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NUTRIVIGILANCE

Histamine poisoning: keep your fish cold!

Histamine poisoning due to fish consumption is common, but can be prevented by maintaining the cold chain at all stages, from when the fish is caught and prepared by professionals through to its storage in the consumer's home. The study of poisoning cases recorded by French poison control centres showed that cases mainly occurred as a result of eating fish purchased in shops and, to a lesser extent, fish consumed in restaurants. In all these cases there is reason to suspect a problem with storage. ANSES reiterates the food hygiene rules to be followed in order to prevent these potentially serious poisonings.

Histamine poisoning is one of the main causes of foodborne illness related to fish consumption.

Why can you get histamine poisoning from eating fish?

Histamine is naturally synthesised in humans and animals. It is found in all fish normally at low levels. It is formed from the breakdown of the amino acid histidine by bacteria present on the skin or in the viscera of fish and in the marine environment, which multiply at room temperature. Histamine is not degraded by cooking or freezing.

The risk of a high histamine concentration depends firstly on the risk of bacterial contamination when the fish is caught and then prepared (evisceration, filleting, etc.), and secondly on the risk of bacterial proliferation in its flesh at every step of its storage, before, during or after sale.

Some species of fish are richer in histidine than others, which can lead to higher histamine production. These are mainly Scombridae such as tuna, mackerel, kingfish and bonito (hence the frequently used name scombroid fish poisoning), or other species such as sardines, herring, anchovies, jacks, swordfish or dolphinfish.

Checks to prevent poisoning

Producers and distributors have defined and implemented guides to good hygiene practices (GGHPs) and are also subject to numerous annual hygiene and cold-chain checks by the Directorate General for Food (DGAL). Fishery products with histamine levels above the regulatory threshold[1] are not sold or are withdrawn from the market if they were already on sale.

The DGAL asked ANSES for an opinion on the sampling strategy for fish to be monitored and assayed.

In this context, ANSES and the poison control centres (PCCs) analysed cases of histamine poisoning after fish consumption reported to the PCCs, paying particular attention to the species of fish consumed, and how it was obtained, stored and prepared.

Amended Regulation (EC) No 2073/2005 laying down food safety criteria for histamine in different fishery products according to their manufacturing process.

Cases of both individual and collective food poisoning

All cases of symptomatic food poisoning from fish recorded by the PCCs from 2012 to 2021 were reviewed by an expert toxicologist from the PCCs to select those consistent with histamine poisoning, based on the symptoms and the species of fish consumed.

Cases were either individual (a single symptomatic person) or collective (at least two symptomatic persons sharing the same fish meal).

This review identified a total of 543 patients who had eaten 173 fish meals causing histamine poisoning in France (both metropolitan France and the overseas territories). Poisoning was individual for 53% of the meals (91 meals) and collective for 47% (82 meals), with the number of diners per meal in the latter ranging from two to 24. In one exceptional case, a meal resulted in the poisoning of 200 consumers.

Poisoning was more common among adults (57% of those contaminated) than children (43%). Two mass poisonings occurred in school canteens, affecting 200 children aged 3 to 5 years in the first case (mentioned above) and six children aged 8 to 10 years in the second. If this foodborne illness outbreak of 200 cases is excluded, the proportion of children involved falls to 10%.

The average number of fish meals causing poisoning over the study period was 17 per year. However, the annual number of meals observed varied from six in 2019 to 45 in 2021, with no identified cause that would explain this change (Figure 1).

1. Amended Regulation (EC) No 2073/2005 laying down food safety criteria for histamine in different fishery products according to their manufacturing process.

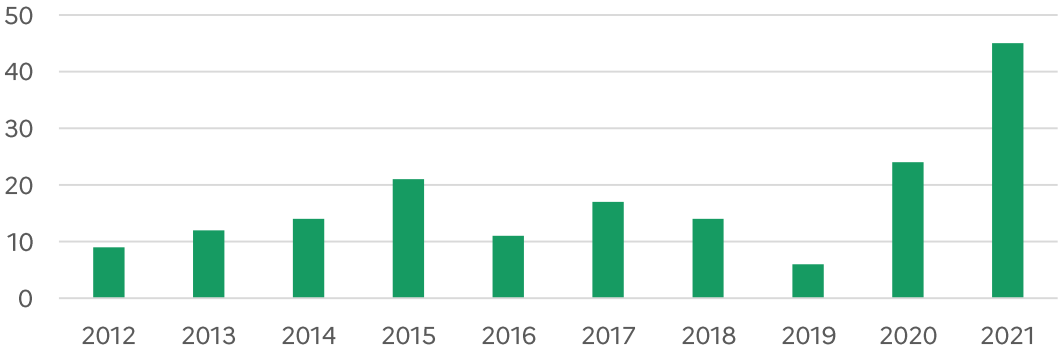

Figure 1: Annual distribution of fish meals causing histamine poisoning recorded by PCCs from 01/01/2012 to 31/12/2021 (N=173). Source: SICAP.

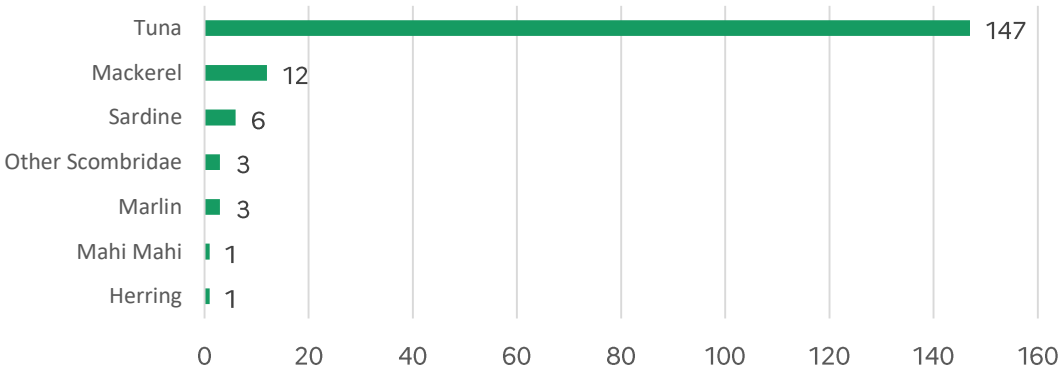

Figure 2: Distribution of fish species causing histamine poisoning recorded by PCCs from 01/01/2012 to 31/12/2021 (N=173). Source: SICAP.

