

9. HEALTH EFFECTS AND EUROPEAN LEGISLATION

TWO FUNGICIDES, TWO DIFFERENT TOXICOLOGICAL STORIES

Let us imagine two bunches of grapes from different vineyards.

In the first, residues attributable to a dithiocarbamate are detected. In the second, phosphonic acid is identified.

Both samples contain substances linked to the use of fungicides.

We might think that the health risks are similar.

But that would be a mistaken conclusion.

As we discovered in the previous chapters, dithiocarbamates include molecules with different toxicological characteristics. Some, such as mancozeb and metiram, have been subject to important restrictions in the European Union, also in relation to their effects on the endocrine system.

Fosetyl-aluminium and phosphonic acid, by contrast, have a different toxicological profile.

The available studies have not identified, for these substances, the same set of concerns that led to the non-renewal of the approval of mancozeb and metiram.

This does not mean that they are completely harmless.

It means that their assessment must be based on their specific properties, the doses capable of producing effects, and the routes of exposure.

Toxicology does not judge a substance on the basis of the category to which it belongs, but on the basis of the available scientific evidence.

WHAT HAPPENS WHEN FOSETYL-ALUMINIUM ENTERS THE BODY?

When we ingest a chemical substance, our body may absorb it, distribute it to the tissues, transform it and finally eliminate it.

These processes make up what toxicologists call toxicokinetics.

In the case of fosetyl-aluminium, experimental studies have shown that the substance is rapidly absorbed and undergoes important transformations.

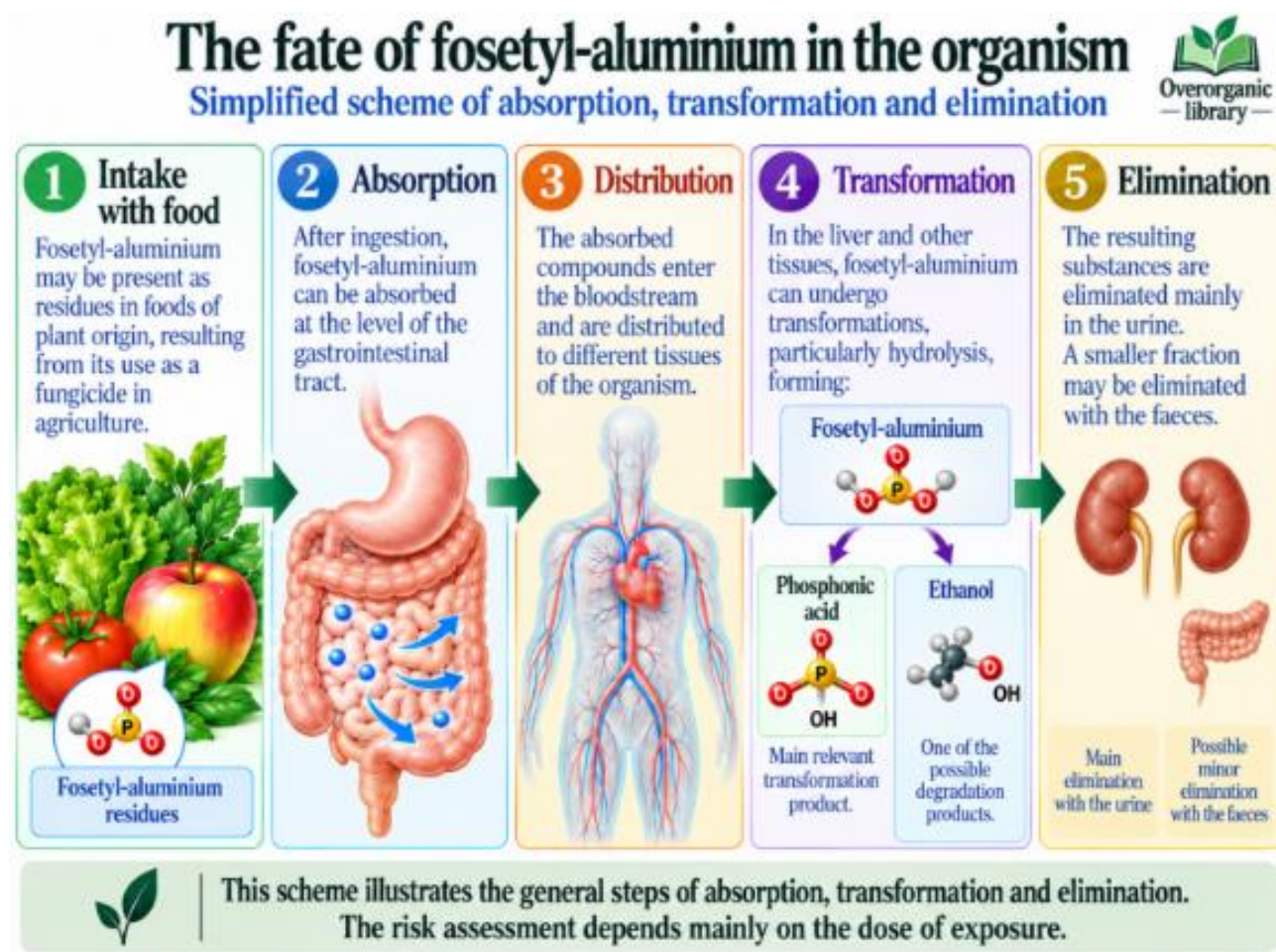
Among the resulting products are phosphonates, eliminated mainly through the urine, and ethanol, which can be further metabolised into carbon dioxide.

