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While cases of food poisoning with digestive signs following the consumption of shellfish are widely known, many people are unaware that some forms can cause neurological signs. The first article of this Issue 13 of Vigil'Anses describes this phenomenon, which can involve **mussels, oysters or other bivalves contaminated by marine neurotoxins.**

The very first issue of Vigil'Anses had drawn consumers' attentions to the risk of **skin reactions associated with the consumption of raw or undercooked shiitake mushrooms.** Four years later, a new overview of these particular cases of poisoning is presented in this issue. Have communication campaigns been effective?

Applying your own **false nails** at home may seem safe. However, the **cyanoacrylate glues** used pose a risk of severe **skin burns** if they get on clothes in contact with the skin. Following two cases reported to Poison Control Centres, the third article of this issue addresses this phenomenon.

Metronidazole is an antibiotic and antiparasitic medication **used in dogs**, alone or in combination with spiramycin. As scientific articles have described **neurological adverse effects** at lower doses than previously known, the French Agency for Veterinary Medicinal Products analysed reports recorded in the national veterinary pharmacovigilance database to look for this type of effect and learn about the circumstances of its occurrence. The results are given in this issue.

The last article reports a new example of a serious adverse effect, recorded by the nutrivigilance scheme, occurring following the consumption of a food supplement. It involved a case of **severe acute hepatitis associated with consumption of the SriSri Kanchanara® food supplement**; the company placing this product on the market claims that it relates to the practice of Ayurvedic medicine. A causal relationship was considered very likely.

Juliette Bloch, Editor-in-Chief of Vigil'Anses

Neurological disorders associated with the consumption of shellfish : health professionals still unfamiliar with their diagnosis

he consumption of bivalve shellfish (mussels, oysters, etc.) can cause serious and even fatal neurological disorders due to the accumulation of natural toxins – whose levels are regulated – in their flesh. In June 2019, a specific case of poisoning associated with the consumption of mussels contaminated by paralytic toxins drew the attention of ANSES and the French Poison Control Centres (PCCs) to a possible lack of knowledge of poisoning with marine neurotoxins in other cases. A retrospective study of cases of shellfish poisoning recorded by the PCCs from 2012 to 2019, and of regulatory monitoring data for shellfish production areas, led to the identification of 15 probable cases of poisoning with neurotoxins. Prospective monitoring for shellfish poisoning causing neurological signs has since been introduced based on the PCCs national database.

Mussels, oysters, clams, scallops and other bivalve shellfish have a two-part shell containing the flesh of the marine mollusc.

These seafood products, which have long been part of the diet of human populations in coastal areas, are consumed throughout France and can cause poisoning.

These shellfish filter large amounts of water as they feed. They therefore absorb the contaminants contained in the water, such as pathogenic micro-organisms (bacteria, viruses), toxic microalgae, heavy metals and other (organic) pollutants, which accumulate in their flesh and can make them unfit for consumption.

More specifically, some species of phytoplankton (microscopic microalgae) produce toxins called phycotoxins; most of them cause digestive signs (diarrheic toxins), although others can be responsible for sometimes serious and even fatal neurological signs of rapid onset: this is the case of the paralytic toxins produced by algae of the genus *Alexandrium*, the best known of which are saxitoxin and its derivatives; there are also amnesic toxins, in particular domoic acid, produced by algae of the genus *Pseudo-nitzschia*, as well as toxins that have emerged more recently in Europe (pinnatoxins, brevetoxins, etc.). The toxins produced by shellfish are not destroyed by cooking. Levels of paralytic toxins – including saxitoxins – and domoic acid in seafood products

are regulated [1]. The thresholds are based on the consumption of "reasonable" amounts. Checks are organised in shellfish production areas. If the thresholds are exceeded, the health authorities temporarily close the shellfish production areas, or in the event of imports, withdraw the contaminated batches from the market, in order to protect the health of consumers.

In France, under the responsibility of the Directorate General for Food, there is a network (REPHYTOX) for monitoring regulated phycotoxins for which monitoring is mandatory (diarrheic toxins, saxitoxins and domoic acid) in shellfish from coastal production areas; it is supplemented by a network for monitoring emerging toxins (EMERGTOX[1]). Depending on the toxin in question, analyses are conducted by the laboratories of IFREMER[2] or by ANSES's National Reference Laboratory for marine biotoxins. Cases of shellfish contamination by saxitoxins were first observed in France in 1988; for domoic acid, the first cases of shellfish contamination date back to 2000 [2].

1.The EMERGTOX network also reinforces the monitoring of regulated toxins, in areas not yet affected by these toxins.
2. IFREMER: French Research Institute for Exploitation of the Sea.

An alert involving imported mussels drew ANSES's attention

In June 2019, RASFF informed the competent European authorities of two batches of mussels imported from Italy that were contaminated by saxitoxins. Although the levels of saxitoxins, measured as part of a self-check by the distributor, did not exceed the regulatory limits, the distributor had withdrawn the product from the market as a precautionary measure. Some batches had nonetheless been distributed and consumed. During the same period, a Poison Control Centre (PCC) informed ANSES of the case of an individual who had developed neurological signs potentially associated with the consumption of contaminated mussels [3]. This person had eaten a large quantity of mussels during two consecutive meals and within two hours of each of the meals, had experienced digestive problems, paraesthesia (or tingling) of the hands and feet, tremors and dizziness. They went to the emergency department and their symptoms spontaneously regressed. The causal relationship with the consumption of mussels was probable; the symptoms and the time to onset were consistent with the clinical picture expected with this type of poisoning. However, confirmation of this assumption met with two difficulties: the concentrations of saxitoxins measured in the mussels from the implicated batch (313 µg/kg mussel flesh) were below the regulatory threshold (800 µg/kg shellfish flesh); and no biological samples (blood, urine, etc.) had been collected to test for saxitoxins. It should be noted that these blood and urine analyses are not routinely performed by biology laboratories. The link between the symptoms and exposure to paralytic toxins was established thanks to the report received by RASFF from the product's distributor, which was not mandatory since the measured concentrations were below the regulatory limit.

A retrospective study of CAP data found cases of poisoning with marine neurotoxins that had gone unnoticed

This alert highlighted the probable under-diagnosis of cases of human poisoning with neurotoxic phycotoxins related to the consumption of shellfish. A retrospective study of cases of poisoning with bivalve shellfish recorded in the PCCs national database from 1 January 2012 to 31 December 2019 was therefore undertaken by ANSES, the PCCs' network and IFREMER. During this study period, 619 cases of food poisoning, all types of symptoms combined, were reported and split into 452 "files" (or shellfish meals, as one meal could be shared by several guests). Nineteen per cent of the meals involved collective food poisoning, with two to eight cases.