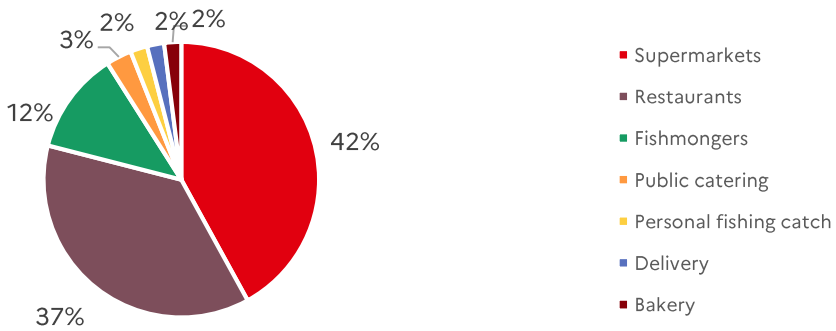

Figure 3: Origin of fish meals causing individual or collective histamine poisonings recorded by the PCCs from 01/01/2012 to 31/12/2021 (N=173). Source: SICAP.

These poisonings were observed throughout the year, but were characterised by a marked seasonality, with more cases in the warmer months. They were most frequent from July to October (36% of meals), then from April to June (29% of meals), as the higher temperatures at these times favour histamine formation if the cold chain is broken.

Poisoning was observed in all regions, and especially in Île-de-France, Provence-Alpes-Côte d'Azur and Nouvelle-Aquitaine, which together accounted for more than half (55%) of the fish meals causing histamine poisoning (these three regions represent 34% of the French population).

Misleading symptoms resembling an allergy

Histamine is known to play an important physiological role in inflammatory and allergic phenomena. Although it is histamine poisoning and not an allergic reaction (patients will be able to eat properly stored tuna on another occasion without becoming ill), the symptoms mimic an allergy in every respect . The 543 patients in the study reported the following signs: urticaria (79% of patients), transient skin redness (71%), headache (50%), itching (37%), tachycardia (33%), nausea (20%) and vomiting (9%). The first symptoms described appeared on average 35 minutes after the meal. Four patients experienced a sudden drop in blood pressure, a marker of clinical severity. A total of 25 patients were hospitalised (4.6%), two of whom in intensive care. All of them recovered.

Poisoning mainly but not exclusively due to Scombridae (tuna family)

While, as expected, the vast majority of poisoning cases were due to consumption of tuna (85% of meals) or other Scombridae (mackerel, 7%, others 3%), other fish were also involved, such as sardines, which accounted for 3% of the incriminated meals.

Fish mostly consumed at home

Of the 173 meals that caused histamine poisoning, the fish had most often been purchased from a retailer: a supermarket (42%) or fishmonger (12%) (Figure 3). Several case files indicated that the consumer had not maintained the cold chain to store the fish (tuna slices left in the sun on the parcel shelf of the car, etc.). Fish eaten in a restaurant accounted for 37% of the meals that caused poisoning.

Fish mostly bought fresh, prepared in a variety of ways

Two thirds (65%) of the fish had been bought or eaten fresh, of which 53% was consumed in restaurants and 41% after purchase in supermarkets or fishmongers. However, poisoning can occur with any type of preservation method, including canned fish, which accounted for 10% of the meals in question. Thirteen per cent of the fish was purchased vacuum-packed, and the remaining 12% was frozen.

More than half (55%) of the fish was grilled before consumption, confirming that histamine is not destroyed by cooking. While raw fish (sushi or tartare) accounted for 15% of meals, all types of preparation were observed: in sauce/baked, fried, steamed, in salads or in sandwiches.

Although the number of cases is probably underestimated, as people prefer to call a doctor for a physical consultation rather than a PCC in the event of a reaction resembling an allergy, this study shows that histamine poisoning following fish consumption is not uncommon, although it is most often avoidable, and provides an opportunity to remind consumers of the risks of serious poisoning if hygiene rules are not followed.

To avoid bacterial proliferation that could promote the formation of histamine in fish purchased from a retail outlet or caught, it is essential to maintain the cold chain before consumption, by:

- refrigerating or freezing fish as soon as possible;
- not leaving fish at room temperature or in the sun;
- if frozen, thawing the fish quickly and then eating it immediately;
- never refreezing fish that has been thawed.

When histamine has formed, it cannot then be destroyed either by cooking, canning or freezing.

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In the event of a life-threatening emergency (swelling of the face or throat, difficulty breathing, loss of consciousness, etc.) immediately call **15 (in France) or 112, or 114 for the deaf and hard of hearing**.

In the event of poisoning, call a PCC or see a doctor.

Keep any leftovers from the fish meal for analysis and screening for contamination by histamine or micro-organisms if necessary.

Ostreopsis: a new invader of Basque beaches?

During the summer of 2021, a new and unexpected phenomenon was seen on the beaches of the Basque Country: symptoms reminiscent of a flu-like illness, affecting entire families but also beach professionals such as lifeguards and beach restaurant waiters. Water samples taken by Ifremer showed high concentrations of a microalgae called *Ostreopsis* that is invisible to the naked eye. No serious cases were observed among the 674 cases reported to the Bordeaux poison control centre (PCC). This phenomenon, which could recur in the future, needs to be monitored in order to better protect populations and professionals.

