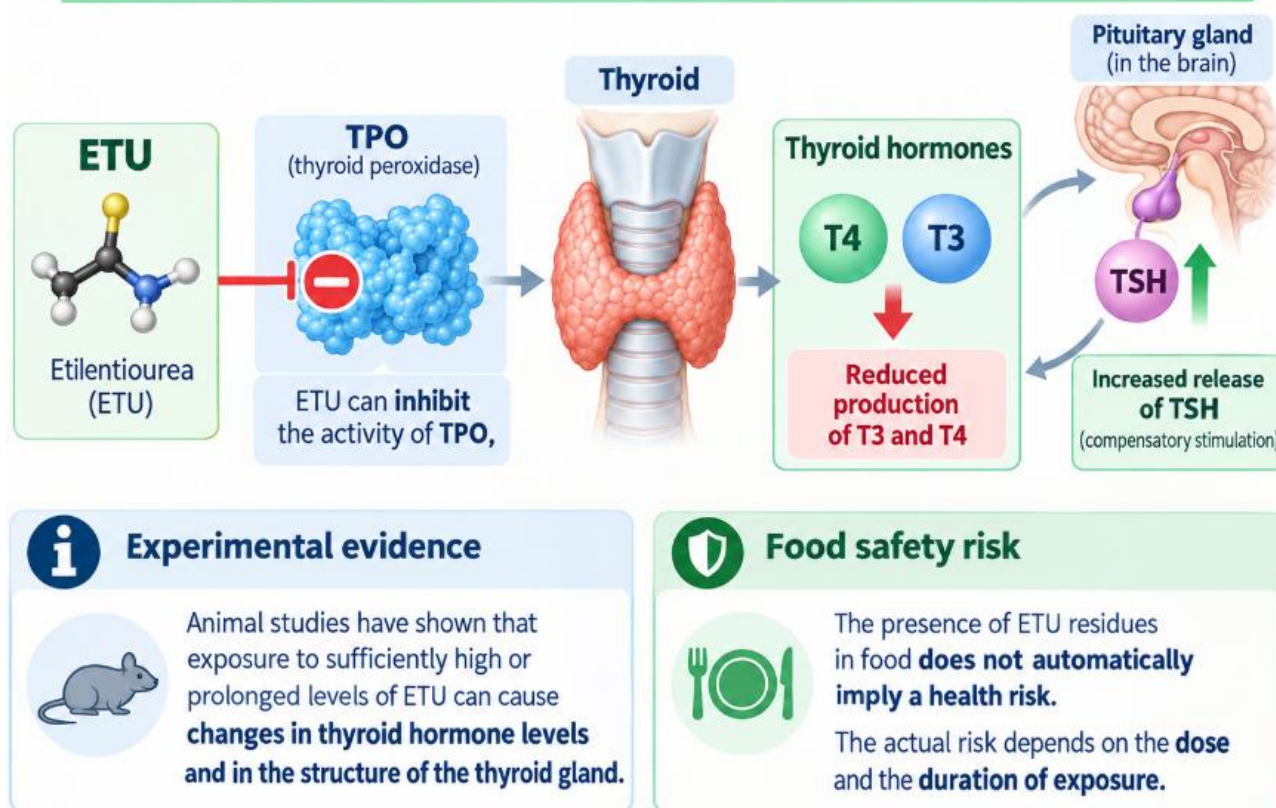
It can form during environmental degradation, food processing and the metabolism of these substances in the body.

Toxicological studies have shown that ETU can interfere with the synthesis of thyroid hormones.

One of the mechanisms identified involves inhibition of thyroid peroxidase activity.

When this activity is inhibited, thyroid hormone production may decrease.

How ETU can interfere with thyroid function



The body then attempts to compensate through a regulatory system involving the pituitary gland, a small gland situated at the base of the brain.

The pituitary gland produces a hormone called TSH, which stimulates the thyroid to work harder.

If thyroid hormone production remains insufficient, stimulation may increase and, under certain experimental conditions, cause changes in thyroid cells.

In animal studies, sufficiently high or prolonged exposure to some of these substances has produced changes in hormone levels and in the structure of the thyroid gland.

These results have made an important contribution to European toxicological assessments.

However, it is essential to distinguish a biological mechanism observed experimentally from the actual risk associated with residues in food.

Demonstrating that a substance can alter thyroid function does not demonstrate that every dietary exposure will cause that effect.

The amount absorbed and the duration of exposure remain decisive factors.

WHAT IS AN ENDOCRINE DISRUPTOR?

Our bodies have a complex chemical communication system: the endocrine system.

Hormones produced by endocrine glands reach organs and tissues, regulating numerous functions.

Certain substances foreign to the body can interfere with this system.