Fifty percent of the meals responsible for the poisoning included oysters; 33% included mussels, 11% scallops, 2% mussels and oysters, and the rest (4%) other shellfish.

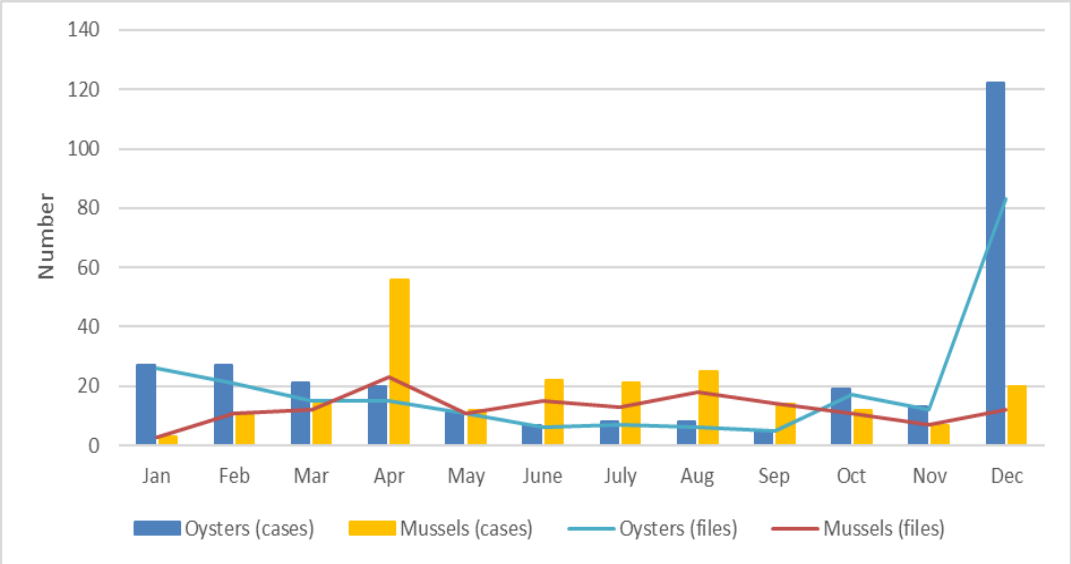

Figure 1: Monthly distribution of poisonings with oysters and mussels, all symptoms combined (number of cases and number of files or meals). January 2012 – December 2019 (Oysters: N cases=288 and N files=224; Mussels: N cases=217 and N files=150). Source: PCCs national database.

3.RASFF: Rapid Alert System for Food and Feed (alert system for EU Member States). RASFF alert notifications are sent when a food or feed on the market in the European Union may be contaminated, regardless of the agent (chemical, biological, etc.). The DGCCRF is RASFF's correspondent for France.

The monthly distribution of the cumulative number of poisoned individuals and meals involved over the 2012 to 2019 study period showed that oyster poisonings primarily occurred in December (42% of cases and 37% of oyster meals) and that mussel poisonings were most common in April (26% of cases and 15% of mussel meals) (Figure 1). However, poisonings with oysters and mussels could be observed all year long. Moreover, the large number of poisonings with oysters in December, added up over the 2012 to 2019 period, was partly due to several clustered cases of acute gastro-enteritis of viral origin (norovirus) that occurred in 2019 [4].

While, as expected, 88% of the poisoned individuals developed one or more digestive signs (vomiting for 61%, diarrhea for 47%, nausea for 27%, etc.), 22% (134 individuals) experienced at least one neurological sign (headaches for 10%, dizziness for 4%, paraesthesia for 3%, etc.), alone or combined with other symptoms. Three-quarters of the individuals who presented with at least one neurological sign also reported a digestive sign, which helped identify the possible food origin of the symptoms. The type of shellfish consumed (mussels, oysters, scallops, etc.) did not differ between the individuals who experienced a neurological sign and those who did not.

A PCC toxicologist thoroughly reread each of the 134 reports of cases where a neurological sign was mentioned, leading to the *a posteriori* identification of 15 cases that may have been due to the consumption of bivalve shellfish contaminated by a marine neurotoxin: 14 cases corresponded to a paralytic syndrome (suggestive of saxitoxins) and one to an amnesic syndrome (suggestive of domoic acid). No poisoning with other marine neurotoxins was suspected based on the available information.

The diagnosis was made retrospectively based on the coincidence between the described clinical signs, the report of shellfish contamination in monitored production areas (REPHYTOX) – or the RASFF notification – and the origin of the shellfish when this was known. No testing for marine neurotoxins (saxitoxins, domoic acid, etc.) was performed in the blood or urine of these 15 patients.

The 14 individuals with paralytic syndrome had shared 11 meals; 10 of them had eaten mussels, whether alone or combined with other shellfish (seven meals), while the others had eaten oysters, scallops or clams.

Six individuals had developed paraesthesia, affecting the hands and/or feet in four cases and the mouth in the two others. Five individuals had experienced muscle pain or cramps; two of these had also developed paraesthesia. Memory disorders had also been reported by family members of two individuals, raising the possibility of amnesic syndrome associated with paralytic syndrome.

While the severity of the reported symptoms was mild in 10 cases, four individuals experienced more severe or persistent neurological symptoms: bilateral paraesthesia of the hands and/or feet, ascending paraesthesia from the hand to arm, and associated muscle stiffness. The symptoms spontaneously regressed within 12 hours in the 11 cases where the clinical outcome was known.

Reading of the PCC files helped determine the origin of the consumed shellfish for six meals (eight individuals); this was retrospectively linked to a shellfish production area where high levels of saxitoxins, or even levels exceeding the regulatory threshold, had been identified for four meals; for the two others, it was linked to the RASFF alert notification from June 2019 for mussels imported from Italy.

Lastly, the 15th individual had developed memory disorders and severe mental confusion requiring them to be admitted to hospital in intensive care, following the consumption of dog cockles and whelks. The origin of the shellfish was known, and the REPHYTOX data for the production area from the same period showed levels of domoic acid above the regulatory threshold, suggesting amnesic syndrome. The patient recovered.

Measures should immediately be taken when a case is suspected!