Climate change and human activities are causing changes in the marine environment. This has led to the emergence of new types of poisoning. In 2010, for example, *Physalia* (tropical aquatic organisms from the Cnidaria phylum) invaded the Aquitaine coast, taking advantage of changes in marine currents [1]. Their stings caused extensive dermal symptoms and severe general neuromuscular symptoms in bathers. Similarly, cases of ciguatera (poisoning from eating contaminated fish, see Issue 16 of Vigil'Anses) have now been described in the Mediterranean, linked to the appearance in the region of the toxic alga *Gambierdiscus* spp., due to the opening of the Suez Canal [2]. The causes of the emergence of these poisoning cases are poorly understood and probably involve multiple factors.

In the summer of 2021, a new and unexpected phenomenon occurred on the beaches of the Basque Country. Numerous people contacted the PCC and the Regional Health Agency (ARS) to report symptoms reminiscent of a flu-like illness, affecting entire families but also beach professionals (lifeguards, beach restaurant waiters, etc.). Some people had been swimming, but others had remained on the beach or seafront without being in contact with the water. Such a phenomenon had already occurred in 2013 on the French Mediterranean coast and was due to a toxic microalgae, *Ostreopsis ovata* [3].

While the species *Ostreopsis siamensis* was first observed and described in 1901, in the Gulf of Thailand (Siam), 11 other species have since been described worldwide, including *O. marina*, *O. labens*, *O. heptagona*, *O. monotis* and *O. ovata*.

These microalgae, which are invisible to the naked eye, grow on macroalgae and on the sea bed. They can also contaminate fish and shellfish through bioaccumulation.

Certain conditions such as wind, roughness of the sea, water temperature, light intensity, salinity and tidal currents can favour a huge increase in Ostreopsis spp., which results in the formation of blooms. These appear as a brown foam on the surface, which can give the water a metallic taste and is an indication of the suffering of marine organisms (high mortality of grazing gastropods such as limpets).

The unique feature of Ostreopsis spp. is that they release toxins in seawater, particularly in these blooms. The toxins then aerosolise in sea spray [4]. A person can therefore be poisoned via inhalation without even putting a foot in the water, or by dermal contact when swimming, or ingestion when eating contaminated products.

These microalgae produce toxins similar to palytoxin, responsible for:

- Neurological signs: tingling, burning and headaches,
- ENT and respiratory signs: runny nose, cough, respiratory discomfort,
- Dermal symptoms resembling hives,
- Cardiac signs: tachycardia, high blood pressure,
- Digestive symptoms: nausea, vomiting, diarrhoea,
- General symptoms: fever, muscle and joint pain.

On 5 August 2021, the local poison control centre received a call about a sudden flu-like illness that had occurred during a swim, suggesting poisoning by *Ostreopsis* spp. An investigation then showed that the first poisoning cases had occurred in July.

The samples taken led to the rapid identification of *Ostreopsis siamensis*.

The poison control centre subsequently compiled all cases brought to the attention of either the PCC or the ARS during the summer of 2021. A total of 830 reports were received and recorded, involving the entire Basque coast. Duplicates between the PCC and the ARS, cases with no symptoms and cases for which the signs could not be attributed to *Ostreopsis* spp. were excluded.

The analysis therefore focused on 674 cases, presented in the rest of this article. The date of exposure was documented for 611 patients, the date of onset of symptoms for 499.

The time curve (Figure 1) shows that the epidemic peak was around 8 August. The latest exposure date was at the end of September. For reasons of readability, the epidemic curve is shown from 1 to 20 August 2021. There were very few cases in July.

The sex ratio was 1.2, indicating a predominance of males, and the median age was 28 years [minimum age six months and maximum age 85 years].

In 72% of the cases, the people had been poisoned while swimming. Just 2% of the patients had only been exposed by the respiratory route via sea spray. In all other cases, the skin had been in contact with contaminated water.

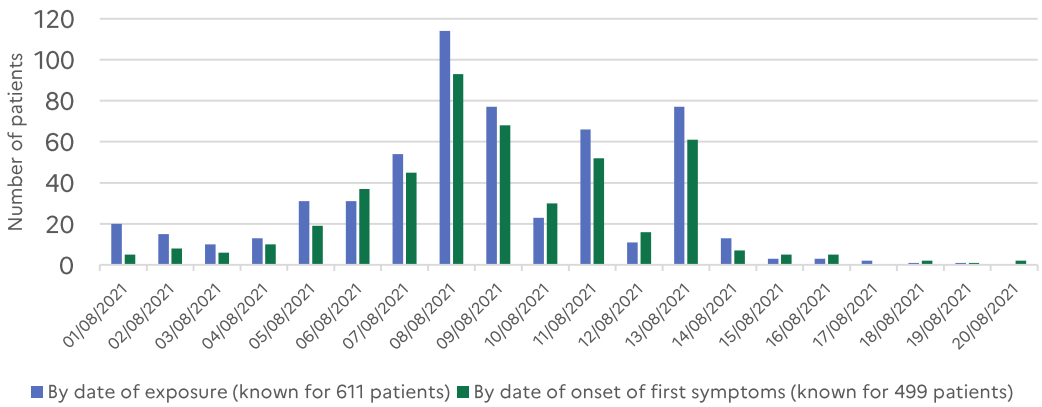

Figure 1: Number of cases by date of exposure and/or date of onset of symptoms from 01/08/21 - 20/08/21 (i.e. 453 out of 611 over the total study period). Source: SICAP.

The clinical signs observed and listed below coincide with those described in the literature for palytoxin (as one person may have several symptoms, the total of the percentages exceeds 100%): oropharyngeal pain (67%), rhinitis (66%), cough (64%), respiratory discomfort (32%), fever above 38°C (26%), headaches (11%), dermal signs (9%), neuromuscular signs (<5%).

The time to onset of symptoms was short, within six hours in almost three quarters of cases.