Research has also shown that the original compound does not tend to remain for long in the body in the same chemical form.

This behaviour is important because toxicological risk does not depend only on the initial substance.

The molecules formed during metabolism must also be taken into account.

For this very reason, European assessments of fosetyl-aluminium also include phosphonic acid, its main transformation product relevant to food residues.



ACUTE TOXICITY: WHAT HAVE THE STUDIES SHOWN?

Acute toxicity describes the effects that may occur after a single or short-term exposure.

Studies on fosetyl-aluminium have shown relatively low acute toxicity by the oral, dermal and inhalation routes.

This means that, under the experimental conditions studied, relatively high doses were needed to produce significant acute toxic effects.

But there is an important distinction.

Low acute toxicity by ingestion does not imply that a substance is free of all hazards.

Fosetyl-aluminium, for example, has properties that require particular attention for the eyes, and its classification includes hazard statements relating to eye damage.

It is an example of how the same substance may have different effects depending on the route of exposure.

For the consumer, however, the main issue concerns intake through food.

To assess it, it is not enough to know the acute toxicity: the effects of repeated exposures must also be examined.

WHAT HAPPENS AFTER PROLONGED EXPOSURES?

To understand the chronic effects of a substance, researchers conduct studies in which groups of animals are exposed to different doses for prolonged periods.

These experiments make it possible to identify any alterations in body weight, organ function, biochemical parameters and tissue structure.

In the case of fosetyl-aluminium, studies have shown effects on certain organs at sufficiently high doses.

Among those considered in the European assessments are alterations of the urinary system, the kidneys and other tissues.

In a two-year study in rats, stones, inflammatory processes and changes in the bladder wall were observed at the highest doses.

Bladder tumours were also observed in some animals exposed to the highest doses.

This result may seem particularly worrying.

But scientific interpretation requires a further step.

Studies on the biological mechanism indicated that these tumours were associated with phenomena of chronic irritation caused by the experimental exposure conditions.

European experts therefore considered this mechanism not relevant to humans at realistically expected exposures.

Overall, EFSA's 2025 assessment concluded that fosetyl-aluminium is unlikely to be carcinogenic.

This conclusion does not stem from the absence of any alteration observed in the experiments, but from the joint analysis of the effects, the doses and the mechanisms that produced them.

DOES PHOSPHONIC ACID HAVE THE SAME PROPERTIES?

Phosphonic acid is a compound that is chemically different from fosetyl-aluminium.

It would therefore not be correct to assume that the two substances have identical toxicological properties.

To assess phosphonic acid, specific studies were used, also conducted with its sodium and potassium salts.

The results showed low acute toxicity and did not provide evidence of genotoxicity in the tests considered.

Genotoxicity is the ability of a substance to damage the genetic material of cells.

This is a particularly important property because some types of genetic damage can contribute to the development of tumours.

In the available studies on phosphonic acid, no signals emerged that would indicate a genotoxic potential.

In experiments with prolonged exposures, however, effects such as changes in certain urinary parameters, variations in organ weight and alterations related to fluid balance were observed at certain doses.

Here too, therefore, the substance is not devoid of biological activity.

The key point is to establish at what doses the effects occur and how far those doses are from consumers' dietary exposure.

