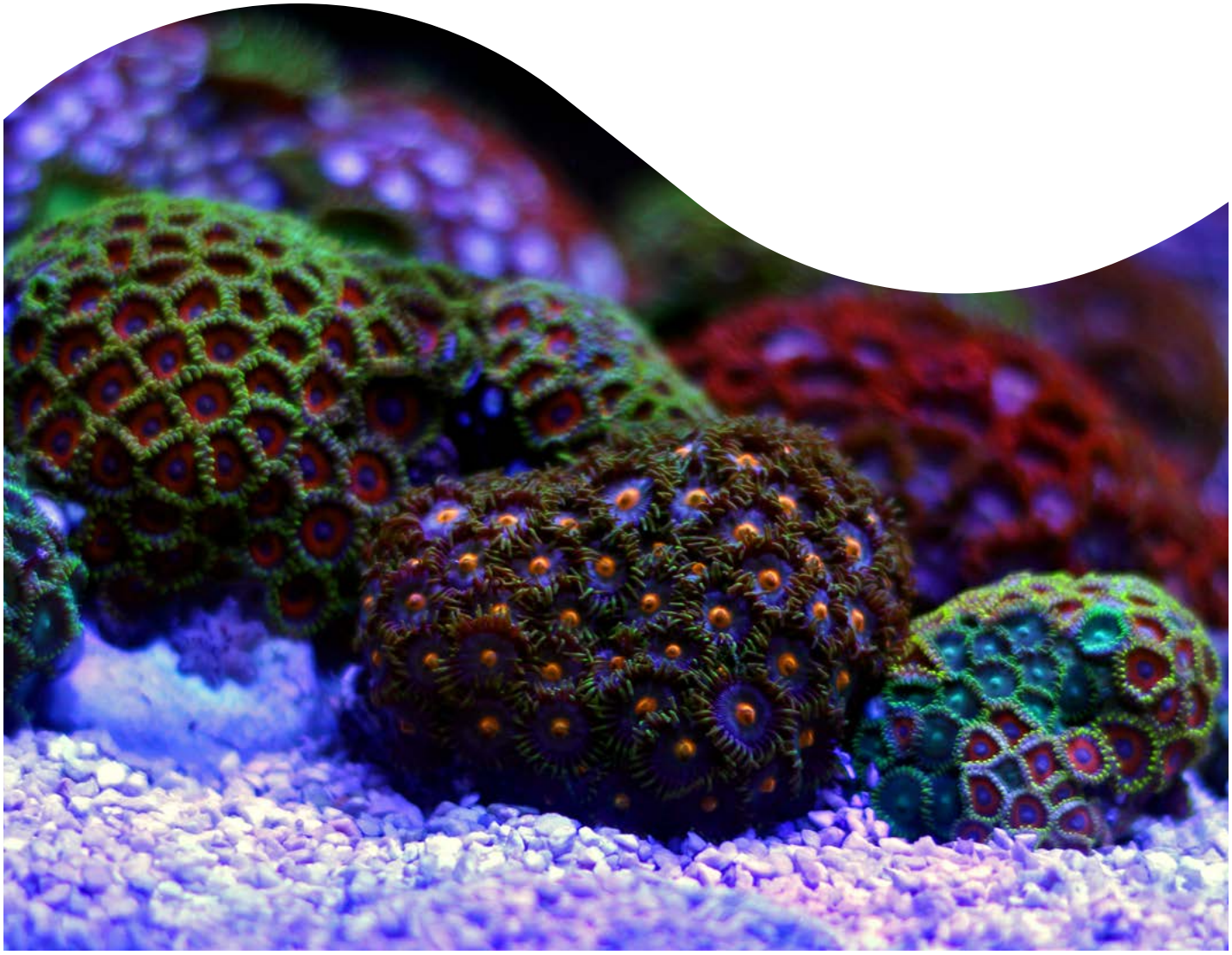
anses
French agency for food, environmental and occupational health & safety
Investigate, evaluate, protect

THE BULLETIN OF VIGILANCE
No.5
June 2018

VigilAnses



The call for applications to become an expert for the "Vigilance for natural toxins" Working Group (WG), which the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) will be setting up in the autumn, has just closed. After "Vigilance for chemical products" and "Vigilance for regulated products", this third ANSES WG dedicated to vigilance will work on cases of poisoning associated with toxins found in plants, fungi, animals and insects. Indeed, nature is host to numerous health hazards, as demonstrated each year by the wild mushroom poisonings and snake bites that Vigil'Anses has highlighted in previous issues.

This fifth issue has three different articles on this theme.

The first concerns a consumer product well known to apricot jam makers: **bitter apricot kernels**. While one kernel added to perfume several jars of jam is not a problem, ingesting them in large quantities – usually because of a scientifically unproven claim that they have anti-cancer properties – exposes consumers to the risk of cyanide poisoning. The article presents cases of poisoning reported by Poison Control Centres (PCCs).

With the recent trend in saltwater aquariums, there has been an increase in trade in live corals, particularly for decorative purposes (cover photo). When stressed, some of these species are capable of releasing **palytoxin**, a very potent toxin. When they are handled or cleaned, therefore, aerosolised palytoxin can reach the handler's eyes, respiratory tract or skin and cause potentially severe injuries. The second article presents the cases of poisoning reported to the PCCs, as well as the precautionary measures to be taken when handling these corals.

Datura is a wild plant that grows very easily and is therefore found all over France, in fields, on wasteland and among ruins, but also in urban centres. Its leaves, flowers and seeds contain substances with hallucinogenic properties, regularly responsible for poisoning cases, as described in the third article. Following an alert from the PCCs, the Directorate General for Health (DGS) recommended that local authorities uproot *Datura* plants in early summer in areas frequented by young people.

Poisoning from household products is a threat to toddlers from the moment they start to move around on their own and grab whatever is within their reach. The availability of **individual liquid detergent pods** has led to an epidemic of poisoning cases among young children, who are exposed to liquid detergent when putting the pods in their mouths or piercing them with their fingers. An article in this issue describes how monitoring of poisoning cases by the PCCs and ANSES identified this phenomenon and then showed the impact of preventive measures taken by the detergent industry.

The last article in this issue reports on a highly innovative **biomedical research study** conducted by ANSES, which sought to link contact dermatitis from the wearing of clothing or shoes to substances identified in the articles in question (**textiles or footwear**). This is because although dimethyl fumarate (DMFu) has been in the news since 2008 and has been banned in the European Union in articles in contact with the skin, cases of allergic dermatitis to textiles and footwear continue to occur. This study, which is still ongoing, has already identified other culprits...

