

# VigilAnses

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## Monitoring ciguatera poisoning to identify contaminated fish species

Ciguatera is a type of food poisoning caused by eating fish contaminated with ciguatoxins. It is most often responsible for digestive, dermal, cardiovascular and neurological signs, the latter sometimes lasting several weeks. Although tropical and subtropical regions are known endemic areas, indigenous cases have also been recorded off the coast of Europe, mainly in Madeira (Portugal) and the Canary Islands (Spain). Toxin analyses in leftover fish, if available, can confirm the diagnosis. ANSES and the poison control centres conducted a review of cases in 2020, a year marked by the absence of ciguatera poisoning among tourists from metropolitan France visiting the overseas territories or foreign countries, due to the drop in tourism caused by the COVID-19 pandemic. Prospective monitoring was set up in 2021. Poisoning victims were asked to freeze their leftover meals in a plastic bag at -18°C, so that they could be analysed for toxins.



### Ciguatera: a type of food poisoning known in French as *la gratte*

Ciguatera is a type of food poisoning caused by eating fish contaminated with marine biotoxins known as ciguatoxins. These are produced by microscopic algae (mainly *Gambierdiscus* spp. dinoflagellates) found in coral reefs. They are ingested by small herbivorous fish, which in turn are eaten by larger carnivorous fish (jacks, groupers, moray eels, barracudas, etc.) where they accumulate in the tissues and organs, most often in the liver and viscera. Ciguatoxins are resistant to cooking and freezing and do not affect the taste of fish. They can also be found in molluscs (gastropods, bivalves) which, if consumed by humans, also pose a risk of poisoning [1].

The first signs of poisoning are usually digestive (abdominal pain, nausea, vomiting, diarrhoea) and occur a few minutes to a few hours after eating contaminated fish. They are quickly followed by neurological disorders such as tingling and itching (hence the common French name *la gratte*) in the hands, feet and face, reversal of hot and cold sensations, muscle pain and profuse sweating.

This may be accompanied by a slowing of the heart rate and a drop in blood pressure, which can last for three or four days.

Balance disorders, visual hallucinations and even a depressive syndrome may be observed in some cases.

While the digestive signs disappear on their own after a few days, the neurological symptoms may last for several weeks. Treatment is only symptomatic. The prognosis may be unfavourable in the case of paralysis of the respiratory muscles or heart attack; however, ciguatera is rarely fatal.

Patients are particularly susceptible to symptoms recurring after ingestion of alcohol or tropical fish flesh, even several months after poisoning. The mechanism of these resurgences is still poorly understood.

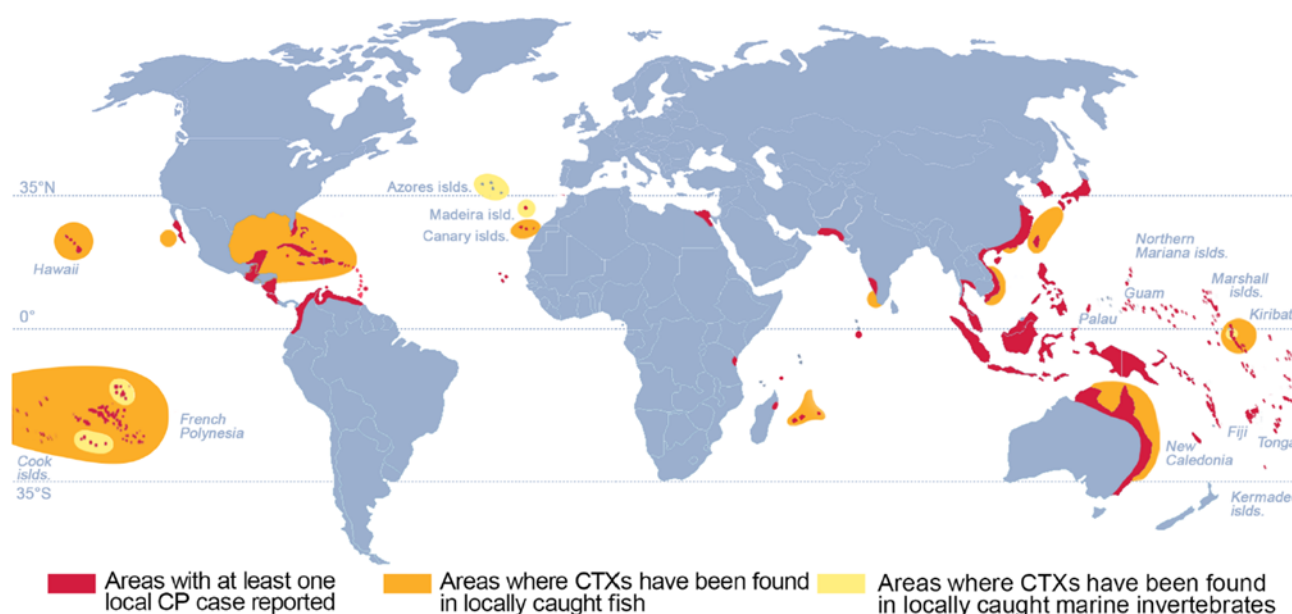
### Northward extension of ciguatera risk areas

Ciguatera is endemic to tropical and subtropical regions where warm waters support coral reefs. It is therefore found throughout the year in the South Pacific (French Polynesia, New Caledonia, Australia, etc.), the North Pacific (Hawaii, Japan, etc.), the Indian Ocean (Madagascar, Reunion, Mayotte, etc.) and the Caribbean (Cuba, Haiti, Guadeloupe, Martinique, etc.) (Figure 1).

Ciguatoxins are grouped into three families according to their geographical origin: Pacific Ocean (P-CTX), Caribbean (C-CTX) and Indian Ocean (I-CTX)<sup>1</sup>.