IS FOSETYL-ALUMINIUM AN ENDOCRINE DISRUPTOR?

In Chapter 5 we discovered that mancozeb and metiram were identified as endocrine disruptors for humans on the basis of European assessments.

But what do we know about fosetyl-aluminium?

The issue was the subject of further scientific investigation.

In 2025 EFSA published an updated assessment of fosetyl, also examining the data relating to possible effects on hormonal systems.

The experts considered in particular the mechanisms linked to oestrogens, androgens, steroid hormone production and the thyroid.

The conclusion was that, on the basis of the available evidence, fosetyl does not meet the European criteria to be identified as an endocrine disruptor for humans and for non-target organisms.

This is an important conclusion, especially when compared with those formulated for some dithiocarbamates.

It does not mean that research on the biological effects of phosphonates has been definitively concluded.

It means that, according to the available scientific assessment, the regulatory criteria required for that specific classification are not met.

This distinction reminds us once again why it is not correct to attribute the same toxicological characteristics to all fungicides.

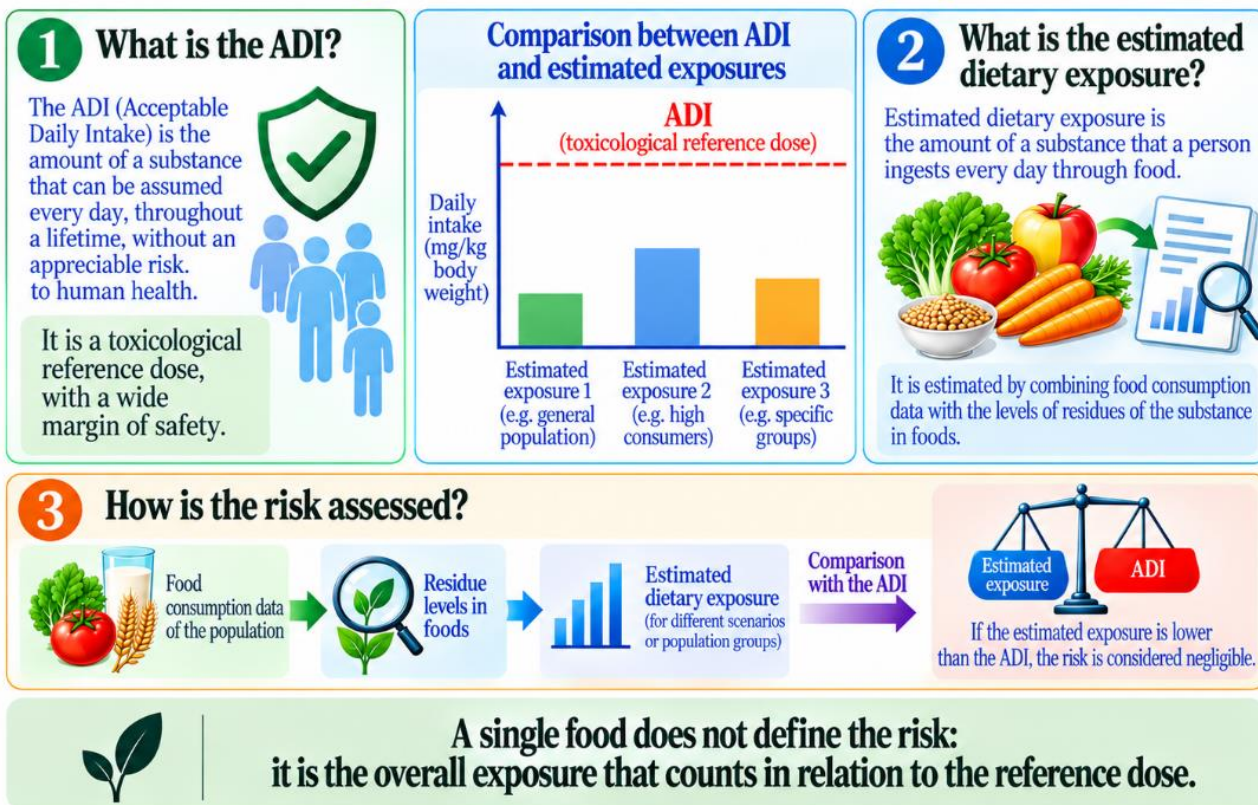
THE ACCEPTABLE DAILY INTAKE

How can we translate all these experimental results into a concrete assessment of food safety?