Lastly, in the news section, you can read or re-read the news update published by ANSES in April 2017 on the risks associated with the consumption of food supplements containing **melatonin**.

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

Food supplements containing melatonin are not suitable for everyone!

Under the national nutrivigilance scheme run by ANSES, reports of adverse effects likely to be associated with the consumption of food supplements containing melatonin have been reported. A retrospective analysis of these reports, combined with the considerable level of consumption of this type of supplement, led ANSES to conduct an assessment of the potential health risks. On 11 April, ANSES published an opinion on the risks associated with the consumption of food supplements containing melatonin (see link below).

In France, melatonin is used in medicinal products, extemporaneous preparations and food supplements. It is a hormone secreted naturally during the night. One of its physiological functions is to promote sleep. In addition to its effects on the biological clock, melatonin has other properties: modulation of mood and the immune system, regulation of body temperature and intestinal motility. It also has vasodilatory, vasoconstrictor and proinflammatory activity. Under certain circumstances, or when interacting with other substances, these physiological effects can lead to the occurrence of adverse effects.

Ninety cases of adverse effects following the intake of food supplements containing melatonin have been reported to the national nutrivigilance scheme. Each case has been analysed individually and the conclusions shared with the parties reporting the cases and the manufacturers. A variety of different effects have been reported: general symptoms (headaches, dizziness, drowsiness, nightmares, irritability) and neurological (tremors, migraine) and digestive (nausea, vomiting, abdominal pain) disorders.

The retrospective analysis of all these cases led ANSES to initiate an assessment of the risks associated with the consumption of these food supplements. The risks were characterised by an in-depth analysis of the literature, leading ANSES to issue recommendations for manufacturers/producers, consumers and healthcare professionals.

The Agency's recommendations for consumers

The Agency recommends that people suffering from inflammatory or autoimmune diseases, as well as pregnant and breastfeeding women, children and adolescents, and anyone carrying out any activity requiring sustained vigilance where drowsiness could pose a safety problem, should not consume melatonin in the form of a food supplement.

People with epilepsy, asthma, or suffering from mood, behaviour or personality disorders, or anyone being treated with medication should seek medical advice regarding the consumption of melatonin in the form of food supplements.

In the absence of sufficient data on the long-term effects of melatonin consumption, the Agency recommends limiting the consumption of these food supplements to occasional use.

More generally, the Agency recommends that consumers seek medical advice before consuming food supplements and inform their doctor that they are taking any food supplements.

Other recommendations

French regulations authorise the marketing of food supplements providing less than 2 mg of melatonin per day. Given the variability in the status of melatonin and the regulatory limits governing its use within the European Union, and in the absence of sufficient data on the safety of daily consumption of 2 mg of melatonin, the Agency has questions about the place of melatonin on the market in food supplement form at doses comparable to those of the medicinal product. It believes it is necessary to define a harmonised regulatory framework at European level on the basis of safety studies conducted for doses below 2 mg.

More generally, ANSES reminds healthcare professionals of the need to report to the national nutrivigilance scheme any adverse effects likely to be associated with the consumption of food supplements about which they become aware.

Lastly, ANSES emphasises the value of setting up a joint international project on the monitoring of adverse effects associated with the consumption of food supplements.

Gwenn VO VAN REGNAULT (Anses)

TO FIND OUT MORE, VISIT:

Opinion of the French Agency for Food, Environmental and Occupational Health & Safety on the risks associated with the consumption of food supplements containing melatonin

Bitter apricot kernels: to be consumed in strict moderation

Cases of bitter apricot kernel poisoning have been reported across Europe in recent years, leading to a warning being issued by the European Food Safety Authority (EFSA) [1].

This is because these kernels contain a significant amount of amygdalin, a cyanogenic glycoside, which releases highly toxic hydrocyanic acid (cyanide) during digestion.

Bitter apricot kernels have been on the market for a few years now, claiming "anti-cancer" properties. While there is no scientific evidence of their value in curative or preventive cancer treatment, the popularity of these kernels can be measured on the Internet, where sites encourage their consumption in large quantities ranging from 10 kernels per day for prevention to 60 kernels for people suffering from cancer.

In cases of acute poisoning, because the brain and the heart are the organs most susceptible to cyanide, the victim very quickly presents with neurological and cardiac symptoms.

At low doses, cyanide poisoning can cause symptoms such as fever, headache, nausea, insomnia, lethargy, joint and muscle pain, and a drop in blood pressure. Poisoning from high doses can lead to convulsions, respiratory problems, decreased heart rate, loss of consciousness and even coma.

Cyanide has very high acute toxicity.

In 2016, EFSA established a safety level for single point exposure (acute reference dose or ARfD[1]) of 20 µg/kg body weight [1]. Based on these thresholds and the amount of amygdalin usually found in raw kernels, EFSA estimated the maximum quantity of kernels that would not exceed the ARfD to be around one to three per day for adults and half a small kernel a day for children.

To better understand the situation in France regarding bitter apricot kernel poisoning, the French Poison Control Centres (PCCs) and ANSES examined the cases reported to the PCC network.

Exposure cases were extracted from the PCCs' National Database of Poisoning Cases (BNCI)[2] between 1 January 2012 and 11 October 2017.

Symptomatic cases were defined as relating to individuals who experienced one or more symptoms within 12 hours of when they last ingested kernels. Asymptomatic cases were also included to document ingested doses that did not result in any clinical signs.

An acute exposure case was defined as one resulting from a single dose and a chronic exposure case as one occurring in a regular consumer of bitter kernels.

To analyse cases according to the amount of cyanide ingested, the maximum amount of cyanide per kernel was estimated at 3.8 mg/g of apricot kernel [1].

A total of 154 cases were selected, including 86 women and 66 men with median ages of 42 and 15 years respectively. Among these 154 cases, 33 were symptomatic and 121 were asymptomatic at the time of the call to the PCC. In 12% of cases (n=18), kernels were consumed for their "anti-cancer" properties, either by people with cancer (n=13) or for preventive purposes (n=5). As this information was not systematically provided in all the medical records, the frequency of this reason for consumption is undoubtedly higher.

Among the cases of acute exposure, the final outcome was known for 61 cases (40 remained asymptomatic and 21 were symptomatic). Table 1 shows the number of apricot kernels consumed according to the clinical situation.