In France, most French overseas territories are affected. Over the last 15 years or so, the range of ciguatoxins has also been spreading towards the Atlantic islands of Spain and Portugal, probably favoured by global warming. For example, several cases of ciguatera due to the consumption of groupers and amberjacks caught in the waters of Madeira and the Canary Islands (Macaronesia) have been reported. In addition, the

microalga *Gambierdiscus spp.* has been found in different parts of the Mediterranean: in the Balearic Islands (Spain) and in the waters around Crete (Greece). Even if the presence of this microalga is not always synonymous with fish contamination, the emergence of ciguatera risk areas in Europe cannot be ruled out. The "EuroCigua" project, which was co-funded by the European Food Safety Authority (EFSA) and in which ANSES participated, sought to acquire new health and environmental knowledge on the risks of ciguatera in Europe [2].



**Figure 1** : Geographical distribution of ciguatera and ciguatoxins [CP: ciguatera poisoning; CTXs: ciguatoxins]. Source: Bulletin of the SCA Platform for food-chain surveillance (BusCA) [3].

### Increased need for monitoring to identify contaminated fish species

Knowledge of the risk of ciguatoxin contamination in fishery products is essential to ensure that prevention and control measures are constantly updated in order to limit population exposure. The Directorate General for Food (DGAL) is responsible for implementing these measures in France. Ciguatoxin poisoning cases must be notified to Regional Health Agencies and/or Departmental Directorates for the Protection of Populations, which must then carry out investigations if two or more diners are poisoned at the same time, as is the case for

all foodborne illness outbreaks (FIOs). Each year, *Santé Publique France* publishes a review of the number of FIOs and the factors that may have contributed to their occurrence.

If the ciguatera diagnosis is based on symptoms consistent with poisoning occurring following the consumption of fish from species known to pose a risk, this can be confirmed by ciguatoxin analyses in the leftovers of the incriminated fish, if available. In the event of suspected poisoning, tests are carried out on imported or locally caught fish, depending on the circumstances, by ANSES's National Reference Laboratory for marine biotoxins (NRL-MB).

1. It should be noted that the initial digestive disorders most often occur in cases of poisoning related to fish from the Atlantic, and may be absent for those from the Indian and Pacific Oceans [3, 4].

Where commercial products are involved, the health authorities can then promptly report contaminated fish consignments to other European Member States<sup>2</sup> in order to get them withdrawn from the market. Prefectoral orders are issued in the French overseas territories whenever a new fish species is identified as responsible for a case, in order to ban the fishing and sale of species from local areas at risk.

A retrospective review of ciguatera cases recorded by poison control centres identified 130 cases of poisoning between 2012 and 2019 [5]. Between one and 15 diners were involved in the 52 incriminated meals. The annual number of incriminated meals varied from two to 12 (on average 6.5 meals per year) and the fish mainly involved were groupers, snappers, jacks, parrotfish and barracudas.

In order to supplement knowledge of the occurrence of ciguatera poisoning, ANSES, which is responsible for the toxicovigilance scheme, conducted a specific review for 2020 and set up prospective monitoring of such poisoning cases.

#### **Noteworthy in 2020: no ciguatera poisoning cases linked to tourism**

Based on an expert appraisal of medical files by a toxicologist from a poison control centre, 13 cases of ciguatera that led to calls to poison control centres in 2020 were identified.

The poisoning victims, ten adults and three children (all siblings), had fallen ill after five meals: three meals involving one person (i.e. three individual poisoning cases) and two meals involving five people each (i.e. two multiple poisonings). Twelve of them were first-time poisonings and one person had a resurgence of symptoms following consumption of a tropical fish, four years after an initial episode in the Caribbean.

The poisonings were all reported after a fish meal in the French overseas territories: two meals consumed in Guadeloupe (including one in Marie-Galante), one in Martinique, one in Saint-Martin and one in Mayotte.

With four meals the fish were identified: two jacks and a barracuda caught locally, and wahoo imported from Vietnam. These species are already known to be vectors of ciguatera. For the fifth meal, the people involved had eaten fillets of an unknown species of fish in a restaurant.

The fish were grilled (short cooking time) for two meals and prepared in soup (very long cooking time including the fish heads, a part of the animal that can be more contaminated) for the other three. For one of the meals (wahoo imported from Vietnam), the presence of ciguatoxins was confirmed in

the leftover fish by analyses carried out by ANSES's NRL-MB.

Symptoms started with classic digestive disorders in 12 patients, and continued with general and neurological signs in all cases. The duration of symptoms varied from one to 10 days for the 12 patients with acute primary poisoning. They lasted one month for the patient with the resurgence.

All patients had mild to moderately persistent transient, non-life-threatening symptoms.

While the number of meals causing cases of ciguatera was comparable to those of previous years, 2020 was characterised by the fact that all the cases occurred in people living in the overseas territories. Indeed, between 2012 and 2019, 56% of contaminated meals had been consumed by tourists from metropolitan France exposed in tropical and subtropical regions (French overseas territories or foreign countries), 38% by people living overseas and exposed at home, and 6% by people exposed in metropolitan France to imported fish. In 2020, no tourists from metropolitan France fell ill after eating contaminated fish during holidays in endemic areas. This is likely due to the context of the COVID-19 pandemic, which severely restricted travel to tropical regions. The temporary closure of restaurants in metropolitan and overseas France may also have helped reduce the risk of food poisoning. The review for 2021, which is still in the same pandemic context, will confirm or refute this hypothesis.

#### **Establishment of prospective monitoring of ciguatera cases recorded by poison control centres**

Following this review, ANSES and the poison control centres set up "real-time" prospective monitoring of ciguatera cases from 2021 onwards, using a specific questionnaire to better document the characteristics of the incriminated fish (fish name, place where it was fished, place of purchase or consumption, etc.) and the circumstances of exposure (method of preparation, quantity consumed, etc.).

When a person calls a poison control centre to report clinical signs that could lead to a suspicion of ciguatera, they will be asked to keep the meal leftovers in a plastic bag in the freezer (-18°C) so that analyses can be carried out to screen for toxins.

Future annual reviews will thus help to update knowledge of ciguatera poisoning in order to limit its occurrence in the general population.