Failure to diagnose neurotoxic syndrome, due to a lack of information about the shellfish involved, can be detrimental to the care of patients. First of all, any healthcare professional suspecting such poisoning should immediately contact a Poison Control Centre to optimise patient care. Following this study, the PCCs developed a specific questionnaire to collect all data necessary to determine, from the first call, the steps to be taken in the event of an individual reporting a neurological sign after consuming shellfish, so as to identify any suspected case. In this situation, it is necessary to investigate the clinical signs described in syndromes associated with marine neurotoxins, estimate the amount of shellfish ingested, and document their origin, place of purchase and production area. It is also important to ask the poisoned individuals to keep and freeze any meal leftovers, which may be used for subsequent analyses. The individual(s) should be referred to the emergency department for the collection of biological samples that may be stored (in particular for *a posteriori* testing for saxitoxins in urine) and will serve to confirm the poisoning.

It is essential to determine the origin of the shellfish to find information about potential toxins detected by REPHYTOX or RASFF notifications involving imported contaminated shellfish. These data contribute significantly to the diagnosis. It should be noted that from the time these toxins started to be monitored to the present day *(March 2021)*, there have been 19 RASFF notifications involving shellfish distributed in or imported into France and contaminated by paralytic toxins; 15 have involved amnesic toxins. When poisoning is associated with shellfish gathered by recreational harvesters in uncontrolled areas, it is essential to measure levels of toxins in unconsumed shellfish.

Lastly, in December 2020, ANSES and the PCCs introduced a system for the daily automatic monitoring of cases of shellfish poisoning recorded in the PCCs national database, to detect any suspected case the day following the call to the PCC. The aims are to launch investigations, alert the competent authorities, and inform the population as soon as possible.

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Nicolas DELCOURT (Toulouse CAP), Eric ABADIE(IFREMER).

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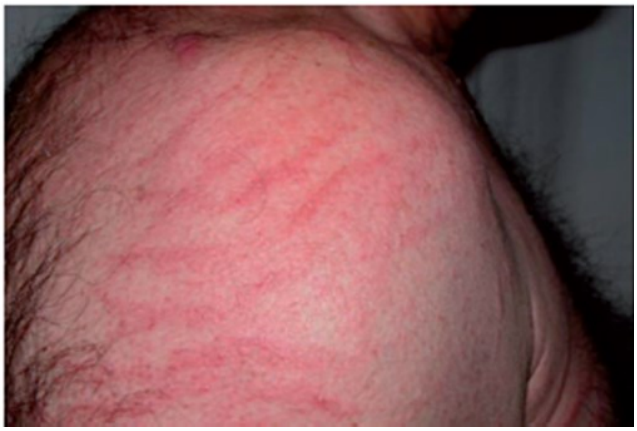
Poisoning from shiitake mushrooms : what's new since 2017 ?

A new review of cases of poisoning with shiitake mushrooms, reported to the French Poison Control Centres between 1 January 2014 and 31 December 2019, shows that the number of poisonings sharply increased in 2018 and 2019; however, the characteristic skin reactions related to the undercooking of these mushrooms remain stable. The provision of information to producers, restaurant professionals and consumers should be reinforced.



An alert in 2015: shiitake mushrooms need to be cooked

In the first issue of Vigil'Anses, we took a look at this curious mushroom that, if consumed raw or undercooked, causes some people to develop a skin reaction, which is sometimes combined with generally moderate digestive symptoms. The skin reaction is called flagellate dermatitis due to its fairly characteristic topography: the entire body is covered with highly pruritic linear lesions, as if the person had been whipped (see photo).

Shiitake mushrooms contain lentinan and trehalose, among other things.

The skin symptoms observed appear to be due to lentinan, a polysaccharide found in shiitake mushrooms that is destroyed by heat. There is no specific treatment and the dermatitis spontaneously regresses within two to three weeks.

The digestive signs are thought to be due to trehalose, which is also prevalent in shiitake mushrooms. Trehalose is a natural sugar that can only be degraded by trehalase, an enzyme in the intestine that is lacking in some individuals. For them, the accumulation of undigested trehalose in the intestine leads it to be fermented, which causes digestive signs such as diarrhoea.

Shiitake mushrooms, native to Asia, have been very common on the European market for the past several years, especially in France where they are grown and produced (see article in Vigil'Anses no. 1, [1]). They are believed to have medicinal properties that help combat certain cancers, high blood pressure and hypercholesterolaemia and stimulate the immune system. In Japan and China, lentinan is used as a complementary therapy in addition to standard cancer treatments (chemotherapy, radiation therapy, surgery) [2]. However, to date, there have been no applications for authorisation to market it as a medicinal product in the European Union. Due to the mushroom's status as a foodstuff, capsules of dry shiitake extract are sold as food supplements, some of which contain high concentrations of lentinan.

On 21 August 2015, after an alert by the Poison Control Centres and ANSES, a DGCCRF press release informed the general public of the need to thoroughly cook this food[1]. On the basis of ANSES's recommendation and in order to inform consumers at the time of purchase of the possible effects of consuming raw shiitake, a Ministerial Order of 5 August 2016[2] suspended "*for a period of one year, the placing on the market intended for the final consumer, whether or not in return for payment, of mushrooms of the species (...)* Lentinula edodes, *when presented fresh, in bulk or prepackaged, if they are not accompanied by clear information informing the consumer of the need for thorough cooking before consumption*".

1.http://www.economie.gouv.fr/files/files/directions_services/dgccrf/presse/communique/2015/cp-champignon-shiitake.pdf
2.https://www.legifrance.gouv.fr/eli/arrete/2016/8/5/EINC1622686A/jo/texte

And since then? There continue to be cases of poisoning...

The provision of such information has no longer been mandatory since August 2017. A new review of cases of poisoning reported to the Poison Control Centres was necessary to present the authorities with any new measures that needed to be taken. As the previous review had stopped at the end of 2013, the analysis dealt with cases reported to the Poison Control Centres between 1 January 2014 and 31 December 2019, with a focus on patients developing a skin reaction. In fact, after eating shiitake mushrooms, some people experience digestive signs such as nausea, vomiting or diarrhoea. However, these can be non-specific to shiitake mushrooms and have another cause, for example bacterial contamination due to poor food hygiene or the fermentation described above.

Over the study period, the Poison Control Centres took calls involving 125 individuals developing symptoms related to the consumption of shiitake mushrooms. Seventy (56%) of them complained of at least one skin symptom, including 59 who described a flagellate dermatitis reaction.

The temporal analysis showed that while the total number of cases was higher in 2018 and 2019 than in previous years, the number of people with skin reactions remained stable (Figure 1). The summer months were relatively spared due to pronounced seasonality (Figure 2).