Given the pandemic context of the summer of 2021 and the similarity of the symptoms to those of COVID-19, 149 patients underwent a COVID-19 test as recommended by the poison control centre. All were negative except for one, who was therefore excluded from the study.

All patients recovered within two (acute exposure) to seven days (subacute exposure). There were no fatalities or serious cases.

Patients who developed more severe forms were those with a medical history of ENT or lung disorders (asthma, chronic bronchitis, etc.), allergy, cardiovascular problems (hypertension, arrhythmia, stroke, etc.) or diabetes.

Some poisoning victims consulted their doctors or went to the hospital emergency department. While some of these consultations were reported to the poison control centres and have been included in this investigation (108 patients (16%) saw a general practitioner, 28 patients (4%) contacted the *SOS Médecins* service and 14 patients (2%) a hospital emergency doctor), many were not. The figures shown therefore underestimate the actual number of people affected.

This episode underlines the importance, in the event of seawater contamination by *Ostreopsis* spp., of paying particular attention to beach professionals (surfing school staff, lifeguards, beach restaurant staff), as well as to beachfront residents, as these individuals are subject to repeated or chronic exposure.

This is the first toxic epidemic of this magnitude in France linked to *Ostreopsis* spp., and the first on the Atlantic coast. Analysing the reports as they came in, in terms of the location and severity, enabled more targeted public information to be issued and regular on-site water sampling to be carried out.

These analyses were coordinated by the French Research Institute for Exploitation of the Sea (Ifremer) and were used to monitor the episode's geographical and temporal evolution.

A coordinated prevention strategy involving all the local, regional and national stakeholders is being put in place for the coming years. It will need to be based on the early detection of *Ostreopsis* spp. through iterative sampling of several beaches, with a view to communicating precautionary measures in the event of a bloom, in particular to recommend that vulnerable people stay away during this period.

Lastly, ANSES, which has already published work on this subject, received a formal request to assess the human health risks of *Ostreopsis* spp. blooms on the Basque coast and establish specific recommendations.

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Inhalation of volatile substances: on the decline but still dangerous

Intentional inhalation of certain volatile substances produces psychotropic effects that users seek for "recreational" purposes. The products that contain them and that are misused for this purpose are legal, in everyday use, inexpensive and readily available. This study, based on data from poison control centres, showed that the users are young and the inhaled products are mainly deodorants, dust removers and air fresheners. Given the severity of the effects and the risk of death due to the recreational inhalation of these substances, and although the number of poisoning cases has been declining since 2015, it seems necessary to increase awareness of the risks associated with these practices – which are wrongly considered to be harmless – and recommend labelling that indicates the danger.

Sniffing (inhaling from a container), huffing (inhaling from an impregnated cloth) or bagging (inhaling from a bag placed around the mouth and nose) refer to the intentional inhalation of a volatile substance for recreational purposes.

In 2012, the death of a teenager by asphyxiation as a result of deliberately inhaling deodorant drew the attention of the public authorities to this practice. In view of the growing number of prominent cases reported to centres for evaluation and information on drug dependence and addiction monitoring (CEIP-As) in recent years, the French Health Products Safety Agency (ANSM), which is responsible for addictovigilance, asked the poison control centres to update their data on recreational inhalation of volatile substances, with the exception of nitrous oxide and poppers, as these have already been targeted by dedicated investigations.

Young consumers and a declining phenomenon

Between 1 July 2013 and 31 December 2019, poison control centres recorded 408 cases of exposure to volatile substances for recreation or in a context of substance abuse/addiction.

The consumers were young: 50% were under 15 years of age, almost 70% were minors and seven of the children were under 10 years of age. While the temporal analysis showed an increase in the number of cases between 2013 and 2015, they then decreased significantly from 2016 onwards, with the lowest number of cases observed in 2019, the last year of the study (Figure 1). This downward trend was confirmed in 2020 and 2021[1] (data not yet published).

In 64% of people, the substance had been consumed at their home or the home of a friend, 13% in a school and 10% in a medical-welfare establishment. The other places of consumption varied (hospital, public street). It should be noted that 18 clustered cases were reported, mostly in schools or homes, involving a total of 64 adolescents and children.

Lastly, when information was available (n=134), 92% of people (n=123) reported chronic use, ranging from several weeks to several years for some.

Inexpensive substances found in many commercial products

The manufactured products involved are lawful, in everyday use, inexpensive and freely available, easily lending themselves to misuse by young adolescents. They include aerosol dispensers[2] (deodorant, air freshener, hairspray, dust remover, etc.), certain glues, lighter fuels, dry-cleaning products, nail polish remover, correction fluid, marker pens and petrol. They contain multiple chemicals, including for example hydrocarbons (propane, butane, isobutane, tetrafluoroethane) and solvents (toluene, trichloroethylene).

In this study, the vast majority of inhaled products were aerosol dispensers (n=306, 75% of products). Petrol (n=34), stain remover (n=15), nail varnish remover (n=8), helium (n=9), correction fluid (n=7), glue (n=5) and white spirit (n=3) were also used to a lesser extent.

Among the aerosol generators, deodorants were the most represented (n=163, 40% of cases), followed by dust removers (n= 59, 15% of cases) and air fresheners (n=42, 10% of cases). The most common aerosol dispenser gas involved in these poisoning cases was butane-isobutane-propane (BIP) (58% of aerosol dispensers), followed by butane-propane (12%) and isobutane alone (11%). These gases are classified as asphyxiating gases because they block oxygen supply and/or diffusion in the alveoli.

In this study, the consumption method was reported in only 22% of cases (n=88). The majority of these involved huffing (65% of cases) and bagging (31% of cases). Sniffing only concerned 4% of people.

In the vast majority of cases (94%), people had inhaled only volatile substances. A small number had also taken alcohol (10 cases), drugs such as cannabis or heroin (6 cases), or medication such as anxiolytics or sleeping pills (6 cases).