The average number of kernels consumed was higher in symptomatic cases ($p<0.01$) The cumulative percentage of symptomatic cases increased with the number of kernels ingested, from 5% for less than five kernels to 80% for more than 50 kernels (see Table 2).

The reported symptoms, occurring in the first few hours after ingestion, were mainly neurological or neuropsychic, with dizziness, discomfort and headache, and other related symptoms such as digestive disorders, cardiac "palpitations" and transient respiratory discomfort.

1. The acute reference dose (ARfD) is the maximum amount of active substance, expressed in mg/kg body weight, that can be ingested by the consumer for a short period, i.e. during a meal or a day, in food or drinking water, without an adverse effect on health.

2. When a call is received by the toxicology emergency telephone hotline (RTU) of a poison control centre, a medical record is created. This contains information on the person(s) exposed, the agents involved, the routes of exposure, and the symptoms, among other things. It is coded with an agent from the National Database on Products and Compositions (BNPC) and then recorded in the National Database of Poisoning Cases (BNCI). These two databases form the PCCs' information system (SICAP).

Table 1: Number of apricot kernels consumed in symptomatic and asymptomatic cases (n=61).

		Asymptomatic cases (n=40)	Symptomatic cases (n=21)	p
Number of apricot kernels consumed	Min	1.0	3.0	
	Max	50.0	90.0	
	Median	4.5	20.0	
	Mean	9.8	27.2	< 0.01

Table 2: Cumulative percentage of symptomatic cases according to the number of apricot kernels consumed at one time.

Number of kernels consumed (Estimated cyanide equivalent)**	Cumulative % of symptomatic cases
<5 (<9.5 mg)	5%
<10 (<19 mg)	12%
<20 (<38 mg)	19%
<30 (<57 mg)	26%
<50 (<95 mg)	30%
≥50 (≥95 mg)	80%

** For a maximum amount of cyanide estimated at 3.8mg/g of apricot kernel [1].

Fifteen cases involved repeated consumption of apricot kernels. The people had contacted a PCC either because they had symptoms (7 cases) or because they had just become aware of the risk of cyanide poisoning (8 cases). In nine cases, consumption was for "anti-cancer" purposes. The duration of exposure was not always specified, while the amounts consumed ranged from one to 40 kernels a day, with a median of 10 kernels a day. Symptomatic cases showed signs of the same type as acute cases.

Among the 154 cases studied, symptoms were more pronounced in two cases. A 54-year-old woman presented with hypotension requiring hospital infusion after consuming 50 kernels in one day. An 87-year-old man suffered a heart attack after ingesting 40 kernels in one day.

These data collected by the PCCs, which only represent some of the cases in which health care was sought, suggest that users should be alerted to the risks of serious poisoning incurred in the event of consumption of "recommended anti-cancer" doses. In this series of cases, while some of the symptoms observed could be explained by anxiety related to the discovery that there is a substance as toxic as cyanide in the food product consumed, the proportion of symptomatic cases was seen to increase with the quantity of kernels ingested, suggesting a dose-response relationship. No very serious cases were reported in these observations.

As anticipating in the EFSA analysis, in view of the uncertainties about the available thresholds for cyanide toxicity in humans, there is probably a margin of safety with respect to the published ARfD.

Given the lack of a scientific basis for data on the use of kernels from apricots and other species containing cyanogenic glycosides in the preventive or curative treatment of cancer, and the existence of serious cases reported in the scientific literature, it seems necessary to encourage consumers to exercise caution. It is still possible to consume these kernels when used to enhance foods, and in this context, EFSA's recommendations guarantee the absence of health risks with a sufficient safety margin.

Juliette BLOCH (Anses)

References

[1] EFSA CONTAM Panel (EFSA Panel on Contaminants in the Food Chain), 2016. Scientific opinion on the acute health risks related to the presence of cyanogenic glycosides in raw apricot kernels and products derived from raw apricot kernels

Saltwater aquarium corals should be handled with care

Known since the 1970s, palytoxin is a highly potent toxin contained in certain soft corals of the genera *Zoanthus* and *Palythoa*[1], which occur naturally in coral reefs in the Indian Ocean, Red Sea and Indo-Pacific region.

Palytoxin may be produced directly by these soft corals, or be produced by microalgae and then secondarily accumulate in the soft corals through filtration, although the exact mechanism remains unknown.

Palytoxin is also found in various marine organisms (certain species of crabs, sponges, sea anemones, shellfish, parrotfish and tropical mackerel, etc.), which become toxic by bioaccumulation through the food chain.

Lastly, "palytoxin-like" toxins can be transported in sea spray contaminated by certain algal blooms (*Ostreopsis ovata* blooms) and can poison not only bathers in direct contact but also walkers near water containing these algae.

Over the past decade, with the development of techniques for maintaining reef aquariums, enthusiasts have been able to reproduce the fragile ecosystem of a coral reef, with the tropical fish, corals, sponges, shells and sand it typically supports.

Because of their ornamental quality and/or their rapid growth in marine aquariums, the marketing of soft corals to the general public through specialised shops or websites appears to be expanding. This has increased the risk of human exposure to palytoxin.

However, the presence of these soft corals in marine aquariums may also be unintentional or even unknown, as their larvae may have come from the purchase of other coral species or from decorative live rocks containing small animals (crabs, worms, shrimps, etc.) useful for the natural recycling of aquarium waste. They may then become undesirable as a result of their proliferation.

Looking after soft corals of the genera *Zoanthus* and *Palythoa* can expose the handler to palytoxin by several routes simultaneously: by contact, especially of the mucous membranes (eyes, mouth), but also by inhalation. The symptoms, which occur immediately, are usually mild (skin irritation, abdominal pain, etc.) and improve within a few days with symptomatic treatment. However, the effects can also be severe and lead to sequelae (corneal damage – keratitis requiring a corneal transplant), or can even be life-threatening (severe respiratory difficulties). Cases of poisoning have been described in the United States and Europe [1], and have even made the headlines, such as the dramatic case of mass poisoning in Quebec. Seven members of the same family were poisoned after installing an aquarium containing soft corals, purchased second-hand, in their home [2]. They immediately experienced sneezing, nausea, breathing difficulties, etc., requiring them to go to the hospital emergency department, with one of them having to stay overnight.