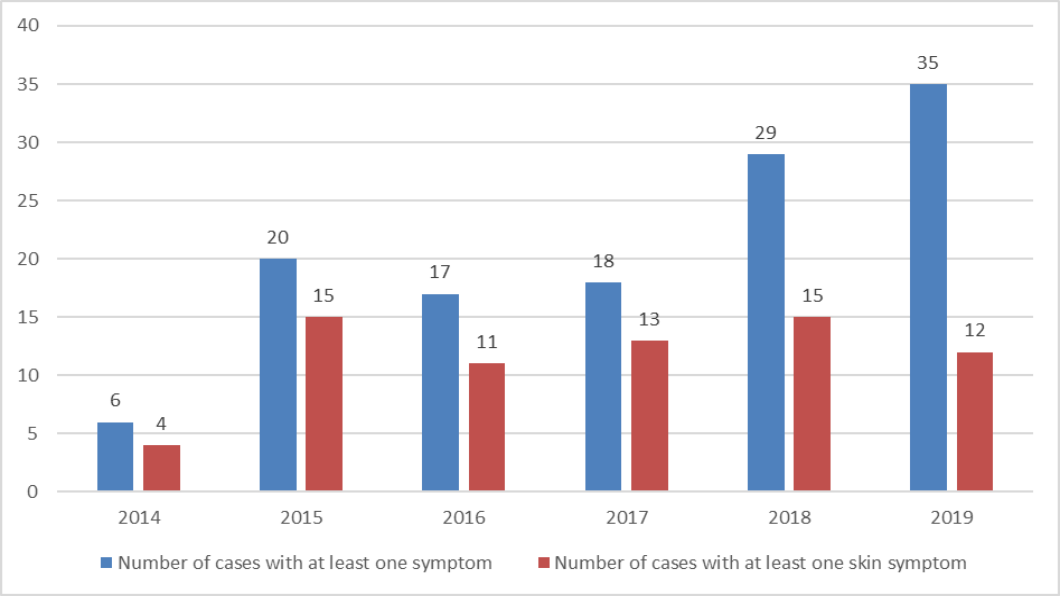


Figure 1: Year-to-year change in symptomatic cases and cases with at least one skin symptom. January 2014-December 2019 (n=125) (source: SICAP)

Who gets poisoned and how?

The 70 individuals who developed skin reactions were fairly young adults, between the ages of 19 and 69 (median: 39), with slightly more men aged 30 to 40. Information about the place of purchase or consumption was available for 41 cases. The shiitake mushrooms had mainly been purchased in supermarkets (61% of cases) or at a farmer's market (17%), or eaten at a restaurant (17%). The skin lesions had appeared on average within 48 hours of consuming the mushrooms, but sometimes the symptoms developed within an hour or conversely at a later time, up to a week following consumption. The mushrooms were consumed fresh in the large majority of cases; the dehydrated form only concerned 15% of cases.

Insufficient cooking was clearly the culprit for the individuals developing skin symptoms: only two of the 70 people said they had thoroughly cooked the shiitake mushrooms (Figure 3). The others had eaten them raw or undercooked (stir-fried, on pizza, or added to soup).

All of the individuals fully recovered, after a time period proportionate to the amount of mushrooms consumed: around four days for consumption of under 60 g, seven days for 60 to 150 g, and 15 days for larger amounts.

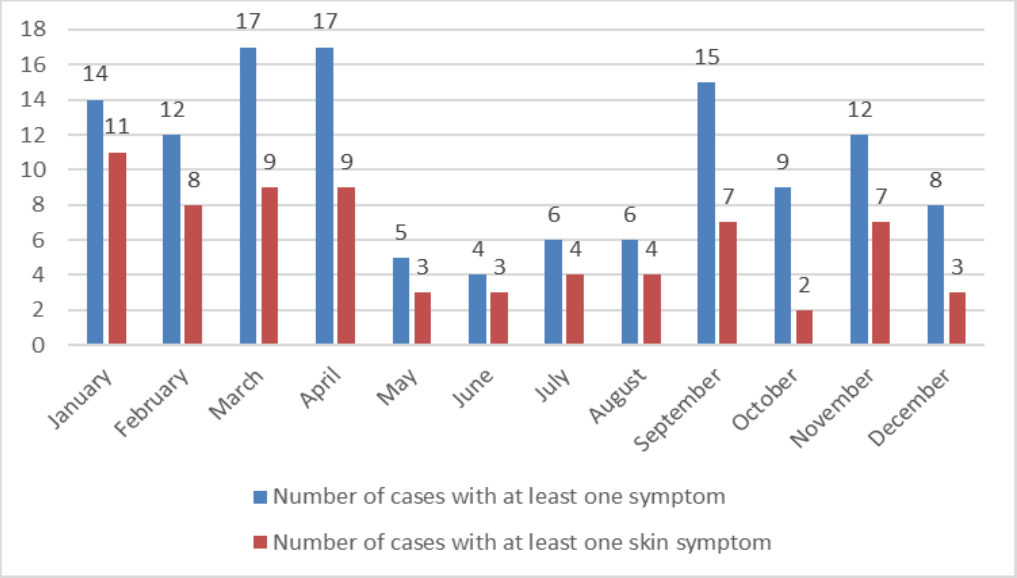


Figure 2: Monthly distribution of symptomatic cases and cases with at least one skin symptom after consuming shiitake mushrooms. January 2014-December 2019 (n=125) (source: SICAP)

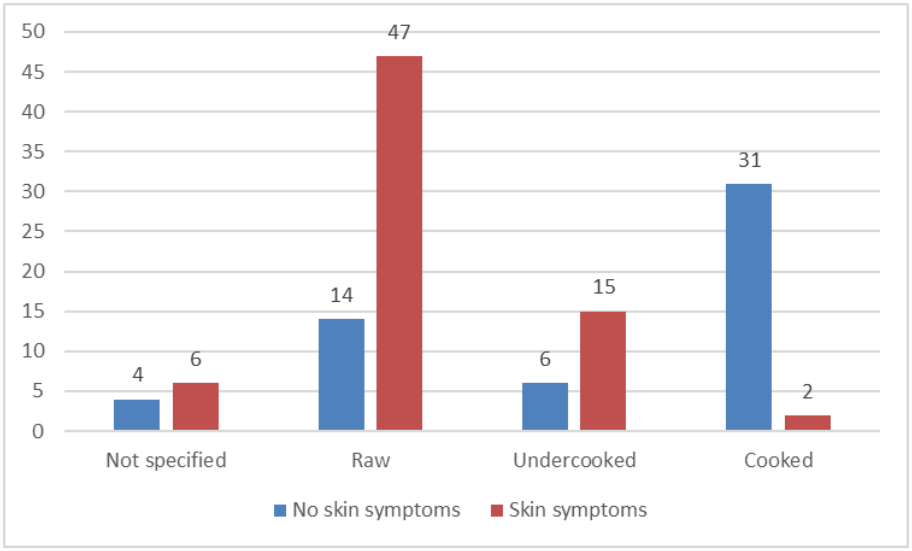


Figure 3: Breakdown of the number of cases with or without skin symptoms based on the method of cooking the shiitake mushrooms. January 2014-December 2019 (n=125) (source: SICAP).