1.Extraction in 2021 of cases reported to poison control centres following a request from the ANSM.

2.Commonly known as aerosols, these are single-use metal, plastic or glass containers holding a product (liquid or solid) specific to aerosol use. The product inside is pressurised with a propellant gas.

Several cardiac arrests and neurological damage

In the study presented here, over half of the people (52%) experienced at least one neurological symptom such as headaches, drowsiness, dizziness or loss of consciousness. Psychological symptoms were reported in one third of patients (inebriation, agitation), digestive symptoms in 15% (vomiting, nausea), respiratory symptoms in 13% (cough, respiratory pain), general symptoms in 11% (asthenia, discomfort) and cardiovascular symptoms in 8% (tachycardia, cardiorespiratory arrest).

No deaths were reported, but 13 poisoning cases were very serious. Eight of these users were male and the median age was 16 years. In all but two cases, the person had inhaled aerosol dispensers, mainly deodorants (n=9). In five cases the nature of the volatile substances was known.

They were deodorants containing ethanol, butane and/or the BIP mixture; a compressed-air spray containing butane and propane that caused cardiorespiratory arrest; a glue and shoe cleaner containing solvents.

Seven out of the 13 users had presented with cardiovascular problems, five of whom had suffered cardiorespiratory arrest with a favourable outcome after external electric shock with a defibrillator. Three of them had inhaled deodorant, a fourth had inhaled a compressed-air spray and the last had inhaled lighter fluid. Four people suffered from neurological disorders (three were in a coma and the fourth had temporarily lost consciousness) and one person with a burnt lip developed aspiration pneumonia[3].

Lung infection caused by inhalation of oral secretions, stomach contents or both, due to swallowing disorders.

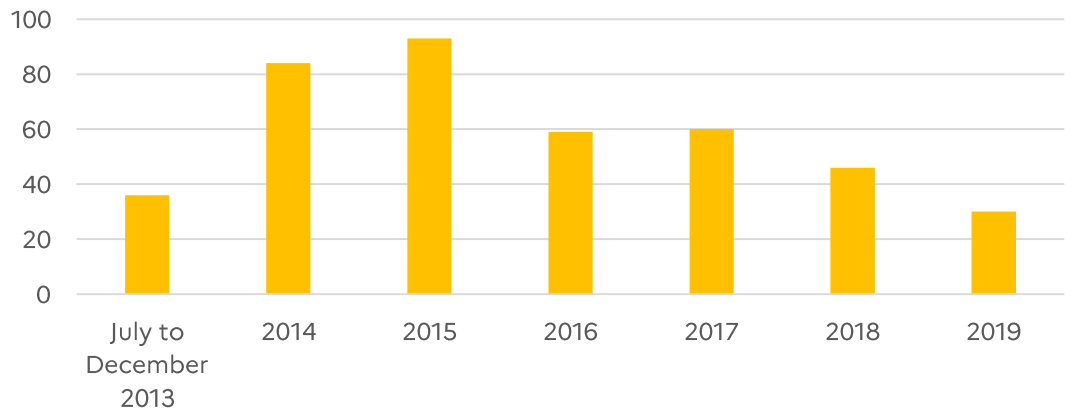

Figure 1: Annual breakdown of exposure cases reported to the poison control centres between 01/07/2013 and 31/12/2019. Source: SICAP.

Similar effects described in the literature

The potential lethality of these asphyxiating gases has been extensively described in the literature. Fatal asphyxiation accidents have been reported in humans almost exclusively as a result of intentional inhalation in the context of substance abuse. Numerous deaths from inhalation of butane emitted from petrol fumes, or contained in aerosol cans or lighter refills, have been reported in the United Kingdom and the United States [2]. The direct cardiac toxicity of hydrocarbons is also well known. This is due to them sensitising the heart, to the effects of adrenaline in particular, leading to arrhythmia that can result in cardiac arrest and death [2].

Serious neurological disorders have also been reported, including severe encephalopathy in consumers of products containing butane, after only a few months of use. In addition, anaesthetic or narcotic effects have been described for butane and isobutane, with an action on the central nervous system and potentially fatal arrhythmia [2].

Moreover, the solvents and halogenated derivatives (chlorinated or fluorinated) also identified in the composition of the products consumed in this study act on the central nervous system by inducing an inebriated narcotic syndrome. Some consumers experience perception disorders that can lead to hallucinations, and then drowsiness sometimes leading to coma. Some halogenated compounds have cardiac toxicity. Several cases of sudden death have been described following the inhalation of volatile substances[5] such as chlorinated solvents, which are known to have pro-arrhythmogenic potential[6], but also with aerosol generators whose propellant gases are hydrofluorocarbons (tetrafluoroethane or norflurane) or difluoroethane. Massive, repeated and prolonged (several months to several years) exposure to solvents can lead to progressive leukoencephalopathy[7] with neurological and neuropsychiatric symptoms [3].

3.Lung infection caused by inhalation of oral secretions, stomach contents or both, due to swallowing disorders.
4.Feeling of drunkenness, dizziness, headache, nausea.
5.Sudden sniffing death syndrome (SSDS).
6.May cause heart rhythm disorders.
7.Neurological disorder due to alteration of brain white matter, regardless of the cause of the injury.

Lastly, the significant drop in the temperature of the gas during its expansion, which can quickly reach negative temperatures (down to -40°C), exposes the consumer to oral, intra-oral, oropharyngeal or respiratory tract burns and can lead to acute respiratory distress.

Raise awareness and improve labelling

There has been a steady decline in the number of cases reported to poison control centres since 2015. These findings are consistent with those of the latest ESCAPAD[8] survey of 2017, which shows a decrease in experimentation with "inhalants" since 2011 [4]. Unfortunately, the decline in the consumption of these substances may be offset by the use of other substances, mainly nitrous oxide, for which the number of poisoning cases has been increasing since 2017 [5]. In view of the seriousness of the cases observed, information campaigns on the risks involved in this practice are still needed.