They are termed endocrine disruptors when they meet scientific criteria linking an alteration in hormonal activity to an adverse effect through a biologically plausible mechanism.

This is an important clarification.

Observing a change in hormone levels is not sufficient to establish that a substance is an endocrine disruptor.

It is necessary to determine whether that change is linked to a harmful effect and whether there is a causal relationship consistent with scientific knowledge.

In assessments published in 2020 and 2023, EFSA concluded that mancozeb and metiram met the European criteria for identification as endocrine disruptors in humans in relation to their thyroid mode of action.

For metiram, for example, the assessments identified hormonal changes and histological alterations of the thyroid in different animal species.

This evidence had significant regulatory consequences.

Endocrine-disrupting properties were among the decisive factors in the European decisions not to renew approval of these fungicides.

THE CASE OF MANCOZEB: EFFECTS ON DEVELOPMENT

The thyroid was not the only cause for concern to emerge from studies on mancozeb.

Experimental research also identified possible effects on embryonic and foetal development.

To understand what these findings mean, we must consider that the development of an organism before birth is an extremely complex process.

During pregnancy, cells multiply, differentiate and gradually form organs and tissues.

Disruption of particular biological processes, if sufficiently severe and occurring at critical stages, can interfere with this development.

In animal studies, mancozeb caused developmental effects, including malformations, at certain doses.

On the basis of the available evidence, mancozeb has been classified in the European Union as toxic to reproduction, category 1B, in relation to developmental effects.

This classification identifies an intrinsic hazard of the substance, based mainly on experimental evidence.

It does not mean that malformations in humans have been demonstrated as a result of normal consumption of foods containing traces of mancozeb.

It does, however, mean that the toxicological properties of the substance are considered sufficiently important to require stringent regulatory measures.

Developmental toxicity was indeed one of the reasons why the European approval of mancozeb was not renewed.

WHAT ABOUT CANCER? WHAT DO THE STUDIES SAY?

When discussing the health effects of pesticides, one of the most frequently asked questions is whether they can cause cancer.

For certain ethylenebisdithiocarbamates, this question has been investigated through long-term toxicological studies.

For metiram, for example, thyroid tumours have been observed in studies on rats.

EFSA's assessments considered these results alongside the hormonal changes observed and the possible biological mechanisms involved.

In the 2023 review, experts considered that the findings could meet the criteria for classifying metiram as a suspected carcinogen, category 2.

It is important to understand that not all tumours observed in laboratory animals necessarily have the same relevance to humans.

Their mechanism of formation, the doses used, differences between species and available information on human exposure must all be investigated.

The potential carcinogenicity of a substance and the likelihood that it will cause cancer under specific exposure conditions are not the same thing.

A sound scientific assessment must consider both.

This is why it is important to avoid both automatic alarmism and the underestimation of experimental findings.

EFFECTS ON THE NERVOUS SYSTEM

Another noteworthy aspect concerns the nervous system.

Its function depends on the transmission of electrical and chemical signals between billions of cells.

Some substances can interfere with these processes or damage cellular structures needed to transmit nerve impulses.

EFSA's assessment of mancozeb also considered neurological effects observed in experimental studies on rats.

These included alterations in nervous tissue at certain doses.

These observations contributed to the characterisation of the fungicide's toxicological profile.

However, they must not be confused with proof of neurological damage in humans caused by normal levels of dietary residues.

Toxicological studies are intended precisely to identify the effects a substance may cause and the conditions under which they arise.

Assessing dietary risk is a subsequent step.

HOW MUCH DOES THE DOSE MATTER?

We have reached the most important question for consumers.

If a substance can cause harmful effects, how can we assess the risk associated with its presence in food?

One of the fundamental principles of toxicology concerns the dose.

The same substance may have very different consequences depending on the amount absorbed and the duration of exposure.

Think, for example, of a medicine.

At a therapeutic dose it may be beneficial, whereas at much higher doses it may cause toxic effects.

The general principle also applies to many chemical substances present in the environment.

To assess pesticides, scientific bodies use experimental studies that allow them to identify the doses at which particular effects are observed.

Toxicological reference values can be derived from these data.

Among the most important are:

ADI — Acceptable Daily Intake. This is the amount of a substance that, according to available knowledge, can be consumed every day throughout a lifetime without appreciable health risk.

ARfD — Acute Reference Dose. This is an estimate of the amount that can be consumed over a short period, generally within a day or a single meal, without appreciable risk.

These values are generally expressed in milligrams of substance per kilogram of body weight.

Uncertainty factors are applied when deriving them, taking account, among other things, of differences between experimental animals and humans and variability between individuals.

Reference values do not represent a sharp boundary beyond which harm automatically occurs.

They are scientific tools used to assess exposure and protect health.