Informing producers, restaurant professionals and consumers

It should be kept in mind that while these figures may seem low, they are merely a pale reflection of reality. Indeed, many cases of shiitake-induced flagellate dermatitis are not reported through calls to Poison Control Centres, in particular because the connection is not always made between the consumption of shiitake mushrooms and the occurrence of lesions, especially when these are of late onset. Following this review, the DGCCRF, ANSES and the Poison Control Centre are once again warning consumers of the risks involved.

On its part, the DGCCRF will launch an informational campaign aimed at shiitake producers to encourage them to include a statement on their products indicating that these mushrooms should be thoroughly cooked. This campaign will also be geared towards restaurant professionals, to remind them that certain modes of rapid cooking, such as stir-frying, are not sufficient to eliminate the risk of toxic dermatitis.

David Boels (Nantes University Hospital) and Juliette Bloch (ANSES)

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Nail glues: risk of severe thermal burns

The application of false nails requires the use of powerful glues, in particular cyanoacrylate glues. Their increasingly widespread domestic use can be responsible for serious injuries, especially deep thermal burns, as reported by Poison Control Centres. Due to differing risk and warning messages on packaging, consumers need to be better informed of the risks, in particular when cyanoacrylate glue gets on textiles/clothes in contact with skin.

The alert

In November 2020, French Poison Control Centres (PCCs) reported two serious cases of burns caused by nail glue.

The first case involved a 20-month-old girl. Glue had dripped on her cotton tee-shirt and then burned through onto her left wrist. The child immediately experienced a deep second-degree burn on this site that required a skin graft.

The nail glue, sold commercially, was a cyanoacrylate glue containing ethyl cyanoacrylate and polymethylacrylate. The product's label included prevention messages, in particular "Keep away from textiles. Contact with clothes can damage them and generate enough heat to burn the skin below them. If the product splashes on clothes, gently remove the affected clothing. If skin bonding occurs, do not pull apart; instead, wash with plenty of soapy water and then gently separate".

The second case involved a two-year-old girl who had played with a nail glue. The product spilled onto the hand and forearm of the child who was probably wearing a cotton long-sleeved pyjama top. The pyjama top adhered to the skin of her hand and the middle and ring fingers, which became stuck together. The mother was able to detach the fingers with cold water. The child developed a second-degree burn on the palm and back of one hand. As the outcome was satisfactory, the graft initially considered did not end up being necessary. According to the child's mother, the nail glue packaging did not include any particular warnings.

Nail glues are cosmetic products. These alerts were therefore sent to the French National Agency for Medicines and Health Products Safety (ANSM), which is charge of cosmetovigilance in France.

A chemically well-explained mechanism that is nonetheless not widely known by clinicians

Direct skin contact with cyanoacrylate glue is generally not serious. However, in the event of splashes through primarily cotton or wool clothing, the polymerisation reaction of the glue is chemically catalysed, i.e. amplified by the fabric: the reaction's acceleration causes instant heat release, inducing a skin burn.

The high fluidity of nail glue can enlarge the area of skin contact by diffusion through garment fabric and thus increase the area of skin burn.

In the scientific literature, around 20 cases have been reported to date; they have almost exclusively involved children. One of the most recent publications described the case of a two-year-old boy who had played with a bottle of nail glue. The product accidentally got onto his hands and cotton tee-shirt at chest level, causing a second-degree burn. Since the surface area of the burn ended up being small, a skin graft was not necessary [1].

An Australian team published the case of a four-year-old girl who had received a skin graft on her leg after cyanoacrylate superglue had splashed onto her cotton trousers. The same team conducted an experimental study to measure the temperatures generated after the splashing of cyanoacrylate glue onto cotton: 90 seconds after application, the measured temperature was 91°C. It took more than three minutes for the temperature to drop below 40°C [2].

What do existing regulations say?

In France as well as in Europe, Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures, known as the CLP Regulation, applies. Mixtures containing substances classified for their toxicity must include hazard pictograms and labelling corresponding to their toxic effects. For example, ethyl cyanoacrylate is classified as a Category 2 skin and eye irritant.

On the packaging of mixtures containing cyanoacrylates, the CLP Regulation additionally provides EUH202 hazard labelling which reads: "Cyanoacrylate. Danger. Bonds skin and eyes in seconds. Keep out of the reach of children". However, this labelling does not take into account the highly likely mechanism of burning in the event of accidental spillage on clothes.

For their cosmetic uses, some compounds such as ethyl cyanoacrylate and ethoxyethyl cyanoacrylate are among the common cosmetic ingredient names used (https://ec.europa.eu/growth/sectors/cosmetics/cosing_en). They are used as film-forming agents (formation of a continuous film on the skin, hair or nails as in nail polish, for example) or binding agents (nail glue, for example). Regulation (EC) No 1223/2009 of the European Parliament and of the Council on cosmetic products therefore states that the packaging of products containing them must indicate their presence.

In Canada, several warnings have been issued, especially in 2020, for bottles of cyanoacrylate glue intended for DIY activities, which did not comply with the Canada Consumer Product Safety Act. These products did not provide information on the risk of burns by direct contact or were not equipped with a child protection mechanism (opening of the product exclusively with a tool not supplied with the container [3]).

An essential reminder of precautions to be taken

Several factors are encouraging the use of cyanoacrylate nail glues at home: growing trend and trivialisation of nail application strengthened by a decrease in visits to professional nail salons in the context of the current pandemic. Therefore, the practice of applying false nails at home seems widespread.

These nail glues are sold freely in shops (speciality stores, large retail outlets, etc.) and on the Internet. Many different products are thus available on the market and for some of them, statements indicating the risk of direct or indirect burns through clothes are unclear or even non-existent, which does not comply with the regulatory requirements.