This information should take the form of specific labelling applied directly on the packaging, explicitly warning of the serious and sometimes fatal risks involved in deliberately inhaling large quantities. In addition to the usual warnings ("avoid intentional inhalation, spraying into the eyes or onto irritated skin"), there should be a message about the risks associated with the abuse and misuse of these aerosol gases. Very explicit labelling such as "SACKI[9]" (Solvent abuse can kill instantly), like the one introduced in the UK, could deter children and young adolescents from trying this practice.

Minors, who were in the majority in this study, should be informed in school settings about the risks and dangers of this practice, which is too often considered to be harmless. Communication in schools should be proposed, in the same way as for the consumption of illicit substances, for example, through associations giving talks that are tailored to the age of the pupils, particularly teenagers, who often begin using due to peer pressure.

Family and friends should also be made aware of this practice, which sometimes begins in childhood, through a national information campaign run by the competent bodies.

This is because some young users engage in recreational inhalation of volatile substances alone at home, without the knowledge of close relatives.

This increases the risk of death by delaying the intervention of emergency medical services in the event of cardiorespiratory arrest.

Healthcare professionals and supervisory staff in educational settings, school health services, paediatricians and general practitioners should also be made aware of these practices. As this study indicates, they involve young children and sometimes occur in the school environment, and may then concern several pupils. It is also important to remind emergency physicians and resuscitators, who are directly involved in treating these poisoning cases, that they can obtain toxicology expertise by calling a poison control centre.

Lastly, people who are already addicted to this consumption should be treated under an addiction treatment monitoring protocol[10] by a doctor or specialised organisation, such as a centre for addiction care, support and prevention (CSAPA), or a young consumers' consultation centre (CJC)[11] if they are minors. These organisations offer a free and confidential service (information, listening, counselling and, if necessary, referral). All the information is available at www.drogues-info-service.fr.

Implementing these measures would help prevent or limit the risks associated with the recreational inhalation of volatile substances, and would also improve the ability to detect and identify practices of this kind that are not exhaustively known. This monitoring will be continued by the CEIP-As as part of their addictovigilance mission, in particular to improve knowledge of medium-term effects or of the occurrence of after-effects.

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TO FIND OUT MORE:

https://www.anses.fr/fr/system/files/Toxicovilance2019SA0217Ra.pdf

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E-cigarettes: only a few serious poisoning cases but vigilance still needed

Since the early 2000s, several studies by poison control centres have focused on electronic cigarettes and their e-liquid refills, describing the circumstances and severity of exposure. In order to continue this work, a prospective study was carried out between 1 July 2019 and 31 December 2020, funded as part of ANSES's mission on tobacco and related products. The majority of cases concerned accidental exposure of children. However, these were not very serious and had a favourable outcome. Some were due to mistaking a bottle of e-liquid for a medicine, or handling e-liquid components while following do-it-yourself recipes. Despite the introduction of regulations governing these products, vigilance is still needed to ensure that they are safe for use by vapers and those around them.

The diversification of e-cigarette devices and their growing popularity since the early 2000s have been accompanied by an increase in cases of accidental exposure, whether through ingestion of e-liquid, eye or skin splashes, or inhalation. While these cases primarily concern adult users of these devices, exposure among children has also been observed.

Poisoning cases monitored by poison control centres for several years

The poison control centres (PCCs) in France published an initial report in 2011 on exposure cases reported from January 1999 to December 2010, then a second report for the period from January 2013 to 2014 [1]. A number of accidental exposure circumstances were described, the most frequent of which were ingestion by children causing digestive problems, splashes of e-liquid when the e-cigarette was being filled by the vape, causing eye irritation, and ocular administration of e-liquid that had been mistaken for eye drops. E-cigarettes were also responsible for respiratory symptoms such as coughing, especially in new vapers. Although overall they were of low severity, most of the cases in these two studies involved children, which prompted the vigilance to be extended and the exposure circumstances and products involved to be further documented.

In addition, when European Directive 2014/40/EU on tobacco products was transposed into French law, the Ministry of Health tasked ANSES with receiving and analysing notifications from manufacturers and importers of vaping products containing nicotine and intended for the French market. Indeed, prior to any marketing in a Member State of the European Union, manufacturers must provide information on their products and, in particular, on the composition of e-liquids containing nicotine [2].

As part of a research and development financial agreement established on ANSES's initiative, the Toulouse PCC coordinated a prospective study to identify cases reported to the eight French poison control centres between 1 July 2019 and 31 December 2020. For each case, as well as the data usually provided by the PCC in the medical file, more detailed information was collected on the exposure circumstances and the products, while ANSES helped with the composition data provided by manufacturers and importers.

Cases of exposure regularly reported but not serious

Over the 18 months of the study, 919 cases were recorded by the PCCs, an average of 51 per month, whether symptomatic or not. There were no peaks during this period, not even during the successive lockdowns and curfews in 2020 due to the COVID-19 pandemic (see Figure 1).

In the majority of cases (71%), calls to the PCCs came directly from the exposed individuals or their close relatives. The remaining calls were from healthcare professionals. In 91% of cases, exposure occurred in the home of the exposed individual.

Exposure victims ranged in age from one month to 89 years, but the majority were very young: half of the cases involved children under 4 years of age, 3% involved children aged 5 to 12 years, and 6% were aged 12 to 18 years. Thus, 60% of those exposed were minors (see Figure 2).

The sex ratio of 1.2 showed a slight male predominance.

The most common routes of exposure were oral (74%) and ocular (17%).

Of the 919 cases, almost 50% were asymptomatic. This proportion was 70% for children under 5 years of age, and 55% for those aged 5 to 12 years. From the age of 12 onwards, symptomatic patients were in the majority: over 70%, and up to 100% of cases among people aged 65 and over (see Figure 3).