ETU AND DIETARY RISK ASSESSMENT

Let us return once more to ethylenethiourea.

In EFSA's assessment of metiram, the following toxicological reference values were used for ETU:

- 0.002 mg per kilogram of body weight per day for chronic exposure (ADI);
- 0.01 mg per kilogram of body weight for acute exposure (ARfD).

To understand the significance of the first value, imagine an adult weighing 70 kilograms.

Multiplying 0.002 mg by 70 gives 0.14 milligrams per day.

According to those reference values, this amount represents the acceptable daily intake of ETU for a person of that weight.

It is not a limit directly applicable to a single food, nor does it mean that reaching that dose automatically causes harm.

To assess risk, it is necessary to estimate how much ETU is actually ingested through all the foods consumed.

EFSA uses models that take account of residues in different food categories and the consumption patterns of different population groups.

Children, for example, may be particularly important in these assessments because they consume different amounts of food relative to their body weight compared with adults.

In its 2023 review of dithiocarbamates, EFSA presented various ETU exposure scenarios. Some estimates were below their respective toxicological reference values, but experts also highlighted uncertainties and gaps in the available data.

In particular, the lack of information on ETU levels in some foods could lead to an underestimation of overall exposure.

This is a concrete example of why scientific assessment must consider not only the results of calculations, but also the quality and completeness of the information used.

HAZARD AND RISK: A FUNDAMENTAL DISTINCTION

At this point, we can clarify two words that are often used as synonyms in everyday language: hazard and risk.



In toxicology, they have different meanings.

Hazard is the intrinsic capacity of a substance to cause an adverse effect.

Risk is the probability that the effect will occur under particular conditions of exposure, also taking account of its severity.

We can understand this difference through an example.

The sun emits ultraviolet radiation that can damage the skin.

This is a hazardous property of exposure to UV rays.

The actual risk, however, depends on the intensity of the radiation, time spent in the sun, individual characteristics and any protective measures taken.

Something similar applies to food contaminants.

Knowing the hazard posed by a molecule is essential, but not sufficient to establish the risk associated with a particular concentration in food.

Exposure must also be assessed.

At the same time, recognising the importance of dose does not mean that every substance necessarily has a clearly identifiable safe threshold.

For certain toxicological effects, particularly when biological mechanisms are complex or knowledge is incomplete, assessment may require different approaches and special precautions.

Science does not always have definitive answers.

WHAT CAN WE CONCLUDE?

The toxicological history of dithiocarbamates teaches us something important.

Substances used in agriculture for decades may be reassessed as knowledge of their biological effects improves.

In the case of mancozeb and metiram, studies have highlighted significant concerns, particularly regarding the endocrine system and thyroid function.

Important concerns about developmental toxicity have also emerged for mancozeb.

This evidence contributed to the European decisions not to renew their approval.

But we must avoid drawing conclusions that go beyond what the data support.

Not all dithiocarbamates have the same toxicological characteristics, and not every measurable residue in food necessarily results in an appreciable risk.

Assessment requires knowledge of the substance, its concentration, possible metabolites, the amount consumed and the scientific uncertainties that remain.

There is one final question.

If some dithiocarbamates have different toxicological properties, how useful is an analysis that simply measures the total amount of carbon disulphide without identifying the original substance with certainty?

The answer will lead us to one of the most interesting aspects of this family of fungicides: the limitations of traditional analytical methods and the true meaning of laboratory results.

We will explore this in Chapter 6.

SCIENTIFIC REFERENCES FOR CHAPTER 5

1. EFSA (2020). Peer review of the pesticide risk assessment of the active substance mancozeb. EFSA Journal, 18(12), 5755. Assessment of toxicity and effects on the thyroid, development and nervous system. [Read the EFSA scientific publication.](#)
2. EFSA (2023). Peer review of the pesticide risk assessment of the active substance metiram. EFSA Journal, 21(4), 7937. Assessment of endocrine-disrupting properties, chronic toxicity and thyroid effects. [Read the EFSA scientific publication.](#)

3. EFSA (2023). Review of the existing maximum residue levels for dithiocarbamates according to Article 12 of Regulation (EC) No 396/2005. EFSA Journal, 21(5), 7987. Review of residues, assessment of dietary exposure and toxicological considerations concerning ETU. [Read the EFSA scientific publication](#).
4. European Commission (2020). Commission Implementing Regulation (EU) 2020/2087 concerning the non-renewal of approval of the active substance mancozeb. [Read the regulation on EUR-Lex \(Italian\)](#).
5. European Commission (2023). Commission Implementing Regulation (EU) 2023/2455 concerning the non-renewal of approval of the active substance metiram. [Read the regulation on EUR-Lex \(Italian\)](#).