The number of serious burns from splashes on fabric, reported to the PCCs, is low but it underestimates the real picture: in fact, when it comes to burns, the primary care provider is an emergency department, whether specialised or not, or a general practitioner. The PCCs are not generally consulted.

With the aim of preventing serious burns, manufacturers should therefore consider reinforcing precautionary messages in the event that these products are used at home. A recent publication reported a second-degree burn on the foot of a young woman who had accidentally spilled nail glue on her cotton pyjamas; a skin graft was necessary. The young woman had not been aware of the risk of serious burns in case of splashing on fabric and wrongly thought that this situation was less serious than the direct splashing of glue onto skin. The authors of this publication stress the need to better inform consumers of the risks, which are too often overlooked [4].

Clearer and more visible labelling could enable consumers to be better informed of the steps to be taken in case of splashes, such as immediately applying cold soapy water to limit the surface area and depth of the burn.

Lastly, as provided for in the European regulations, these products should not be left unattended and must be kept out of the reach of children.

Cyanoacrylate glues are also used for other purposes such as modelling and have the same characteristics (large bottles, glue with low viscosity, quick setting). Therefore, our recommendations also apply to these products and the corresponding population.

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Neurotoxicity of metronidazole, an antibiotic and antiparasitic medication, in dogs: risks even at low doses

The neurotoxicity of metronidazole, an antibiotic and antiparasitic medication, has been reported in humans and animals since the 1980s. In dogs, it mainly causes balance disorders and/or tremors. Whereas up to now, high doses of metronidazole (above the usual dose, which can reach 50 mg/kg/day) were generally implicated, a recent study described neurological adverse effects occurring from 26 mg/kg/day. An analysis of the pharmacovigilance data corroborated this study's results, identifying a risk related to prolonged use of the medication, even at low doses. Special precautions for use are therefore necessary to limit the risk of occurrence of these adverse effects.

Surveillance of veterinary medicinal products once they have been placed on the market is based primarily on pharmacovigilance, via spontaneous reports of adverse effects observed by stakeholders in the field (veterinarians, farmers, etc.). However, scientific publications can help provide additional information and shed light on certain events notified through the adverse effect reporting channel.

For example, a study on the neurotoxicity of metronidazole in dogs, published in 2018 in the Australian Veterinary Journal [9], was analysed by the French Agency for Veterinary Medicinal Products (ANMV). Its results were compared with the data recorded in the national veterinary pharmacovigilance database.

Metronidazole is a nitroimidazole antimicrobial that has been used in humans since the 1960s to treat infections with anaerobic bacteria and certain protozoan parasitic diseases.

Metronidazole in dogs

Several veterinary medicinal products containing metronidazole combined with another antibiotic, spiramycin, have been authorised for pets since the 1990s in particular for the treatment of oral infections, with recommended doses of metronidazole ranging from 12.5 to 16.7 mg/kg/day for six to 10 days.

Since 2015, several products for pets have been authorised that exclusively contain metronidazole. They are indicated for the treatment of giardiasis (a protozoan infection responsible for diarrhoea in dogs) and infections with anaerobic bacteria, with higher doses and a treatment regimen tailored to these infections: 50 mg/kg/day, in one or two doses per day, for five to seven days.

Known toxicity

The neurotoxicity of metronidazole has been reported in humans and animals since the 1980s [2, 3]. In humans, damage to the peripheral nerves and optical nerve, encephalopathies and damage to the inner ear and cerebellum[1] have been described. The mechanism behind this neurotoxicity remains unclear but may involve the formation of free radicals or thiamine analogues or be related to the action of metronidazole and its metabolites on the cellular RNA of neurons, altering protein synthesis and inducing their degeneration [5]. The use of doses above 42 g per day for an adult is considered as posing a risk, but recent studies indicate that this neurotoxicity, while rare, can occur regardless of the dose or duration of treatment [6]. In dogs, damage to the cerebellum or vestibule[2] is generally reported, in connection with the use of doses of metronidazole exceeding 60 mg/kg/day [4, 7].

1. Part of the brain, playing a role in motor balance in particular
2. Part of the inner ear, involved in motor balance

The study mentioned in the introduction describes a total of 26 dogs presenting with neurological signs attributed to metronidazole in several veterinary hospitals in the United Kingdom from 2004 to 2017 [9]. The average age of the included animals was 7.2 years (from 1.5 months to 12 years). Metronidazole had been prescribed for diarrhoea in 54% of cases and for infections with anaerobic bacteria (arthritis, endocarditis, abscesses, etc.) in the others. The doses of metronidazole used ranged from 26 to 112 mg/kg/day administered in two doses, with an average of 42 mg/kg/day. The average duration of treatment was 35 days. The symptoms occurred after 10 days of treatment in 92% of cases. The main symptoms encountered were gait disorders and/or abnormal eye movements. The symptoms generally disappeared within three days of discontinuing use of metronidazole. In the majority of cases, diazepam treatment was introduced to accelerate recovery. This was the first study reporting metronidazole-induced neurotoxicity at doses below those previously described, from 26 mg/kg/day.

Toxicity supported by French veterinary pharmacovigilance data

The data from the national pharmacovigilance database were reviewed for the period from January 2001 to June 2019. Cases where the role of metronidazole in the adverse effect could be ruled out with certainty were excluded, as were cases where several medications were involved.

In total, over this period, 124 reports of adverse effects possibly related to metronidazole were recorded, including 99 reports in dogs.

As shown in Figure 1, the number of reports related to metronidazole remained stable and very low from 2001 to 2015 and then increased from 2016, when the first medicinal product containing metronidazole alone was placed on the market. However, this increase should be put in perspective since the number of corresponding reports was low, the veterinary pharmacovigilance system had only been operational since 2003, and reporters are generally more likely to report adverse effects of new medicinal products than those of medicinal products that have been used for several years.