Of the 464 symptomatic cases, 94% were of low severity, with digestive symptoms (nausea, vomiting, abdominal pain), ocular symptoms in the event of contact with the eye (pain, conjunctivitis) or headaches.

The cases of moderate severity (5%, or 24 cases) involved young adults who accidentally ingested e-liquid or were poisoned while vaping during normal use. In addition to the symptoms already mentioned, four patients reported persistent vomiting, and there was one case of bradycardia, one case of tachycardia, one case of convulsions, one case of hallucinations and one case of hematemesis (vomiting blood).

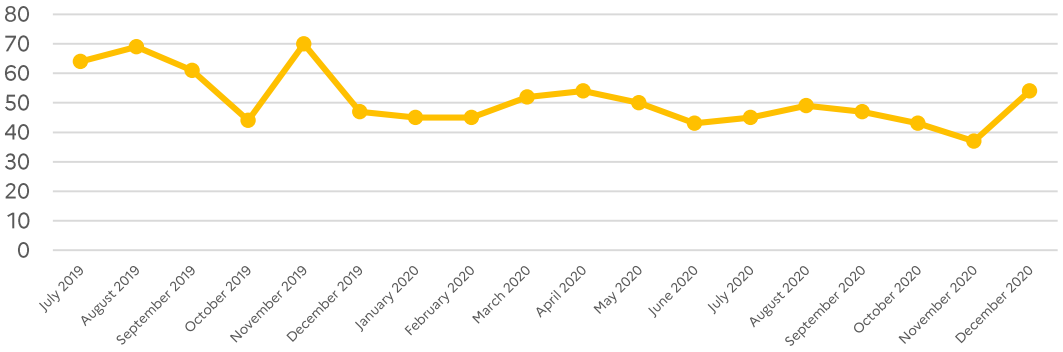

Figure 1: Monthly change in the number of cases of exposure to vaping products reported to poison control centres (N=919). Source: SICAP (July 2019 - December 2020).

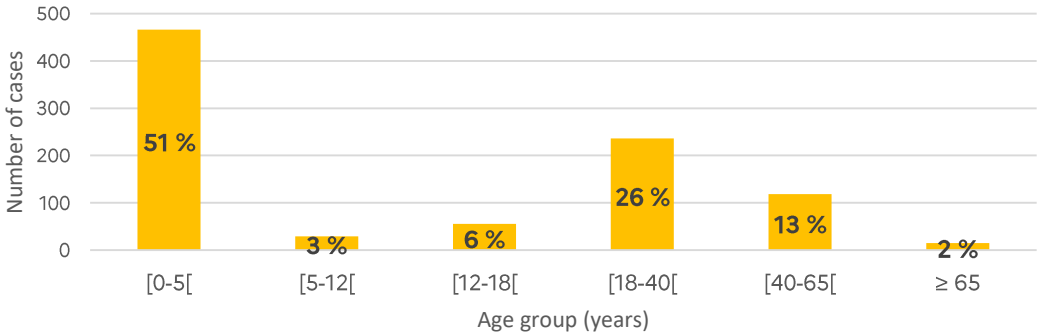

Figure 2: Number and percentage of cases of exposure to vaping products reported to poison control centres, by age group (N=919). Source: SICAP (July 2019 - December 2020).

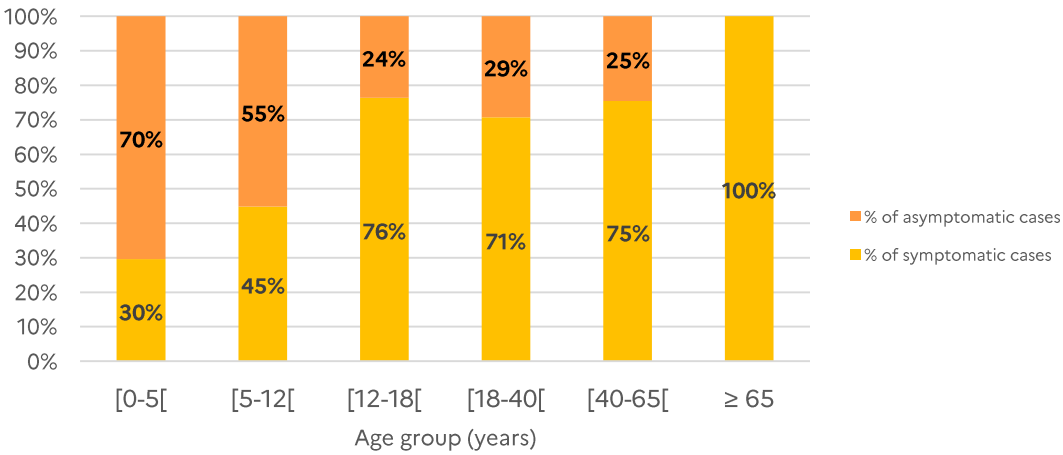

Figure 3: Percentage of symptomatic and asymptomatic cases by age group (N=919). Source: SICAP (July 2019 - December 2020).

Three cases were very serious, including a two-year-old child who swallowed a small amount of e-liquid after unscrewing the tank of an e-cigarette. The child experienced a tachycardia of 220 beats/min shortly afterwards, and was admitted to the hospital emergency department. They were discharged a few hours later, as the tachycardia had spontaneously resolved. The other two high severity cases were in adults:

- a man who ingested 10 ml of e-liquid containing 6 mg/ml of nicotine with the intention of committing suicide, and who suffered two generalised convulsive seizures and cardiovascular shock[1] in the hours following ingestion. He was admitted to hospital for one day, then his condition improved;

- a woman who had been vaping for nine months as part of an effort to give up smoking was hospitalised for 12 days with pneumothorax (collapsed lung). However, the lung specialist did not establish a definite link with the vaping.

When known, the outcome of the symptomatic cases was always favourable (91% of cases).