**Sandra SINNO-TELLIER (ANSES)  
and Luc DE HARO (Marseille Poison Control Centre)**

2. Through notification to the Rapid Alert System for Food and Feed.

**Recommendations to prevent the risk of ciguatera poisoning:**

- Do not eat the offal (liver, viscera, etc.), head, skin or eggs of fish from regions where the toxin is present.
- Do not eat fish that the locals do not eat.
- Ask a local fisher for advice before eating any fish caught.
- Pay attention to the origin of the fish you buy. Favour known species.
- **In the event of suggestive symptoms following consumption of fish from a risk area, call a poison control centre immediately or consult a doctor.**
- **Immediately place the leftover meal in a plastic bag in the freezer (-18°C) and store it for toxin analysis.**
- Avoid eating tropical fish within days of the occurrence of poisoning symptoms.
- Avoid drinking alcoholic beverages as they can make symptoms worse.

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**TO FIND OUT MORE :**

ANSES. (2021). Ciguatera: Review of cases registered by poison control centres in 2020. Toxicovigilance study report (Study report no. 2021-VIG-0132). ANSES. Maisons-Alfort. 27 p.

<https://www.anses.fr/fr/system/files/Toxicovigilance2021VIG0132Ra.pdf>

## Bitterness and taste disorders after eating pine nuts: what's new since 2017?

Inedible types of pine nut may accidentally or fraudulently find their way onto the market and cause lingering taste disturbances. This phenomenon peaked in 2009, with 700 cases reported to the network of poison control centres in August of that year alone. Although there have been far fewer cases in recent years – around ten annually – the problem has not gone away and a slight increase was observed in 2021. ANSES reiterates the recommendations regarding this type of poisoning: report any persistent bitterness after eating pine nuts and keep the packaging so that the product batch concerned can be withdrawn or recalled.



Our first article in Vigil'Anses issue 4 drew consumers' attention to taste disorders associated with the consumption of inedible pine nuts. This new article provides an update on this phenomenon, which may be decreasing but still persists, and sets out what to do about it.

As a reminder, pine nuts are small oilseeds that are generally consumed as is, or used to garnish a dish or a drink, or in culinary preparations such as pesto. Despite health controls, inedible (and therefore cheaper) varieties of pine nuts are offered for sale, often mixed with edible pine nuts, and can cause a particularly unpleasant taste disturbance called dysgeusia. This leaves a metallic and/or bitter taste in the mouth, which is exacerbated by eating or drinking any kind of food or drink. This occurs 24 to 48 hours after eating the pine nuts, and can last for several days or weeks. Sensitivity varies according to the individual: after consuming the same product, some will experience the adverse effect and others will not [1].

### An alert that peaked in August 2009

An earlier retrospective study from March 2008 to January 2010 had counted more than **3000 symptomatic cases** in France reported to the network of poison control centres after exposure to pine nuts. Most of these occurred in 2009 (see Figure 1) with a peak of around 700 cases in August 2009 [2].

This peak was due to the consumption of inedible pine nut species from China that had only recently arrived on the market. At the request of the European Commission, therefore, the Chinese authorities put in place strict export measures for

their pine nuts and European import controls were stepped up.

Between January 2010 and September 2017 (see Figure 1), the number of cases fell sharply from around 1200 symptomatic cases in 2010 to around 50 per year between 2015 and 2017 [3]. Several years after the alert, cases were still therefore being regularly observed.

### And since then? Fewer poisoning cases but a problem that still persists

For the period from 1 October 2017 to 31 December 2021 (see Figure 2), the number of cases further declined to an average of about 10 symptomatic cases per year from 2018 onwards, although with an upturn in 2021 ( $n = 27$ ). These figures are still well below those observed in 2009.

In this study period, 68 people who were symptomatic after consuming pine nuts were counted in the poison control centres' database. Dysgeusia was reported in 90% of these cases. The pine nuts had been purchased in various places in France<sup>1</sup>: supermarkets, organic food shops and markets. In seven cases, i.e. about 10%, they were presented for sale loose (in bulk). It is important to note that in 19 cases (i.e. almost 30%), the consumers were unable to provide any information about the place of purchase, the commercial name of the product or the batch number. Without this information, the health authorities cannot withdraw or recall inedible pine nuts from the market to prevent others from suffering the same discomfort.

1. The study did not include people poisoned by pine nuts that were not purchased in France.

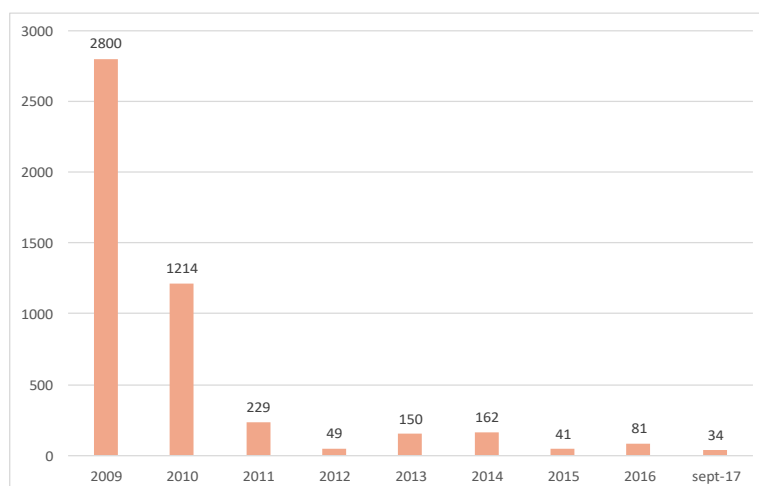


Figure 1 : Number of reports of symptomatic poisoning cases due to pine nuts in metropolitan France between 2009 and September 2017 (source: SICAP).