A study of palytoxin exposure cases reported to the network of French Poison Control Centres (PCCs) between January 2000 and December 2017 and involving the handling of aquarium soft corals [3] identified 23 cases, all symptomatic, with non-null causality[2]. While the first case was reported in 2006, 74% of cases were recorded in 2016 and 2017 (see Figure 1), reflecting the increasing availability of these corals on the market.

The sex ratio was 4 (16 males, 4 females, not specified in three cases) and the ages ranged from 12 to 74 years (median 42 years). While the exposure cases, all accidental, mainly involved private individuals (16 cases), 30% of them concerned professionals (7 cases). Two thirds were exposed by several routes simultaneously (respiratory and/or dermal and/or ocular), causing several simultaneous local and/or diffuse symptoms.

These symptoms were mainly general (fever, fatigue – 17 cases, 74%), neurological (headache, muscle pain – 14 cases), digestive (nausea, vomiting – 11 cases), respiratory (breathing difficulties, coughing – 10 cases), ocular (conjunctivitis, keratitis – 8 cases) and/or dermal (pruritus, irritation – 7 cases).

1. While *Palythoa toxica* is still considered the most toxic, other species, not all of which have been identified, also contain palytoxin. These include *P. caesia*, *P. caribaeorum*, *P. mammillosa*, *P. heliodiscus*, *Zoanthus solanderi* and *Z. sociatus*.
2. Causality established according to the method for determining causality in toxicovigilance (Version 7.6 – June 2015), which determines, using five levels (causality excluded I0, unlikely I1, possible I2, likely I3 and very likely I4), the strength of the causal link between exposure to an agent and the occurrence of a symptom, syndrome or disease (https://tv.toxalert.fr/v7.6/Calcul_imputabilite_v7.6.html).

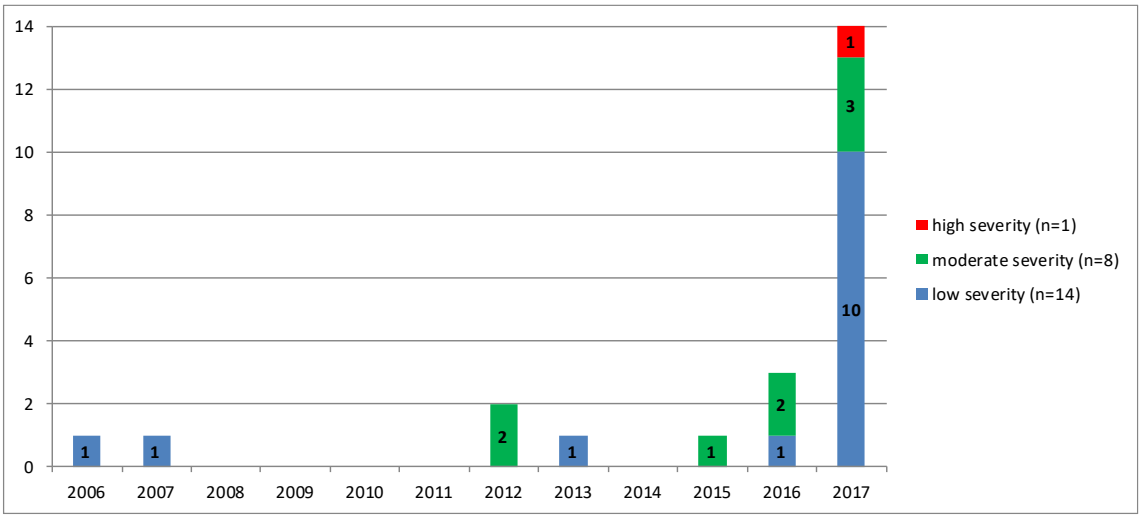


Figure 1: Number of cases of palytoxin exposure, according to their level of severity, reported to the network of poison control centres in the context of marine aquarium handling, from 2000 to 2017. (Source: PCCs' information system).

Although almost two-thirds of the cases presented with mild symptoms (14 cases), eight (35%) were more severe, with respiratory difficulties, high blood pressure or persistent fatigue for several days. One person developed corneal damage (keratitis) requiring a transplant.

Of the 23 cases, only four people, all professionals, were wearing some personal protective equipment (PPE), although this was insufficient in relation to the risk of palytoxin poisoning.

A detailed study of the poisoning circumstances found various actions or behaviours posing a risk:

- Some people poured boiling water on the stones on which the soft corals were growing, in order to wash or kill them, resulting in palytoxin being released in micro-droplets; this action is both ineffective and dangerous if suitable PPE is not worn, as the toxin is thermostable and therefore resistant to heat;

- Other people cut corals with their bare hands to make cuttings or to get rid of them, which resulted in direct contact of the toxin with the skin;

- One person scrubbed soft corals directly with an iron brush to kill them, without any protection, while another scraped a coral-covered stone with another stone and then rinsed it with hot water, without wearing gloves;

- Lastly, several people in the vicinity of another person handling corals were poisoned despite not being in contact with them.

Furthermore, based on their statements to the PCCs, 11 people knew nothing about soft corals, seven knew about soft corals but not about palytoxin, three knew about palytoxin but not about its risks, and only two professionals knew about the risks of palytoxin.

Lastly, no regulations on labelling or the mention of possible dangers when purchasing these soft corals have been identified to date. No palytoxin-producing or -releasing corals appear on the French list of hazardous non-domestic species [4].

Given the health risks involved, it seems necessary to ensure that the public and professionals are aware of the presence of soft corals of the genera Zoanthus and Palythoa in their aquariums, and are therefore sufficiently informed of the risks of palytoxin exposure when handling them and of the protective measures to be taken. This is especially important for professionals in the aquarium sector, who may be required to handle these corals in a number of situations (when receiving imported corals, selling to the public, cleaning aquariums in shops or homes).

To ensure that aquarium keeping remains a real pleasure for amateurs and that professionals in the aquarium sector can work in complete safety, collective and individual preventive measures, developed following the study of cases reported to the PCC network and various organisations (INRS, OATA [5], etc.) are proposed in the box below!