One of the most important tools is the acceptable daily intake, abbreviated as ADI.

The acceptable daily intake (ADI)

Toxicological reference dose and dietary exposure



The ADI represents the amount of a substance that can be ingested every day, for a lifetime, without appreciable risk to health according to the available knowledge.

It is expressed in milligrams per kilogram of body weight per day.

To understand the concept, let us imagine an adult weighing 70 kilograms.

If a substance has an ADI of 1 mg/kg of body weight per day, the corresponding value for that person will be 70 milligrams per day.

This does not mean that ingesting 71 milligrams automatically causes harm.

The ADI is a reference value derived from toxicological studies by applying uncertainty and protection factors.

For fosetyl-aluminium, EFSA's 2025 assessment reports an ADI of 1 mg/kg of body weight per day.

For phosphonic acid, EFSA's joint review of 2021 used two reference values:

- 2.25 mg/kg of body weight per day, the value applicable in the assessment at that time;
- 1 mg/kg of body weight per day, a more precautionary value proposed in the scientific review process.

In the second case, the same exposure level represents a greater percentage of the ADI.

This difference becomes particularly important when evaluating the dietary intakes of the most highly exposed populations.

WHAT DO THE DIETARY EXPOSURE ESTIMATES TELL US?

At this point we can ask a concrete question.

If phosphonic acid is present in various foods, what fraction of the acceptable daily intake could be reached through the diet?

To answer this, EFSA uses models that combine residue data with the dietary habits of different population groups.

One of these tools is PRIMo, the European model for assessing pesticide residue intake.

Not everyone, in fact, consumes the same foods in the same amounts.

A small child, for example, may eat a relatively large quantity of fruit in relation to his or her body weight.

For this reason, assessments include different consumer groups, with particular attention to those potentially most exposed.

In the 2021 review on phosphonic acid, EFSA obtained two particularly interesting results.

Maximum chronic exposure estimated in EFSA models (2021)

36%

Of the ADI of 2.25 mg/kg of body weight per day

80%

Of the proposed ADI of 1 mg/kg of body weight per day

Both results refer to the group of Dutch toddlers, which showed the highest exposure in the scenarios considered. Source: EFSA, 2021.

The difference does not depend on a change in the amount of residues present in food, but on the use of two different toxicological reference values.

The foods contributing most to the estimated exposure included apples, potatoes and wheat.

EFSA did not identify an apparent risk for consumers in the scenarios assessed, but pointed out that some information needed to complete the assessment was lacking.

Consequently, the conclusions on dietary exposure were considered indicative.

This is a fundamental aspect of scientific research: a reassuring result must not conceal the uncertainties on which it was built.

AND EXPOSURE TO ALUMINIUM?

The name fosetyl-aluminium contains a chemical element that we must not overlook: aluminium.

When the compound transforms, it may release aluminium-containing species in addition to phosphonic derivatives.

Aluminium is a very widespread element in the environment and can reach food through different sources.

Its toxicological assessment, however, does not coincide with that of phosphonic acid.

In the updated 2025 review, EFSA drew attention precisely to the need to consider the contribution of aluminium resulting from the use of fosetyl-aluminium.

This aspect is important because overall exposure to aluminium does not necessarily come from a single source.

To assess the risk, the set of relevant dietary contributions must be considered.

EFSA therefore recommended further investigation of consumers' exposure to aluminium associated with the uses of fosetyl-aluminium.

The case shows how a plant protection product must be assessed not only through its active substance and its metabolites, but also by considering other toxicologically relevant components.

HOW DO EUROPEAN LIMITS WORK?

Let us imagine buying a bag of apples and having them analysed.

The laboratory determines a concentration of phosphonic acid.

How can we know whether the product complies with the legislation?