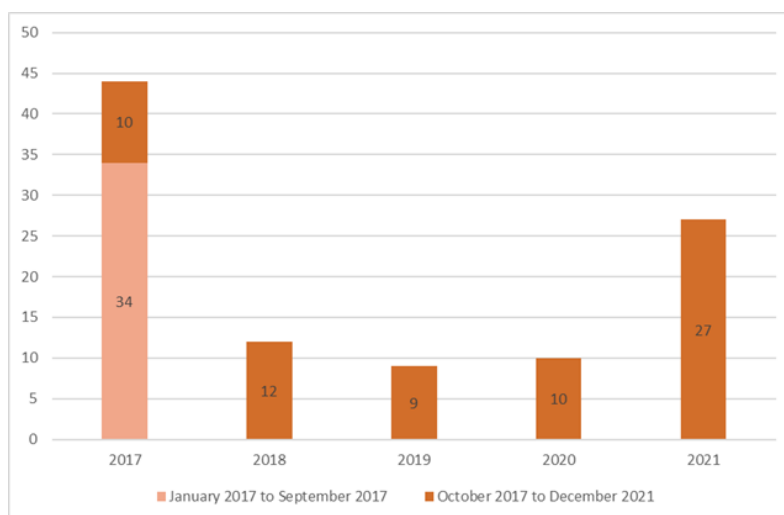


Figure 2: Symptomatic cases of exposure to pine nuts between 1 January 2017 and 31 December 2021 (source: SICAP)

### Recommendations for consumers

These new data show that cases of dysgeusia after pine nut consumption continue to occur, albeit in smaller numbers.

ANSES reminds consumers of the importance of reporting any lingering bitterness after eating pine nuts. This can be done either by contacting a poison control centre directly (especially when medical advice is needed) or through the Ministry of Health's adverse health events reporting portal<sup>2</sup>. In the latter case, the report will automatically be transferred to the regionally competent poison control centre, which may contact the consumer to obtain further information. For action to be taken, it is particularly important to **keep the product packag-**

**ing** so that the name, batch number, expiry date and place of purchase can be provided. This information will enable the withdrawal or recall of the product batch concerned to be triggered, and will prevent the occurrence of new cases.

In January 2022, ANSES established daily monitoring of cases of poisoning by pine nuts reported to the poison control centres, in order to be able to promptly identify non-compliant batches circulating in France and report them to the competent authorities.

**Christine TOURNOUD (Nancy poison control centre) and Rachel PAGES (ANSES)**

2. [https://signalement.social-sante.gouv.fr/psig\\_ihm\\_utilisateurs/index.html#/accueil](https://signalement.social-sante.gouv.fr/psig_ihm_utilisateurs/index.html#/accueil)

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## New chemicals involved in skin allergies related to clothing and footwear

Clothing and footwear contain dozens of chemicals, either used intentionally or found as impurities. Some of them can cause skin allergies. ANSES set up a study between 2016 and 2018 to improve knowledge of the substances responsible for these allergies and update the regulations. It identified allergens in clothing and footwear that are responsible for skin allergies and deserve to be regulated, as well as substances that are already banned or for which the regulations have turned out to provide inadequate protection of consumer health. ANSES then joined with Sweden to propose a regulation at European level that would restrict over a thousand skin allergens in clothing and footwear.



### A known problem

Clothing and footwear contain dozens or even hundreds of chemicals. Some of these substances, such as dyes, are used intentionally at the time of manufacture, while others are residues or impurities found in varying concentrations, such as residues left over from the manufacture of rubber. Many substances are already known to be allergenic but others have yet to be identified. Dermatologists regularly see patients with eczema or even skin burns as a result of wearing shoes or clothing. They then carry out patch tests, i.e. they apply very small quantities of various known allergens to the patient's skin. If the patient develops redness and/or swelling of the skin after several hours or days of contact with one or more substances, it is a sign that they are allergic to it. However, the dermatologist has no way of verifying that the substance(s) were actually in the clothing or footwear in question, and thus confirming with certainty the source of the problem.

This is because the regulations covering clothing and footwear do not require manufacturers or distributors to list the

chemicals present in the items they sell. The manufacture of an item of clothing can involve dozens of different companies, making traceability sometimes very difficult. The European regulation<sup>1</sup> currently only covers 12 classes of chemicals in these items. It includes nickel, for example, which is known to cause skin allergies and which must not be present in metal parts (e.g. jacket buttons, shoe buckles) at a level exceeding  $0.5 \mu\text{g}/\text{cm}^2/\text{week}^2$ . The concentration of chromium VI, another known skin allergen, must not exceed 3 mg/kg in leather items.

Reference laboratories specialising in the chemical analysis of leather or textiles carry out hundreds of tests every day on behalf of the authorities or manufacturers wishing to ensure compliance with existing regulations. However, some substances are identified, sometimes in non-negligible concentrations, without any link being established with possible allergenic effects. These are mainly substances for which no toxic effects have been reported in the literature.

1. Annex XVII of Regulation (EC) No 1907/2006 of 18/12/06 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).

2. Amount of nickel released per  $\text{cm}^2$  of metal over a period of one week of contact with this metal, in the presence of a sweat simulant to mimic dermal exposure

### ANSES's proposal to address this

As already mentioned in the article in the June 2018 issue of Vigil'Anses [1], and following a request from the Directorate General for Health (DGS) and the Directorate General for Competition Policy, Consumer Affairs and Fraud Control (DGCCRF), ANSES conducted a study to identify the chemicals responsible for skin allergies observed in patients and confirm their presence in the clothing or footwear worn [2].

This study had several objectives:

- to confirm the medical diagnosis of allergy to a substance by chemical analysis of the item by the laboratory, or confirm the involvement of a substance identified by the laboratory through a new series of patch tests on the patient;
- to identify new skin sensitizers in order to update the regulations and improve the safety of these items.

The results of this study have been used for both health and regulatory purposes [3].

### Unregulated chemicals clearly identified as causing allergies

For 15 of the 50 patients in the study, the substances causing the skin allergies were identified with certainty because they yielded positive patch tests and were also found in the suspect items.

These were substances whose skin sensitising potential has been reported in the literature and which are included in the batteries of patch tests routinely used by dermatologists. However, they are not subject to any regulations limiting or prohibiting their presence in these items.

The substances found in the clothing and footwear were as follows:

- a formaldehyde-based resin, used in footwear as an additive in rubber adhesives (p-tert-butylphenol formaldehyde resin);
- a substance found in shoe adhesives (rosin);
- plasticiser for polymers used in the manufacture of footwear textiles (benzyl benzoate);
- synthetic textile fibre dyes (CI Disperse Red 17 and CI Disperse Blue 106).