Sandra SINNO-TELLIER (Anses)

- Learn about the soft corals you buy and how dangerous they can be;
- Be aware of which actions are safe and how to avoid handling errors;
- Wherever possible, handle soft corals in the aquarium underwater and while fully submerged;
- Switch off aquarium pumps and skimmers when tending to soft coral;
- Handle soft corals in well ventilated areas;
- If soft corals need to be moved, transport them in plastic bags or containers filled with water;
- Wear suitable personal protective equipment (PPE) when handling them (gloves, mask covering nose and mouth, goggles and plastic apron);
- Do not boil or pour hot water on soft corals;
- Do not put them in the microwave;
- Wash and dry hands thoroughly after handling soft corals;
- Clean equipment and surfaces with bleach;
- Avoid handling corals in the presence of other people; anyone wishing to remain nearby should wear PPE, even when not handling soft corals;
- Keep your usual medication on hand if you suffer from asthma;
- If you have difficulty breathing, phone the emergency services (dial 15 in France) immediately;
- In the event of eye splashes: rinse eyes with tap water for about 10 minutes and seek medical advice or contact a poison control centre;
- In the event of skin contact, rinse skin with tap water and seek medical advice or call a poison control centre.

References

[1] Pelin M, Brovedani V, Sosa S, Tubaro A. Palytoxin-containing aquarium soft corals as an emerging sanitary problem. Mar Drugs 2016; 14.

[2] http://www.cbc.ca/news/canada/ottawa/toxic-coral-blamed-for-sickening-gatineau-family-1.4633810

[3] T. Calon, S. Sinno-Tellier, L. De Haro. Palytoxin exposure induced by soft corals in aquariums: Cases report of French PCC network from 2000 to 2017. Internal request by the Toxicovigilance Coordination Committee, April 2018, 32 p.

http://www.centres-antipoison.net/cctv/CCTV_Rapport_Palytoxine_Vf.pdf

[4] Ministerial Order of 10 August 2004 laying down the conditions for authorising the keeping of animals of certain non-domestic species in establishments for the breeding, sale, hire, transit or presentation to the public of non-domestic animal species.

[5] Recommendations to marine reef aquarists on how to prevent palytoxin poisoning. OATA – Ornamental Aquatic Trade Association Ltd. United Kingdom, 2p, April 2018. (https://ornamentalfish.org/wp-content/uploads/OATA-palytoxin-guidance-to-marine-reef-aquarists_April-2018.pdf) in collaboration with several partners (Health Protection Scotland, UK; Tropical Marine Centre, UK).

TO FIND OUT MORE, VISIT:

Palytoxin exposure induced by soft corals in aquariums: Cases report of French PCC network from 2000 to 2017

Jimsonweed or "the flowers of evil"

Datura is a genus of plants well known for their majestic trumpet-shaped flowers. It is often grown in gardens for ornamental purposes. Some species such as *Datura stramonium L.* (jimsonweed) also grow in the wild and, because they are spread by the wind, sometimes end up in unexpected places. The fruit is a capsule (see photo 1), 5 to 10 cm in diameter, covered with tapering spines and containing several hundred seeds.

This plant contains toxic substances in its leaves, flowers and seeds. These substances (which include scopolamine, atropine and hyoscyamine) cause symptoms combining neuropsychic signs (hallucinations, agitation or even coma with convulsions) and neurovegetative effects (dry skin and mouth, fever, cardiac signs, etc.). The clinical picture can be particularly severe in children. Despite this plant being highly dangerous, it is misused for its hallucinatory properties, particularly by some adolescents who consume it recreationally because the plant is ubiquitous and easily accessible.

Following the occurrence of several cases of severe *Datura* poisoning in August 2017, French Poison Control Centres (PCCs) alerted the French Agency for Food, Environmental and Occupational Health & Safety (ANSES). A national extraction of PCC data showed an upsurge in cases in 2017, mainly in Nouvelle Aquitaine (see photo 3).

The poisoned patients interviewed reported finding jimsonweed near their homes in urban areas. The implementation of new regulations[1] may explain why these plants are growing in towns and cities (Figure 1) more often than in the past.

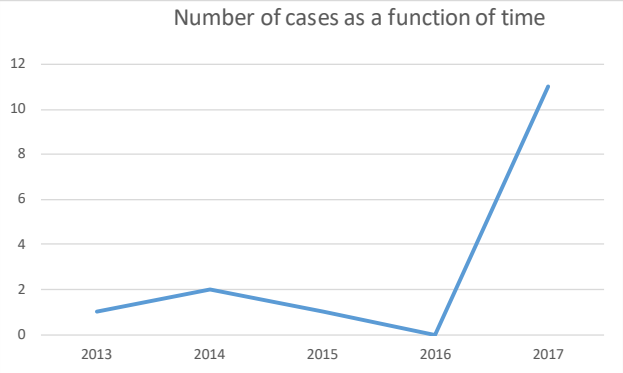


Figure 2: Jimsonweed poisoning: data from the Nouvelle Aquitaine Poison Control Centre (Source: SICAP)

Photo 1 : Jimsonweed fruit (Source: P. Rolland, CIRE)

Photo 2 : Jimsonweed growing naturally in an urban area (Photo: Dr A. Daveluy, CEIP-A)

Following this report, information was sent to the Ministry of the Interior by the Directorate General for Health, with a view to asking municipalities to remove *Datura* plants, especially in places frequented by young people. In Nouvelle Aquitaine, the PCC, the regional intervention unit (CIRE) of *Santé Publique France* and the centre for evaluation and information on drug dependence and addiction monitoring (CEIP-A), in conjunction with the Nouvelle Aquitaine regional health agency (ARS), forwarded this request to municipal professionals in charge of maintaining green spaces for application in their daily work.

Magali LABADIE (Bordeaux Poison Control Centre)

1.Labbé Act amended by Article 68 of the Energy Transition Act and the Potier Act prohibiting, as of 1 January 2017, the use of plant protection products by public authorities for maintaining green spaces, forests, walkways and roadways accessible or open to the public.

Liquid detergent pods should be kept away from children!

The first studies warning about the risks of exposure to water-soluble laundry detergent pods were published as early as 2005 in France [1] and Europe, and from the 2010s in the United States [2]. Since then, many international studies have been published.

Kept in hard plastic boxes or soft plastic bags, which take up relatively little storage space, liquid detergent pods (also known as "capsules" or "packs") are sold for their convenience: the liquid is packaged as a single dose of detergent surrounded by a water-soluble film that seals the pod completely. A single pod is recommended for each wash; it is simply placed directly into the machine drum, limiting waste and overdosing. The water-soluble film then dissolves spontaneously on contact with water.

According to sales figures provided by industry, pods have been used in homes since 2010, where they compete with conventional liquid detergents. Looking like small, soft balls filled with coloured liquid, they are easy for toddlers, beginning to explore their environment, to pick up if left within reach. The water-soluble film then breaks on contact with saliva or hand moisture. Combined with the internal pressure of the pod, this can lead to splashes on the face (in the eyes or mouth) or on the rest of the body (arms, etc.).