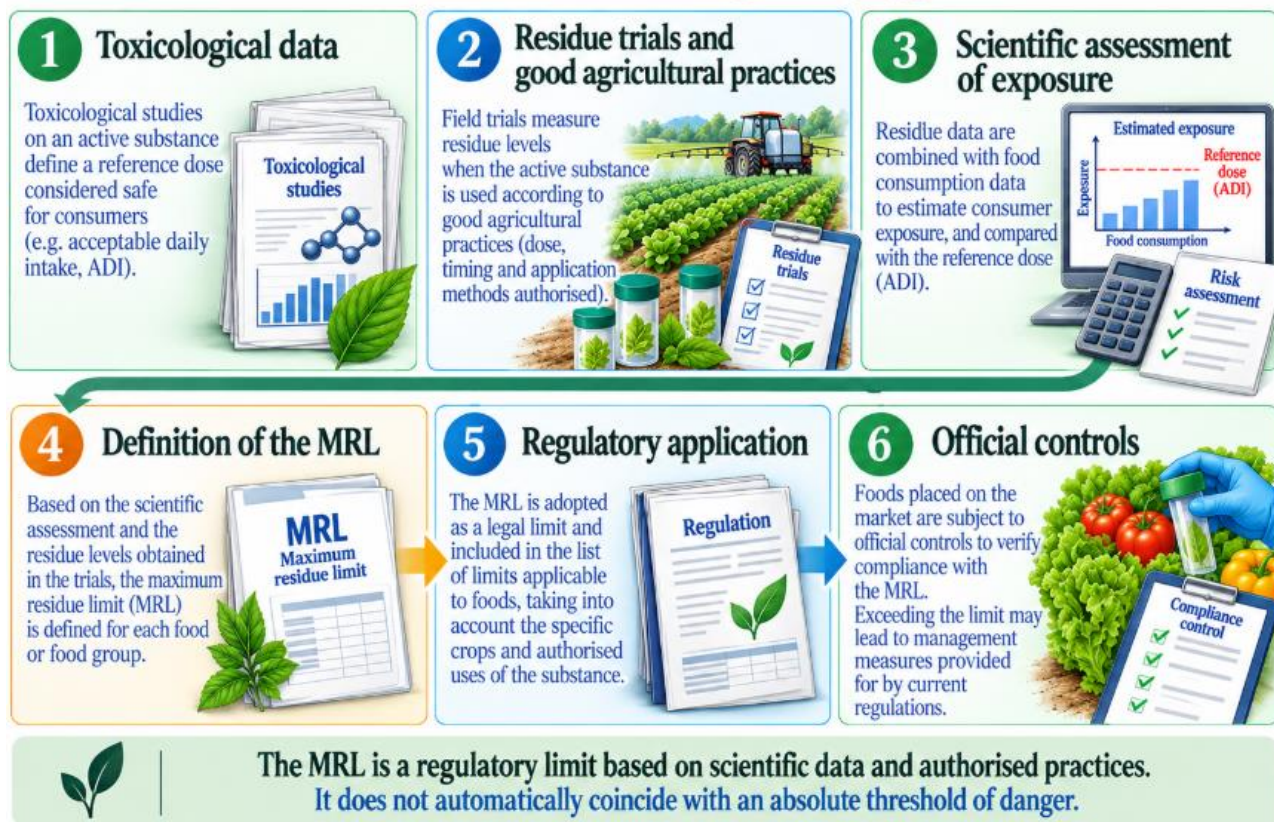
We must compare the result with the maximum residue limit, abbreviated as MRL.

The MRL is the maximum level of a pesticide residue legally permitted in or on a given food.

The value is not established arbitrarily.

How maximum residue limits (MRL) are defined

From scientific assessment to regulatory application



To define it, experimental residue data, the relevant agricultural use conditions and consumer safety assessments are taken into account.

It is important, however, to clarify a distinction.

The MRL does not necessarily coincide with the threshold above which a substance begins to cause toxic effects.

It is first and foremost a regulatory limit, which must be compatible with the protection of health.

A food that exceeds the limit may be non-compliant even if the exceedance does not necessarily involve an immediate health risk.

Conversely, compliance with the MRL does not mean that no residue is present in the food.

It means that the measured concentration complies with the maximum level established by the legislation.

Health risk assessment requires a separate analysis, which considers exposure and the toxicological characteristics of the substance.

THE REGULATORY TURNING POINT OF 2024

For many years, European legislation used an overall residue definition that included fosetyl, phosphonic acid and the related salts, expressed as fosetyl.

This approach presented some interpretative difficulties.

As we have discovered, in fact, phosphonic acid may originate from different substances and sources.

It would therefore not be correct to attribute its presence exclusively to fosetyl-aluminium.

In 2024 the European Commission adopted Regulation (EU) 2024/2619, which amended Annexes II and III to Regulation (EC) No 396/2005.

The new system distinguishes fosetyl from phosphonic acid and its salts.