For one patient, the dye causing the allergy (CI Disperse Orange 37/76) was identified at a later stage through an addi-

tional patch test, as it was not included in any of the commercial batteries of patch tests. The laboratory that identified this substance in the suspect item sent a small amount to the dermatologist, who fabricated an ad hoc patch test that proved positive.

For five patients, laboratory analyses ruled out any responsibility of the clothing or footwear in the occurrence of the allergies. The laboratories instead concluded that the items had been contaminated by external substances such as perfume, paint or detergent. Thanks to the medical questionnaires completed previously by the dermatologists, it was confirmed that substances applied to the items were indeed responsible.

The doctors were able to inform these 15 patients of the substances responsible for their allergies and advise them on how to avoid any recurrence: no longer buy or wear clothes made of similar materials or colours, and no longer use certain types of household products containing these allergens.

### Breaches and shortcomings of the current regulations

The analyses carried out by the laboratories revealed several non-compliances with regard to the substances responsible for the patients' skin allergies:

- Nickel concentration above the regulatory threshold in shoe buckles for one patient;
- Chromium VI concentrations above the regulatory threshold in pairs of shoes for four patients;
- The presence of benzidine (a chemical intermediate in the synthesis of dyes) in an item of clothing. Benzidine is a carcinogen<sup>3</sup> and should never be found in finished products such as clothing.

These substances are regularly mentioned in reports by the European inspection authorities<sup>4</sup> of non-compliance of items leading to their withdrawal from the market. The non-compliances identified here were therefore forwarded to the DGCCRF.

Another situation arose during this study: a patch test confirmed an allergy to an already regulated substance that had also been identified in the item but at a concentration below the regulatory threshold, and therefore in compliance. One patient was allergic to nickel in clothing, while four others were allergic to chromium VI in shoes. These cases show that the threshold in the regulation does not provide adequate protection for allergic consumers and should be lowered.

3. According to the European Regulation 1272/2008 on Classification, Labelling and Packaging (CLP).

4. <https://ec.europa.eu/safety-gate-alerts/screen/webReport>

**An unprecedented biomedical study in Europe**

ANSES received a favourable opinion from the health and ethical authorities, which is an essential step for any research involving examinations on the human body.

To be included in this study, a patient had to have a skin allergy suspected of being caused by clothing or footwear purchased new. They had to give their consent and agree to hand over the offending item.

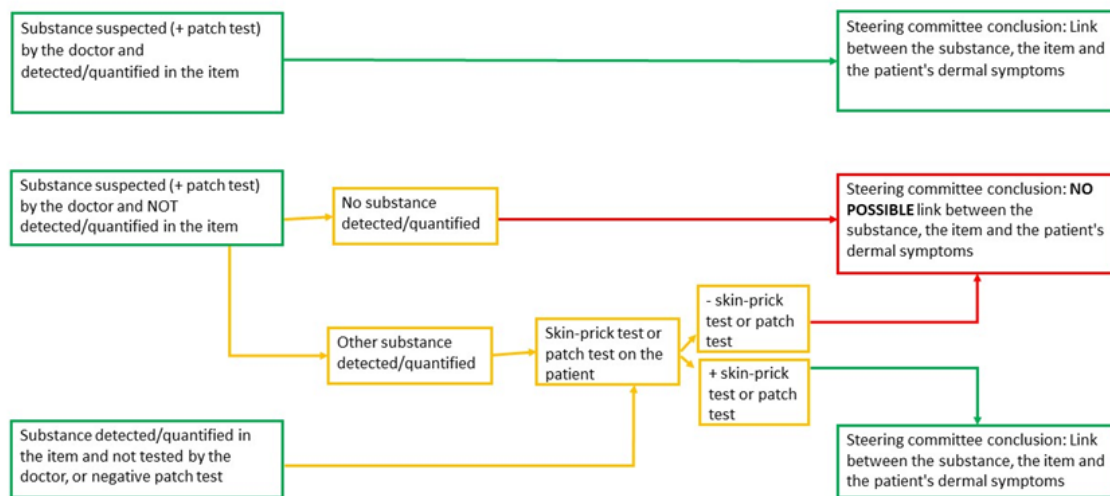
The study excluded pregnant or breastfeeding women, individuals receiving immunosuppressive treatment and patients with injuries due to personal protective equipment intended for professional use only, or items purchased second-hand.

The allergy had to be diagnosed by one of the doctors participating in the study:

- dermatologist-allergists from the Revidal-Gerda network<sup>5</sup> practising in hospitals;
- a doctor from each of the eight poison control centres;
- a doctor from each of the occupational disease consultation centres.

Two laboratories also took part in the study: the Technical Centre for Leather (CTC) for footwear, and the French Textile and Apparel Institute (IFTH) for clothing.

In the end, 50 patients were included and 60 items (30 pairs of shoes and 30 garments) were analysed. The results were then compared with the patch test data to correlate, or not, the presence of an allergen in the item worn by the patient. The approach followed is summarised in the diagram below:



**Figure 1 : ANSES biomedical study on footwear and textile clothing: decision tree followed by the steering committee for investigating the cases**

5. Dermato-allergology vigilance network, bringing together 130 allergists from France, Belgium and Switzerland (association governed by the French Act of 1906).

### Proposal for a more protective European regulation

These results led ANSES, jointly with Sweden, to suggest a specific framework under the REACH Regulation for textiles, leather, fur and animal hides used in clothing and footwear in particular. A specific restriction in these items was therefore proposed, for more than 1000 skin sensitisers, including those identified in this study.

If adopted, such a regulatory step forward, designed to achieve stronger consumer protection, will limit the presence of substances whose allergenic potential is known but for which no regulation currently applies. It will prohibit all so-

called disperse dyes, which, as this study has shown, are often implicated in skin allergies. It will lower the regulatory thresholds for nickel and chromium VI, which do not currently provide enough protection. Any new substance classified as a "skin sensitiser" under the CLP Regulation will be added to the 1000 substances already proposed, further enhancing consumer safety in relation to these items.