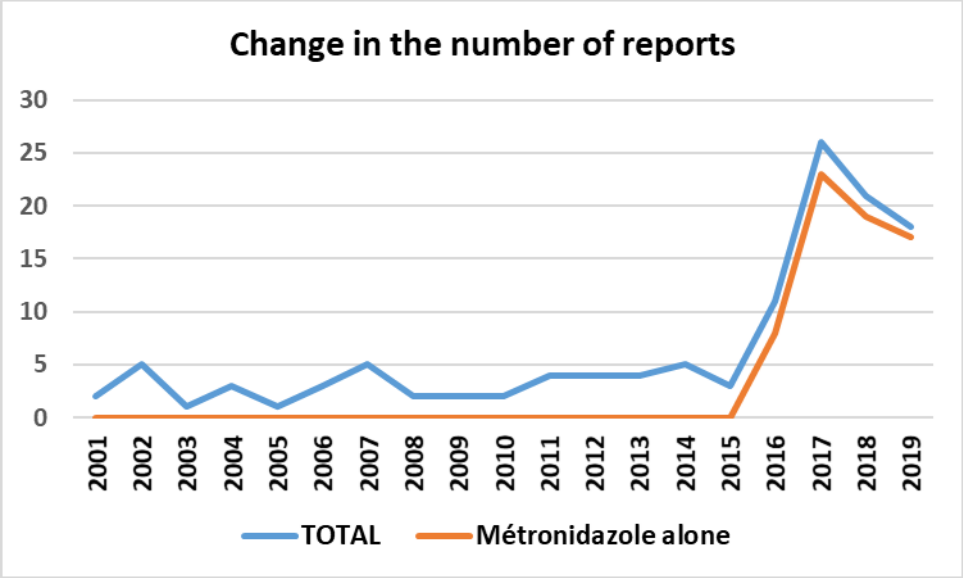

Figure 1: Change in the number of reports from 2001 to 2019 (source: national veterinary pharmacovigilance database)

The analysis focused on dogs, the main species involved in these reports (99/124). The proportion of reports involving medicinal products combining metronidazole and spiramycin was studied, in addition to the percentage of reports for medications containing metronidazole alone. While the results show that these proportions were similar (respectively 44.4% vs 55.6% of reports), neurological adverse effects were more often observed with medicinal products containing metronidazole alone than in combination with spiramycin (82% vs 38.6%).

Table 1: Breakdown of the 99 reports in dogs by medicinal product and type of adverse effect

	Metronidazole + Spiramycin % (N)	Metronidazole % (N)	Total % (N)
% (N) of reports	44.4 (N=44)	55.6 (N=55)	100.0 (99)
Including % (N) of reports with neurological signs	38.6 (N=17)	82.0 (N=44)	61.6 (61)

This finding was probably due to different indications depending on the medicinal product and therefore to different administered doses of metronidazole and treatment durations. Regardless of the type of medicinal product (metronidazole alone or in combination), balance disorders made up the majority of the reported neurological disorders.

Uses frequently not compliant with the recommendations

A more detailed analysis was conducted for cases with neurological signs reported since 2016, the first year in which veterinary medicinal products containing metronidazole alone were placed on the market.

Over this period, there were 48 reports of neurological adverse effects related to the use of metronidazole in dogs. The majority of these adverse effects were observed with medicinal products containing metronidazole alone (45/48, i.e. 93.8%) (Fig. 1). The age of the animals in question ranged from two months to 14 years, with an average age of 5.2 years. The average weight was 18 kg (from 1.4 to 50 kg), with no significant over-representation in terms of breed or sex. For half of the animals, the reason for using metronidazole was a digestive disorder.

The main reported symptoms were ataxia[3] and muscle fasciculations.

The product was only used in accordance with the recommendations of the Summary of Product Characteristics (SPC) in nine cases, in terms of dosage and duration of treatment. The disorders occurred two hours to seven days after the start of treatment, with doses of metronidazole ranging from 25 to 53 mg/kg/day. No information on the progression of the symptoms was available in these cases.

Conversely, the product was not used in accordance with the SPC in 81.2% of cases (39/48). For 17 dogs, the treatment duration was longer than that recommended in the SPC (ranging from eight days to five months). Nine dogs received a dose above that mentioned in the SPC (ranging from 60 to 160 mg/kg/day). Thirteen dogs received a dose above that recommended and for a period longer than that recommended. In these 39 cases, the disorders occurred within less than two hours to six months after the start of treatment and lasted from one hour to 15 days.

When using metronidazole, precautions should be taken for the animal…

The possible occurrence of neurological signs is already mentioned in the SPCs of medicinal products containing metronidazole authorised since 2015.

While the available data seem to show a high level of interindividual variability in the occurrence of metronidazole-induced neurological toxicity in dogs, they also reveal an increased risk in the event of use not compliant with the SPCs, whether in terms of the dose and/or duration of treatment. These data seem to corroborate the study by Tauro *et al.* in which administration for longer than the period of treatment recommended in the authorisations was reported in 92% of the cases of neurological adverse effects [9].

Prolonged use of metronidazole for chronic digestive diseases for example (a common reason for use in dogs) should therefore lead practitioners to be particularly attentive when monitoring the treated animals. It should be emphasised that prolonged therapeutic regimens remain outside of the framework of these products' marketing authorisations (MAs) and are the responsibility of the prescriber, who should therefore assess the benefits and risks and adapt the dosage and treatment duration based on the situation.

Special attention should also be paid to the daily dose administered, especially for small animals. The dose must be calculated as accurately as possible and the formats used should be suited to the size of the animal.

… **and for the user**

Metronidazole and some of its metabolites are likely to interact with the DNA of the cells of humans and animals such as rats, mice [2, 5] and, more recently reported, cats [8].

3. Ataxia is a neurological disorder that affects balance and the coordination of movements

In rats and mice, a significant increase in the number of mammary tumours, lymphomas and lung adenomas was demonstrated after 100 days of oral administration of metronidazole, which led the drug to be considered as carcinogenic in animals and as possibly carcinogenic (2B) in humans based on the classification of the International Agency for Research on Cancer (IARC) [2].

This mutagenicity and potential carcinogenicity qualified metronidazole to be classified as a prohibited substance in food-producing animals such as cattle, pigs and poultry [1]. When treating pets, special precautions for use should be taken to keep people from being exposed to metronidazole. For example, the SPCs of the medicinal products authorised since 2015 clearly state that those administering the medicinal product need to wear impervious gloves.

Conclusion: a useful medicinal product if properly used

While metronidazole still has major benefits in veterinary medicine, its use should be rational, with appropriate doses and durations of treatment taking into account the animal and the clinical and infectious context, with a view to limiting the adverse effects, especially in terms of neurotoxicity. A better understanding is needed of the mechanism behind this toxicity and of the circumstances in which it occurs in dogs and other species (cats, horses) in which metronidazole is also used. Post-MA surveillance of these medicinal products will help refine the risk assessment for metronidazole used in animals.