In particular, for phosphonic acid the residue definition for enforcement purposes is:

Phosphonic acid and its salts, expressed as phosphonic acid.

The amendment applies from 29 April 2025, with transitional provisions for products already placed on the market before that date.

This change does not mean that controls have been removed.

On the contrary, it makes it possible to distinguish better the substances subject to analytical determination and to apply the respective limits.

It is a concrete example of how European legislation can evolve to incorporate new scientific knowledge.

WHY DO LIMITS DIFFER BETWEEN FOODS?

A question arises spontaneously.

If a substance is the same, why can the maximum residue limit change from one food to another?

The answer depends mainly on the conditions of agricultural use, the characteristics of the crops and the available experimental data.

A treatment on a vineyard does not necessarily produce the same amount of residues as a treatment on a citrus grove.

Application timings, plant growth, metabolism and harvesting methods may also differ.

For this reason, specific limits are established for numerous food categories.

Risk assessment then considers the amounts that people may ingest through the overall consumption of foods.

A higher MRL, therefore, does not necessarily mean that a food is considered less important for health.

It means that, for that combination of substance and agricultural product, a certain maximum level has been established within the regulatory system.

A LEGAL LIMIT IS NOT A QUALITY TARGET

Let us return to our apples.

Let us imagine we have two samples belonging to the same food category.

Both comply with the European limit for phosphonic acid.

In the first, the concentration is just below the MRL.

In the second, the laboratory is unable to quantify the substance because its concentration is below the limit of quantification of the method used.

From a regulatory point of view, both may be compliant.

From an analytical point of view, however, the results are different.

In the second sample, no concentration equal to or above the method LOQ was quantified.

This does not prove that the substance is completely absent, but it documents a concentration lower than that quantifiable with the procedure adopted.

It is an important distinction when seeking quality standards that are stricter than simple regulatory compliance.

However, a misunderstanding must be avoided.

A lower concentration does not necessarily imply a measurable reduction in health risk, especially when both exposures are already very low compared with the toxicological reference values.

The search for the lowest quantifiable presence and the assessment of health risk are two related, but not identical, objectives.

The former describes an analytical characteristic of the food.

The latter requires a toxicological assessment of exposure.

WHAT DOES THE STORY OF FOSETYL-ALUMINIUM TEACH US?

We started with two bunches of grapes, both potentially containing fungicide residues.

We discovered that substances used for similar agricultural purposes may have very different toxicological characteristics.

Fosetyl-aluminium and phosphonic acid have been the subject of numerous scientific assessments.

Studies have shown biological effects at certain doses, but have not identified the same pattern of endocrine concerns that characterised some dithiocarbamates.

EFSA also examined the possibility of chronic exposure through the diet, identifying scenarios that did not show an apparent risk for consumers, although some uncertainties remained.

European legislation subsequently modified the residue definition and the related maximum limits, in order to take account of knowledge about the behaviour of the substances.

But above all we have learned that food safety cannot be described through a single number.

To interpret a result correctly, it is necessary to know the substance measured, its toxicity, the amounts ingested, the analytical method and the regulatory framework.

A legal limit tells us whether a food is compliant. A toxicological assessment helps us understand the risk. A chemical analysis tells us which substances we have been able to measure.

These are three different kinds of information, all of them important.

In the next and final chapter, we will bring together the knowledge acquired on dithiocarbamates and phosphonates to address a fundamental question: what can laboratory analyses really demonstrate, and where do their limits begin?

SCIENTIFIC REFERENCES FOR CHAPTER 9

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2. EFSA (2021). Reasoned opinion on the joint review of maximum residue levels (MRLs) for fosetyl, disodium phosphonate and potassium phosphonates according to Articles 12 and 43 of Regulation (EC) No 396/2005. EFSA Journal, 19(8), 6782. Joint review of residues and assessment of chronic consumer exposure to phosphonic acid.[Read the EFSA scientific publication.](#)
3. European Commission (2024). Regulation (EU) 2024/2619 of 8 October 2024, amending Annexes II and III to Regulation (EC) No 396/2005 as regards maximum residue levels for fosetyl, potassium phosphonates and disodium phosphonate.[Read the regulation on EUR-Lex \(Italian\).](#)
4. European Parliament and Council (2005). Regulation (EC) No 396/2005 on maximum residue levels of pesticides in food and feed of plant and animal origin.[Read the regulation on EUR-Lex \(Italian\).](#)