**Céline DUBOIS, Cécilia SOLAL and Juliette BLOCH (ANSES)**

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## Effects of human topical hormone therapy on pets

Hormonal treatments for humans applied to the skin can pose a risk not only to other family members, but also to pets. This is because if the animal touches the impregnated skin of the treated person or any fabric that has been in contact with them, the active substance can penetrate the animal's body. This has led to recent reports in several European countries of hyperoestrogenism in dogs and cats in contact with people treated with such products. Users should therefore take precautions to avoid the discomfort this causes to their animals.



Crédit photo : Corinne Piquemal

### Background

Patients treated with skin gels containing synthetic hormones are generally well informed about the precautions to take with regard to other family members, to avoid any potential adverse effects from repeated involuntary contact with skin impregnated with this type of medicine. However, they are less aware of the danger to their pets of exposure to these products.

### Adverse effects in animals reported in several European countries

Several cases of adverse effects involving small dogs, cats, puppies and kittens – both female and male – have been reported in several European countries. They were caused by repeated contact with hormonal treatments applied to their owner's skin. All of the products involved were oestrogens. These tend to be applied to surfaces of the body such as the thighs, abdomen or arms, which can then potentially come into contact with the animal. This contact with the medicine can also occur through bed sheets, if the treated person and the animal sleep in the same bed.

### Exposure that results in signs characteristic of a hyperoestrogenic<sup>1</sup> state

The exposed animals mainly developed symptoms suggesting hyperoestrogenism, in particular swollen mammary glands and/or vulvas in females. Signs of spayed females going into heat were also described.

In addition, dermatological problems were reported, with hair loss mainly on the ventral side of the thorax and abdomen [1]. Moreover, oestrogen's toxicity to bone marrow can eventually cause anaemia that may be life-threatening to the animal [2].

The time to symptom onset varies, ranging from a few weeks to several years. Symptoms generally improve or even disappear when the animal is no longer exposed to the hormones.

The clinical signs observed in these reported cases are consistent with the data published in the scientific literature.

### No cases recorded in France to date

No cases mentioning such events have been reported so far in the national pharmacovigilance database of the French Agency for Veterinary Medicinal Products (ANSES-ANMV) or by veterinary poison control centres in France.

If symptoms suggestive of a hormonal disorder are detected, owners are strongly urged to get their animal examined promptly by a veterinarian, making it clear that someone in the household is undergoing topical hormonal treatment (oestrogen, progesterone or testosterone).

1. Hyperoestrogenism is defined as an elevated level of oestrogen, a hormone secreted by females.

### Protecting both people and pets in the household

In order to avoid any discomfort to their animals, users of these medicines are reminded to:

- wash their hands after applying gel;
- cover the treated areas with clothes;
- prevent animals from licking the treated areas;
- avoid sleeping with their pets;
- if the pet comes into direct contact with a treated area, prevent the animal from grooming itself and use water to rinse any body surfaces onto which the medicine may have been transferred.

ANSES-ANMV reiterates that these precautions for use are valid for all human medicinal products on the market, intended for dermal application.

**Corinne PIQUEMAL and Sylviane LAURENTIE  
(Anses-ANMV)**

### References

- [1] Wiener DJ, Rüfenacht S, Koch HJ, Mauldin EA, Mayer U, Welle MM. Estradiol-induced alopecia in five dogs after contact with a transdermal gel used for the treatment of postmenopausal symptoms in women. *Vet Dermatol.* 2015 Oct;26(5):393-6, e90-1.
- [2] Sterman AA, Mankin KT, Barton CL. Stump Pyometra Secondary to Human Topical Estrogen Hormone Exposure in a Spayed Female Chihuahua. *J Am Anim Hosp Assoc.* 2019 Nov/Dec;55(6):e55604.

To report an adverse effect in an animal following the use of a veterinary drug:

<https://pharmacovigilance-anmv.anses.fr/>

## "Natural" products... that contain dangerous drugs

Some aphrodisiac or slimming products conceal the fact that they contain potent drugs such as tadalafil or sildenafil (both of which are subject to compulsory medical prescription in the treatment of erectile dysfunction), or sibutramine (an appetite suppressant that has been banned in France for several years). Consumers are therefore unknowingly exposed to the sometimes very serious adverse effects of these compounds. They are therefore advised to avoid buying these products from parallel traders, through social media or on the Internet. Any unexpected side effects should be reported to the nutrivigilance scheme or a poison control centre in order to obtain medical advice and, if necessary, to conduct screening for drugs in any remaining tablets or capsules. This enables the health authorities to take the necessary measures and withdraw these very dangerous products from the market.



### Recent alerts

#### *Aphrodisiac honeys*

In February 2021, a poison control centre notified ANSES of a new case of serious poisoning due to a "love honey", an aphrodisiac product called Black Horse Vital Honey, which, according to its leaflet, contains honey, ginseng, royal jelly and *Eurycoma longifolia*, a plant believed to have aphrodisiac properties. The evening before admission to the hospital emergency room, the patient had consumed a quantity of this product that was difficult to determine. In the morning, he was admitted to the intensive care unit for convulsions, cerebral oedema, and major respiratory and kidney failure.

A search of the poison control centres' database identified another case with the same product from December 2020. That time, the symptoms were benign. The patient, who had only taken a few drops, rapidly felt hot and thirsty, with a dry mouth. He had stayed at home and the symptoms had soon regressed.

Analyses of the product identified tadalafil at a concentration of 8 mg/ml. For comparison, medicines contain 5-20 mg per tablet. A consumer ingesting several millilitres of aphrodisiac honey in one go (one tablespoon contains about 10 ml or 80 mg of medicinal substances), therefore absorbs the equivalent

of several tablets of this medicine, whereas the usual dosage is 10 mg, with a maximum of 20 mg.

In July 2021, the Directorate General for Competition Policy, Consumer Affairs and Fraud Control (DGCCRF) and the ANSM issued a joint press release alerting consumers to the danger of aphrodisiac honeys, in particular Jaguar Power and Black Horse Vital Honey, which have been withdrawn or recalled [2].