It has also been found that these pods are more toxic than conventional liquid detergents: firstly, the liquid detergent has a higher concentration of surfactants (more than 15%), making it more irritating or even corrosive in the event of contact with the skin or mucous membranes (eye, digestive system), and secondly, the detergent's higher viscosity means it is more likely to remain in prolonged contact with the skin or mucous membranes, making it more difficult to clean them if exposed.

To quantify the accidents due to contact with detergent pods and assess their trends and severity alongside those involving other detergents, a retrospective study compared cases of exposure[1] to liquid detergent pods and conventional liquid detergents excluding pods reported to the network of French Poison Control Centres (PCCs) from 2005 to 2012 [3].

Over the whole study period, the number of cases of exposure to pods was higher than those for conventional detergent (7,562 and 6,871 cases respectively); the annual number of cases of exposure to pods became higher than those for conventional liquid detergents from 2010 [3]. The individuals exposed to the pods were also younger than those exposed to conventional liquid detergents (respectively 93% and 80% of cases 0-5 years of age; 7% and 4% of cases under 1 year of age). In addition, they were more frequently symptomatic (67% of cases) and these symptoms were often more serious (2.0% of symptomatic cases) than in cases of exposure to conventional detergent (45% of symptomatic cases, of which 0.8% were serious).

The 104 serious cases due to pods corresponded mainly to eye injuries (83 cases of keratitis, including one paediatric case requiring a corneal transplant), respiratory signs (20 cases) or digestive bleeding (1 case). The 26 serious cases related to conventional liquid detergent also included eye injuries (13 cases of keratitis), digestive and/or respiratory signs (13 cases); one cognitively impaired elderly person died from choking complications after inadvertent ingestion of liquid detergent.

With the paediatric cases, in order to describe the precise circumstances of the accident and in particular how the child had managed to get hold of the pod, an additional prospective study was carried out among children under 6 years of age exposed to a pod between 12 January and 15 February 2015. This involved a specific questionnaire for each new case, conducted by PCC toxicologists with the person present at the time of exposure [4].

In total, 253 questionnaires were collected (83% participation rate). In more than a quarter of the cases (27%), the child had taken the pod after it had already been removed from the box or bag: usually from directly inside the washing machine, but sometimes picked up from the floor, a table, etc. In the other cases (73%), the child had managed to take the pod out of an already-open box or bag, or had even managed to open it themselves. In less than half of cases (41%), this box (or bag) was stored in a place that was considered inaccessible to the child (closed cupboard or high shelf); however, in almost 60% of cases, the box or bag was within the child's reach (on a table, the floor, the washing machine or in a basket).

1. Here, a case of exposure refers to a person who has been in contact with liquid detergent and for whom a poison control centre was called.

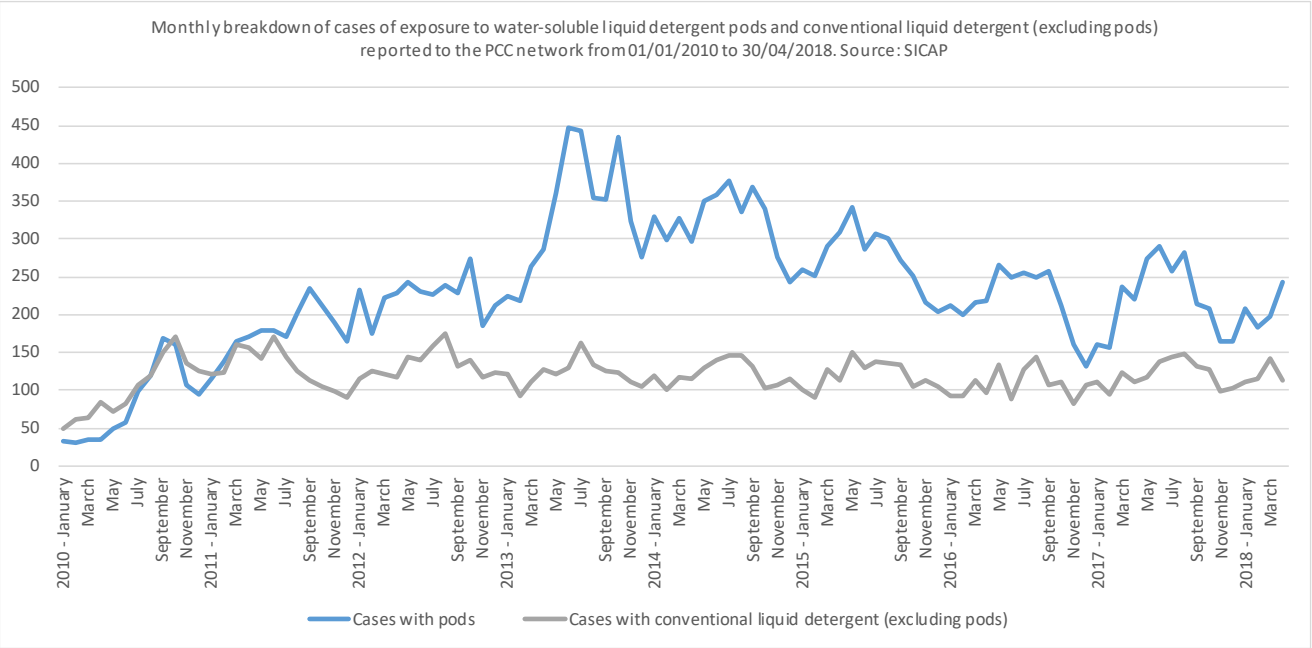


Figure 1: Monthly breakdown of cases of exposure to water-soluble liquid detergent pods and conventional liquid detergent (excluding pods), reported to the PCC network from 01/01/2010 to 30/04/2018. (Source: French PCC national database).

As with any situation where there is a risk of a domestic accident, these results highlighted the accessibility of these pods and how this can be prevented: pods should not be taken out of their box or bag, which should be properly closed and stored out of the reach of children.

Starting in 2013, the International Association for Soaps, Detergents and Maintenance Products (AISE), whose member brands in France represent 85% of the market, progressively introduced preventive measures [5]; these measures have become mandatory since 1 June 2015 under Regulation (EU) No 1297/2014.