Sylviane LAURENTIE (ANSES-ANMV)

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TO FIND OUT MORE :

Neurotoxicité induite par le métronidazole chez le chien, J. Bietrix, M.A. Moriceau, S. Laurentie, Point vétérinaire No 413/414, January-February 2021

Severe acute hepatitis associated with consumption of a food supplement claimed as being Ayurvedic

ANSES received a report of severe acute hepatitis probably associated with consumption of the SriSri Kanchanara® food supplement; the company placing this product on the market claims that it relates to the practice of Ayurvedic medicine[1]. Causality 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 health professionals [1]. It recommends paying special attention to the adverse effects likely to occur following the consumption of all products containing kanchanara bark and stresses that such effects should be reported to the national nutrivigilance scheme.

As part of its nutrivigilance scheme set up in 2009, ANSES received a report of severe acute hepatitis probably associated with consumption of the food supplement SriSri Kanchanara® marketed by the company Shankara France. This product is made exclusively of the bark of kanchanara, whose scientific name is *Bauhinia variegata*. This plant has traditionally been used in Ayurvedic medicine for its anti-diabetic, antibacterial, antifungal and anti-tumour properties.

The alert

The report involved a 59-year-old woman who had no prior medical history and was not taking any medication. Her alcohol consumption was moderate and occasional.

In late May 2019, she began taking the food supplements SriSri Kanchanara® and SriSri Amruth®. The product SriSri Amruth® was discontinued in late August 2019, i.e. after three months of use.

In mid-October, i.e. after four and a half months of consuming the food supplement SriSri Kanchanara®, she began complaining of fatigue. In late October, the patient observed conjunctival icterus[2]. She stopped taking the food supplement. Four days later, she was hospitalised in a hepatology unit. Clinical examination found no anomalies, aside from conjunctival icterus. Biological examinations revealed acute cytolytic hepatitis with hepatocellular failure[3]. A complete aetiological investigation was conducted to identify the cause of this severe acute hepatitis. It ruled out the main infectious diseases, alcoholic liver disease, vascular or biliary disease, Wilson disease[4], autoimmune disease and a drug-related cause. The results of the liver biopsy were in favour of a toxic disease, but without formally ruling out an infectious disease.

The clinical and biological course was then slow but favourable. The patient returned home in late November 2019, although her liver panel results remained abnormal until February 2020.

Link with the use of these food supplements

The food supplements' causality in the occurrence of the severe acute hepatitis was assessed using the method developed for the nutrivigilance scheme (ANSES, 2019) [2]. Causality takes three criteria into account: the time to onset, the outcome after discontinuing use of the product in question and after its reintroduction where applicable, and other potentially excluded aetiologies.

1.Ayurveda is a natural, traditional medicine system that originated in India more than 5000 years ago.
2.Conjunctival icterus refers to the yellowing of the white of the eye.
3.Hepatocellular failure is defined as a set of clinical and biological signs, due to the impairment of liver cell function, such as asthenia, jaundice, hepatic encephalopathy, skin and endocrine symptoms, haemorrhagic syndromes, and infections.
4.Wilson disease is a genetic disorder characterised by excess copper in the body, especially the liver.

For the SriSri Kanchanara® food supplement, the time to onset of the effect was considered "compatible". The adverse effects regressed when the SriSri Kanchanara® product was no longer consumed and the slow regression kinetics were due to the severity of the hepatic disorders. The outcome was therefore described as "suggestive". The aetiological investigation ruled out the most frequent causes of acute hepatitis. The SriSri Kanchanara® product was therefore deemed **very likely** responsible for the occurrence of this severe acute hepatitis, i.e. **I4**, on a scale ranging from I0 = excluded to I4 = very likely.

This same expert assessment was undertaken for the SriSri Amruth® food supplement. The time to onset of the effect was deemed "incompatible", as the product had been discontinued around two months before the onset of the first clinical signs. The responsibility of the product SriSri Amruth® in the occurrence of this severe acute hepatitis was therefore excluded (i.e. I0).

Have similar cases been described in the scientific literature?

The literature search focused on the potential hepatotoxicity to humans of the ingredient in the SriSri Kanchanara® food supplement, i.e. kanchanara *(Bauhinia variegata*) bark. Only one clinical case of liver damage has been published involving the consumption of kanchanara. It describes the case of a 44-year-old woman who developed jaundice, discoloured stools and dark urine after six months of consuming three plant-based products/homoeopathic medications (*Kanchnar guggulu*, *Punarnava Mandur* and a third unidentified product). Following an aetiological investigation, toxic hepatitis was diagnosed. The outcome was favourable upon discontinuation of the three products. As several multi-ingredient products were consumed and one could not be identified, the occurrence of this hepatitis reported in the literature cannot be exclusively attributed to kanchanara. No other cases have been published and in particular, there have been no published cases where kanchanara was the sole plant in question.

Have similar cases been reported to the nutrivigilance scheme?

Another case of liver damage involving a product named "Kanchanara" was reported to the nutrivigilance scheme. In this case, two other food supplements had been consumed simultaneously (*Curcuma longa* and *Bringaraj)*. Since the ingredients in these three products could not be precisely identified, no causality analysis could be conducted for this case.

Conclusion and recommendations

For the case reported here, the causality of the SriSri Kanchanara® food supplement in the occurrence of severe acute hepatitis was deemed very likely. The current data are not sufficient to formally conclude as to the hepatotoxic nature of the kanchanara plant, traditionally used in Ayurvedic medicine. However, in view of the various identified signals and growing public interest in these products, special attention should be paid to the adverse effects likely to occur following consumption of this plant.

ANSES reiterates its usual recommendations concerning food supplements. It recommends that:

- Consumers should:

- notify a healthcare professional of any adverse effect occurring after consumption of a food supplement;

- 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, pharmacist, etc.);

- be wary of the therapeutic properties attributed to food supplements;

- exercise great caution regarding the purchase of products via alternative channels (Internet, gyms, etc.) and without personalised advice from a healthcare professional.

- Healthcare professionals should communicate cases of adverse effects they suspect of being associated with the consumption of food supplements and report these to the nutrivigilance scheme.

Fanny Huret and Gwenn Vo Van Regnault

Where should reports be sent?

Adverse effects can be reported on the Adverse Health Event Reporting Portal of the Ministry of Social Affairs and Health or directly by completing the online reporting form.

References

[1] ANSES Opinion on a case of severe acute hepatitis associated with consumption of the SriSri Kanchanara® food supplement

[2] ANSES Opinion on updating the method for determining causality in reports of adverse effects in nutrivigilance

ANSES is in charge of several health vigilance systems: pharmacovigilance for veterinary medicinal products, nutrivigilance, 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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