However, other cases were recorded by poison control centres after July 2021, sometimes in people who had consumed the product and reported problems after reading the alert. In others, consumption took place well after the alert was issued, indicating that the products were still available. For example, in October 2021, a 36-year-old man with no previous medical history experienced a permanent erection resulting in irreversible penile damage after taking Black Horse Vital Honey.

Lastly, in December 2021, a new aphrodisiac honey, Honey Palace Special Power, was found to have caused poisoning in several people. This honey had also been circulating in Belgium where it was withdrawn from the market due to the presence of sildenafil. The DGCCRF and the ANSM were alerted, to enable them to take the necessary measures for France.

### *The Inci slimming supplement*

In January 2021, a woman experienced symptoms of fatigue, insomnia, vomiting, dry mouth, accelerated heart rate and chest pain after taking a weight-loss product called Inci Naturel for four days. This prompted her to seek medical advice after seven days. The product had been purchased on an internet platform and the patient brought a leftover capsule to the medical consultation. Its analysis confirmed adulteration with sibutramine and sildenafil, thus explaining the observed symptoms.

French poison control centres then received numerous calls about this product, totalling about 100 cases of exposure, of which about 80 were in the same community between January and June 2021.

An investigation by the DGCCRF identified one company, one supplier and several sellers. The ANSM reminded them that the product was dangerous and its sale illegal (illegal practice of medicine). Action by the Departmental Directorate for the Protection of Populations led to the products being seized.

No other cases have been reported since.

#### **They are effective... but why are they dangerous?**

These adulterated food supplements present a real threat to consumers' health. They think they are using "natural" products whose ingredients only mention plants, whereas in fact they are ingesting drugs that can be highly dangerous.

Some drugs have been banned because their risks outweigh the expected benefits. This is the case with sibutramine or fenfluramine, which are found in slimming supplements and which expose consumers to the risk of serious cardiovascular events. Other medicines are authorised but only on prescription, so that a doctor can verify that there are no contraindications to their use and explain how to use them at a suitable dose. This is the case for compounds that are effective on erectile dysfunction, such as sildenafil (the compound in Viagra®) and tadalafil (the compound in Cialis®), to name just those most often found in adulterated food supplements. The most common adverse effects are headaches, facial flushing, digestive disorders, vision disorders mainly affecting colour perception, decreased visual acuity, hypersensitivity to light and dizziness. There is also the potential for more serious problems, such as prolonged and painful erection, high or low blood pressure with loss of consciousness, stroke, heart

rhythm disorder or hearing loss. These substances must under no circumstances be taken in combination with certain medicines or by individuals suffering from certain diseases. Only a doctor can assess the balance between benefit and risk of taking these compounds for a person with erectile dysfunction.

#### **Lessons to be learned**

ANSES points out that an adequate, balanced diet provides all the elements necessary for good health, without the need for food supplements.

However, if people still wish to take them, they are encouraged to buy them from conventional channels, including food supplements for slimming or aphrodisiac purposes. They are advised to talk to their doctor before starting to use these products, especially people with a medical condition and/or taking medicine with which the supplements may interact.

After taking a food supplement, in the event of side effects or very high effectiveness that seem disproportionate for a product supposed to contain only plants, consumers should always consider the possibility of adulteration, especially when the product has been purchased outside conventional channels, and should call a poison control centre for medical advice, keeping some capsules or tablets for analysis. Only by screening for the drug will it be possible to identify any fraud and take the necessary steps to withdraw the product from the market and **prevent others from falling victim to poisoning, sometimes more severely.**

Healthcare professionals are invited to report any adverse effects of food supplements observed in their patients on the Ministry of Health's reporting portal<sup>1</sup> or directly on the ANSES nutrivigilance website<sup>2</sup>. These reports will be analysed by ANSES as part of the nutrivigilance scheme. Users who have not called a poison control centre can also report adverse effects on the Ministry of Health's website. They may be contacted by a poison control centre if further information is needed.

Websites selling fraudulent products of any kind can be reported on the Ministry of the Interior's portal<sup>3</sup>. The sale of prescription-only medicines over the Internet is prohibited in France.

**Juliette BLOCH (ANSES)**

1. [https://signalement.social-sante.gouv.fr/psig\\_ihm\\_utilisateurs/index.html#/accueil](https://signalement.social-sante.gouv.fr/psig_ihm_utilisateurs/index.html#/accueil)

2. <https://www.nutrivigilance-anses.fr/nutri#!>

3. <https://www.internet-signalement.gouv.fr/PortailWeb/planets/Accueil>



**References**

- [1]. [https://vigilances.anses.fr/sites/default/files/VigilancesN1\\_adult%C3%A9rationscompl%C3%A9mentsalimentaires\\_0.pdf](https://vigilances.anses.fr/sites/default/files/VigilancesN1_adult%C3%A9rationscompl%C3%A9mentsalimentaires_0.pdf)
- [2]. [https://www.economie.gouv.fr/files/files/directions\\_services/dgccrf/presse/communique/2021/CP-Mise-en-garde-concernant-des-denrees-alimentaires-frauduleuses.pdf](https://www.economie.gouv.fr/files/files/directions_services/dgccrf/presse/communique/2021/CP-Mise-en-garde-concernant-des-denrees-alimentaires-frauduleuses.pdf)

## Seizures associated with consumption of a food supplement containing melatonin designed to promote sleep

ANSES received a report of life-threatening seizures following consumption of the food supplement Novanuit® Triple Action by a man with no history of epilepsy. Causality of the product was deemed to be very likely in this case. Given the severity of the adverse effect described, ANSES is bringing this case to the attention of the general public and healthcare professionals. It recommends paying close attention to the adverse effects that could occur following consumption of any product containing melatonin, and calls for such effects to be reported to the national nutrivigilance scheme.



As part of the nutrivigilance scheme that it has been running since 2009<sup>1</sup>, ANSES received a report of seizures potentially associated with consumption of the food supplement Novanuit® Triple Action marketed by Sanofi. This product, designed to promote sleep, contains melatonin, California poppy (*Eschscholzia californica*), lemon balm (*Melissa oï cinalis*), passion flower (*Passiflora incarnata*) and vitamin B6.