They consist firstly in reducing the child's access to the pods: packaging in an exclusively opaque box instead of a transparent one, lid closure reinforced by a safety flap, affixing of a prevention pictogram "keep out of the reach of children", and secondly, in the event of access to the pod, making direct contact with the detergent product more difficult: addition of a (non-toxic) bittering agent to the water-soluble film to encourage the child to quickly spit out the pod after it has been put in the mouth; lowering the film's solubility when it comes into contact with saliva, so that it is less likely to be pierced; and increasing the resistance to pressure when handled.

From 2014 onwards, AISE conducted a dedicated information campaign in the European media and on social networks (http://www.keepcapsfromkids.eu), which it updated in 2017.

In March 2015, following requests from the Organisation for Economic Co-operation and Development (OECD) and from the European Commission to its Member States, the French Directorate General for Competition, Consumer Affairs and Fraud Control (DGCCRF) issued a press release on the risks of pods for young children [6].

What has been the health impact of the preventive measures taken? To answer this question, ANSES analysed the trends regarding cases of exposure to water-soluble pods reported to the PCC network and those due to conventional liquid detergent during the same period, from January 2010 to April 2018, i.e. before and after introduction of these preventive measures.

First of all, regardless of the type of detergent (pods or conventional liquid detergent), this exposure showed a strong seasonal pattern, with cases being less numerous in winter than in summer.

Apart from the phenomenon of seasonality, the number of exposures to conventional detergents remained constant from January 2010 to April 2018 (about 100 to 150 cases per month, peaking in summer), and was systematically lower than that of pods from mid-2010.

While the temporal distribution of cases showed a sharp increase in exposure to pods (from 350% to 400%) from mid-2010 to mid-2013, it also showed a steady decline from mid-2013 to mid-2016, with a 40% to 50% fall in the total number of cases in these last three years. This could be the result of the preventive measures taken from 2013 onwards.

However, it can also be seen that the decline in cases of exposure to pods has stalled in the last two years, from mid-2016 to April 2018 (the date when the data were last updated), with numbers having flattened out at between 250 and 260 cases per month in the summer peak. It would be interesting to study the reasons for this levelling off, and to see whether the positive health impact of the measures put in place from 2013 onwards could be even greater.

Sandra SINNO-TELLIER (Anses)

References

[1] Nisse P, Durak C, Peucelle D, Mathieu-Nolf M. Nouvelle forme de risque d'intoxication : les dosettes de lessive [New form of poisoning risk: laundry detergent pods]. 43rd Congress of the French Society of Clinical Toxicology, 8-9 December 2005, Lille, France.

[2] Centers for Disease Control and Prevention (CDC). Health hazards associated with laundry detergent pods, United States, May-June 2012. MMWR Morb Mortal Wkly Rep. 2012 Oct 19;61 (41):825-829.

[3] Rigaux-Barry F, Patat A-M, Cordier L, Manel J, Sinno-Tellier S. Risks related to pods exposure compared to traditional laundry detergent products: Study of cases recorded by French PCC from 2005 to 2012. Toxicologie Analytique & Clinique (2017) 29, 257-266.

[4] Sinno-Tellier S, Rigaux-Barry F, Cordier L, Patat A-M. Dosettes hydrosolubles de lessive liquide : étude prospective des circonstances d'accidents domestiques des enfants de moins de 6 ans rapportées aux centres antipoison du 12 janvier au 15 février 2015 [Water-soluble liquid detergent pods: a prospective study of the circumstances of domestic accidents in children under 6 years of age reported to Poison Control Centres from 12 January to 15 February 2015]. Internal request by the Toxicovigilance Coordination Committee, July 2016, 32 p.

http://www.centres-antipoison.net/cctv/CCTV_Rapport_Dosettes_VF_Nov_2016.pdf

[5] AISE – Product Stewardship programmes for liquid laundry detergent capsules (12/2012, 03/2015, 06/2017).

https://www.aise.eu/our-activities/product-stewardship-programmes/liquid-detergent-capsules/aise-product-stewardship-programme-for-liquid-laundry-detergent-capsules-122012.aspx

[6]https://www.economie.gouv.fr/dgccrf/Publications/Vie-pratique/Fiches-pratiques/lessive-liquide-en-capsule-et-risques-associes

New substances responsible for contact dermatitis due to clothing or footwear

In 2008, dimethyl fumarate (DMFu) was responsible for cases of allergic and irritative contact dermatitis in several European Union countries. It had been used as an antifungal agent on furniture (sofas, armchairs, etc.), footwear and clothing during maritime container transport or storage in warm and humid places.

French poison control centres (PCCs) were alerted to the first cases in 2008 by the French Institute for Public Health Surveillance (InVS), which became *Santé Publique France* on 1 May 2016. Following this alert and at the request of the Directorate General for Health (DGS), several studies of the cases recorded by the PCCs were carried out, in collaboration with the dermato-allergology vigilance network (Revidal-Gerda) and the National Network for the Monitoring and Prevention of Occupational Diseases (RNV3P) in 2009, 2011, 2012 and 2015. Each of these studies found around a hundred cases of contact dermatitis associated with the wearing of clothing or footwear. However, it was difficult to link them to DMFu exposure because analyses of the articles had rarely been carried out, mainly because of their cost and the difficulty in identifying a testing laboratory able to perform them. Moreover, patch testing, which might have demonstrated the patient's allergy to one or more substances contained in the incriminated article, had rarely been performed, because the patient did not consult an allergist or dermatologist-allergist once cured, or because the specific patch test for a substance was not available or was too expensive for a general practitioner.

The last study by the PCCs carried out in 2015 showed that despite the inclusion of DMFu in Annex XVII of the REACH Regulation in May 2012[1], which prohibited its use and marketing in articles at concentrations above 0.1 mg/kg, cases of allergies and/or skin irritations were still being reported to the PCCs (see photos). The symptoms observed may have been related to another, unidentified substance, but this could not be confirmed in the absence of analysis of the articles and patch tests on the patients concerned.

This led the DGS and the General Directorate for Competition, Consumer Affairs and Fraud Control (DGCCRF) to ask ANSES to identify the skin irritant or sensitising chemicals, regulated or non-regulated, liable to be found in footwear and textiles, and in particular to propose a method for investigating cases of skin allergy or irritation reported by medical specialists, in order to improve knowledge of the substances in question.

ANSES therefore set up a ground-breaking biomedical research study in France to link the presence of one or more substances contained in clothing or footwear with the symptoms of patients having worn these articles. To do this, ANSES mobilised a group of volunteer hospital doctors specialised in dermatology-allergology and toxicology: 18 dermatologist-allergists from the Revidal-Gerda network, toxicologists from eight PCCs and specialist doctors from four occupational disease consultation centres (CCPPs). ANSES also organised the collection and analysis of suspect articles by two specialised laboratories, in order to identify and characterise the chemicals found in them.

Each clinical case was reviewed by a steering committee of toxicologists, dermatologist-allergists and chemists. The committee compared the results of the medical diagnosis (which included patch tests performed by the physician participating in the study), the results of chemical analyses by the testing laboratory and, if applicable, the results of additional patch tests not included in the standard batteries.

Between January and September 2017, 31 patients including 21 women (between 24 and 68 years of age) and 10 men (between 27 and 64 years of age) were recruited. One patient was unable to take part, living too far away from the dermatologist-allergists participating in the study. These 31 patients were matched with 42 articles to be analysed (one patient provided several articles suspected of being responsible for their contact dermatitis).

This study, which is currently being finalised, has already identified the imputable chemical in six articles causing symptoms. Some of these substances, in addition to their skin sensitising or irritant property, have carcinogenic, mutagenic or reprotoxic (CMR) potential, such as chromium VI, nickel and 4-aminoazobenzene. Substances not screened for by the dermatologist-allergists were found in the chemical analysis of the articles: this was the case with benzidine and the dyes CI Disperse Orange 37/76 and CI Disperse Yellow 23.

1. Commission Regulation (EU) No 412/2012 of 15 May 2012 amending Annex XVII to Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).

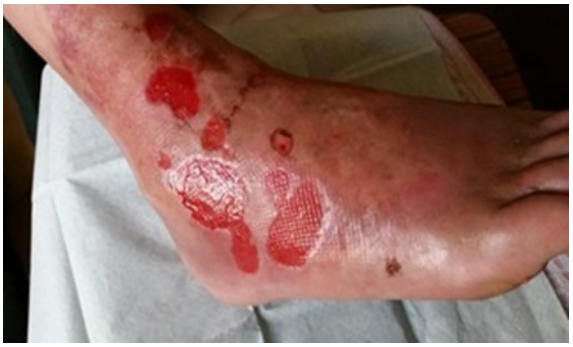
For two articles, it was concluded that the symptoms were related to another cause than the suspect article. For five suspect articles, it was not possible to reach a conclusion due to cross-contamination with cosmetics or paint, or intensive washing of the article that may have caused the contact dermatitis.

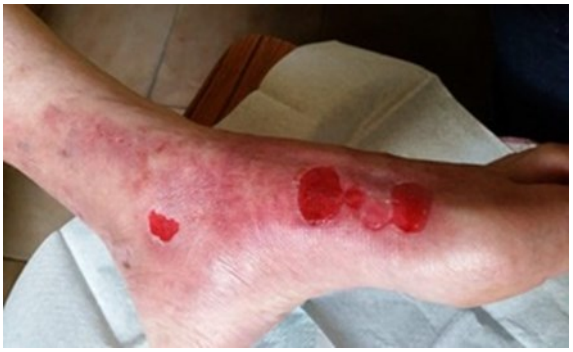
It should also be noted that DMFu was never detected in the articles analysed.

This study also identified articles that did not comply with the regulations in force, leading ANSES to report them to the DGCCRF. In addition, it showed that, as with chromium VI, the regulatory thresholds currently recommended do not provide sufficient protection against elicitation, i.e. a new allergic reaction in people already sensitised to this substance.

All these results led ANSES to recommend revising the regulatory threshold for chromium VI in leather articles and setting regulatory thresholds for sensitising or irritant substances currently without a threshold, such as 1,4-paraphenylenediamine in clothing or drometrizole in leather. ANSES is also taking part in and supporting the European regulatory actions under way, designed to restrict the presence of sensitising, irritant and CMR substances in textiles and footwear.

Because of these initial results, ANSES has decided to extend this study in 2018, by increasing the number of patients recruited and doctors participating, in order to improve its territorial coverage and representativeness of clothing and footwear placed on the market in France.





Photos: Foot injuries from wearing shoes (CCTV, 2018)

Cécilia SOLAL (Anses)

TO FIND OUT MORE, VISIT:

ANSES. 2018. Safety of footwear and textile clothing. Request No. 2014-SA-0237 "Textiles". ANSES Collective expert appraisal report and Opinion on the assessment of the skin sensitising/irritant effects of chemicals found in footwear and textile clothing.

Toxicovigilance Coordination Committee (CCTV). 2009. Risks associated with the presence of dimethyl fumarate. http://www.centres-antipoison.net/CCTV/Rapport_CCTV_DMFU_2009.pdf

CCTV. 2011. Diméthylfumarate ou articles susceptibles d'en contenir : recensement des cas symptomatiques notifiés entre janvier 2009 et février 2010 [Dimethyl fumarate or articles that may contain it: identification of symptomatic cases notified between January 2009 and February 2010]. http://www.centres-antipoison.net/CCTV/Rapport_CCTV_DMFu_2009-2010_VFINALE.pdf

CCTV. 2012. Diméthylfumarate ou articles susceptibles d'en contenir : recensement des cas symptomatiques notifiés entre mars 2010 et novembre 2011 [Dimethyl fumarate or articles that may contain it: identification of symptomatic cases notified between March 2010 and November 2011]. http://www.centres-antipoison.net/CCTV/Rapport_CCTV_Dimethylfumarate_Mars_2012.pdf

CCTV. 2018. Cas d'intolérance aux textiles et articles chaussants susceptibles de contenir des substances allergisantes et irritantes telles que le diméthylfumarate [Cases of intolerance to textiles and footwear that may contain allergenic and irritant substances such as dimethyl fumarate]. Retrospective study of cases of accidental exposure recorded by the French poison control and toxicovigilance centres from 01/01/2015 to 31/12/2015 http://www.centres-antipoison.net/CCTV/Rapport_DMFu_2015_GT_VPC_VFINALE.pdf

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.

anses

French agency for food, environmental
and occupationnal health and safety
14 rue Pierre et Marie Curie
94 701 Maisons-Alfort Cedex

www.anses.fr / @Anses_fr

ISSN : 2556-1790 – Legal deposit : June 2018- © Anses Edition : June 2018– Achievment : ANSES – Photo credit : Fotolia