### The alert

The report concerned a 47-year-old man with no history of epilepsy. He was not taking any long-term medication, and only drank alcohol at weekends. In 2020, while suffering from sleep disorders, he began to take the food supplement Novanuit® Triple Action. After nine days of use, he experienced involuntary contractions of the muscles around the eye, along with dizziness, which soon disappeared without treatment. On the tenth day of taking the product, he had a seizure that caused him to fall. The medical examination, which included a brain scan, Holter heart rhythm monitor<sup>2</sup>, electroencephalogram (EEG), electrocardiogram (ECG), cardiac ultrasound and computed tomography angiogram, found nothing unusual and ruled out a recent ischemic<sup>3</sup> or haemorrhagic<sup>4</sup> stroke. The biological test results did not reveal any abnormalities. The patient returned home and continued taking the food supplement until the sixteenth day, when a new seizure occurred. In

the hospital emergency room, the patient's brain imaging results (MRI) were unremarkable, the clinical and biological examinations showed no particular anomaly, the blood alcohol level was zero and the ECG was normal.

He stopped taking Novanuit® Triple Action and began an anti-epileptic treatment after consultation with a neurologist. The neurologist prescribed neurological monitoring and the continuation of the anti-epileptic treatment. The subsequent outcome was favourable and the patient did not experience any further seizures under treatment.

### Link with use of the food supplement

The causality of the food supplement in the occurrence of the seizures was assessed using the method developed for the nutrivigilance scheme [1]. Causality takes four components into account: the onset time, the outcome after discontinuing the product, whether or not the effect reappears upon reintroduction, and the absence of any other possible explanation for the observed adverse effect. For the food supplement Novanuit® Triple Action, the time to onset of the effect was considered "compatible". The outcome was described as "suggestive", although specific treatment was initiated because this adverse effect was life threatening to the patient.

1. <https://www.anses.fr/en/content/everything-you-need-know-about-nutrivigilance-scheme>.

2. The Holter device records heart rate and rhythm over an extended period of time.

3. Clogged vessel.

4. Ruptured vessel.

Reintroduction would have been considered "positive" if the effect had reappeared after each intake and "negative" if it had not. As the seizures did not occur systematically each time the product was taken, it was not possible to reach a conclusion on the reintroduction component; it was therefore classified as "inconclusive". The aetiological investigation ruled out the most common causes of seizures through tests of neurological, cardiac, hepatic and renal function and biological analyses. The Novanuit® Triple Action product was therefore deemed **very likely** responsible for the occurrence of the seizures, i.e. **I4** on a scale ranging from I0 (excluded) to I4 (very likely).

#### Have similar cases been described in the scientific literature?

The literature search focused on possible human cases of seizures and epilepsy associated with the active ingredients of the food supplement Novanuit® Triple Action, namely California poppy (*Eschscholzia californica*), lemon balm (*Melissa officinalis*), passion flower (*Passiflora incarnata*), vitamin B6 and melatonin.

The available studies on melatonin's influence on the onset of epileptic seizures are contradictory, with some reporting an anticonvulsant action while others showed a proconvulsant effect. In addition, they were conducted with doses ranging from 1.5 mg/d to 10 mg/d. Novanuit® Triple Action contains 1 mg of melatonin per tablet.

The literature search did not identify any studies or clinical cases reporting seizures related to the other active ingredients in the food supplement Novanuit® Triple Action.

#### Have similar cases been reported to the nutrivigilance scheme?

To date, no other similar cases concerning the food supplement Novanuit® Triple Action have been reported to the nutrivigilance scheme.

#### References:

- [1]. ANSES. 2019. "Revised ANSES opinion of 10 July 2019 on updating the method for determining causality in reports of adverse effects in nutrivigilance".
- [2]. ANSES. 2018. " ANSES Opinion on the risks associated with the consumption of food supplements containing melatonin". Maisons-Alfort.

#### Conclusions and recommendations

The causality of the food supplement Novanuit® Triple Action in the occurrence of seizures in a patient with no history of epilepsy was deemed highly likely. One of its ingredients, melatonin, has already been the subject of an opinion by ANSES [2]. This opinion advised against the consumption of food supplements containing melatonin by people suffering from epilepsy without seeking the advice of their doctor.

In general, ANSES recommends that consumers of food supplements:

- notify a healthcare professional of any adverse effect occurring after consumption;
- comply with the conditions of use specified by the manufacturer;
- avoid taking food supplements on a multiple, prolonged or repeated basis throughout the year without having sought the advice of a healthcare professional (doctor, dietician, etc.);
- exercise great vigilance with regard to improper claims;
- exercise great vigilance regarding the purchase of products sold through alternative channels (internet, gyms, etc.) and without personalised advice from a healthcare professional.

ANSES also reminds healthcare professionals that they must report to its nutrivigilance scheme any cases of adverse effects they suspect are associated with the consumption of food supplements.

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#### TO FIND OUT MORE :

[Opinion on a case of seizures associated with consumption of the food supplement Novanuit® Triple Action](#)

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ANSES is in charge of several health vigilance systems: pharmacovigilance for veterinary medicinal products, nutriviigilance, phytopharmacovigilance, toxicovigilance and vigilance for occupational diseases. Our vigilance activities make little noise and are therefore poorly known to public health actors, health professionals, marketers and users in general. And so, in order to make our work more visible we have decided to create a dedicated newsletter entitled Vigil'Anses.

As news on each of our vigilance topics crops up, this quarterly newsletter presents the main results of the work carried out by ANSES within the framework of its vigilance missions, in conjunction with its partners, professional networks and expert groups, as well as the actions we have undertaken.

The articles are deliberately short, and are intended for all those involved in the occupational and environmental health and safety field: public authorities, health agencies, institutes and expert bodies that are partners of ANSES, prevention policy managers, the scientific community, professionals, associations and users. Vigil'Anses also invites the interested reader to delve deeper and discover publications, opinions and reports available online that will further their knowledge.



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