Circumstances specific to children

Among under-fives (n=469), the exposure cases were accidental in origin and mainly concerned ingestion of e-liquid (95%), due to the exploratory behaviour of this age group. The e-liquid bottles had either been opened by the children themselves, left open by others or were damaged. The other exposure circumstances were e-liquid splashes in the eyes or on the skin or, more rarely, inhalation after mimicking vaping while handling an e-cigarette.

For adolescents (n=55), although the sale of e-liquids is legally prohibited for them as it is for tobacco, 27% of the exposure cases in this age group resulted from "normal" use of e-cigarettes, 11% were due to e-liquid leaking into the mouth while vaping, and 11% were the result of e-liquid splashes when filling the e-cigarette tanks. The other circumstances, when known, were accidental in 36% of cases (confusion of an e-liquid refill with another product, accidental ingestion, exposure after unsuitable decanting of a vaping product), and intentional (suicide attempts) in 11%.

Between the ages of 18 and 40 years, the majority of exposure cases when using e-cigarettes were accidental, due to splashes when filling (33%) or leaks of e-liquid while vaping (19%). This trend was also found in the 40-65 age group. In people over 65 years of age, most exposure cases involved accidental ocular administration of e-liquid, due to confusion with eye drops (87% of cases).

Do It-Yourself[2] recipes and product confusion constitute significant sources of exposure

Despite the difficulty in collecting information that would enable the e-cigarettes or e-liquids involved to be characterised with certainty, in most cases the product could be precisely identified. The e-liquids responsible for exposure were ready-to-use products in 79% of cases and mostly contained nicotine, with levels ranging from 0.1 to 20 mg/ml. Eleven patients reported that their e-liquid contained cannabidiol (CBD).

In more than 20% of all cases in this study, the person had been exposed to an e-liquid from a DIY recipe, or to one or more of its components. The proportion of children under 12 years of age exposed to a DIY product (either already prepared or to one of its components) was 25%, compared with 15% of those over 12 years of age.

In 8% of all cases, the individual had used the e-liquid bottle instead of a medical product. In more than 75% of these cases, the individuals concerned had administered the e-liquid into their eyes instead of their eye drops. In the other cases, the bottle of e-liquid had been used instead of a bottle of vitamin D for children, or ear drops. The proportion of symptomatic patients in these circumstances was higher (81% versus 48% for other circumstances), mainly due to ocular damage from confusion with eye drops.

Results supported by the literature

These results are in line with those of the study by German poison control centres, which analysed the cases received between January 2015 and February 2019: they recorded about 20 cases per month, over half of which concerned minors; 50% of cases were asymptomatic and 83% involved accidental ingestion [3].

In the study by French poison control centres, half of the exposed individuals exhibited symptoms, in particular nausea and vomiting in the case of ingestion, the main route of exposure in the study. These symptoms are due to the nicotine present in more than 80% of the e-liquids involved in this study, and its pharmacological and irritant effects on the intestinal mucosa [4]. Children under five years of age were more often asymptomatic than adults, which is consistent with the small amounts of e-liquid ingested. Two studies by American and European poison control centres confirmed this by showing that a majority of cases in children under five years of age involved accidental exposure to e-liquids with low severity [5].

Monitoring to be continued to improve vaper safety

From a regulatory point of view, European Directive 2014/40/EU, which came into force in 2016, requires manufacturers to implement specific processes to avoid accidental exposure, such as child-resistant packaging that is impossible to open and nicotine concentrations below 20 mg/ml. The public authorities are well aware of the importance of introducing ways of regulating e-liquids to protect children and adolescents, by imposing restrictions on the sale and advertising of this type of product.

This study highlights the central role of the PCC network in monitoring these exposure cases. The large number of calls concerning children under five years of age most likely reflects the greater concern of parents, who are more likely to call a PCC for toxicology advice. However, although these young children had virtually no symptoms, it is important to reiterate that vaping products (e-cigarettes and e-liquids) should never be left unattended and within the reach of children. Refill cartridges should not be stored with medicines, to avoid confusion with eye drops or bottles of vitamins intended for children.

1.Cardiovascular shock is an excessive lowering of blood pressure leading to an inadequate supply of oxygen-rich blood to vital organs.
2.Vapers preparing their own e-liquids from ingredients purchased separately (dilution base, nicotine and concentrated flavours).

The growing trend for vapers to make their own e-liquids from DIY kits justifies the continuation of monitoring. Although the study found that most cases of exposure involved ready-to-use bottles, DIY kits warrant special attention because of the high concentration of ingredients used (flavourings and nicotine, which sometimes exceeds the maximum permitted level of 20 mg/ml) and because of the proportion of children under the age of 12 who were exposed to them. According to a survey conducted by BVA for ANSES in 2020, 33% of vapers use DIY liquids on a regular or exclusive basis. However, these products are not currently regulated.

ANSES therefore recommends that the European regulation, and particularly the associated reporting obligations, should be extended to all vaping products on the market, whether or not they contain nicotine, and whether they are sold ready to vape or made by the users themselves [6].

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Birth control pills for female cats and dogs are medicines whose use must be supervised by a veterinarian

Birth control pills intended for pets can have serious side effects in treated animals. Since 2012, therefore, they must be prescribed by a veterinarian and used in accordance with a number of recommendations. Despite this, the incidence of adverse effects has continued to rise. In order to improve the prevention of risks to treated animals, additional information will be provided in the summaries of product characteristics and package inserts of these medicines, and the number of pills sold in each box will be reduced. Information messages will again be issued to alert owners and healthcare professionals (veterinarians and pharmacists). Lastly, the monitoring of adverse effects will be increased, in order to assess the effectiveness of the risk minimisation measures taken.

Megestrol acetate or medroxyprogesterone birth control pills have long been a common form of contraception for pets, as they are inexpensive and readily available without a prescription from pharmacies or veterinary clinics. Nevertheless, veterinary pharmacovigilance data accumulated over time have revealed the occurrence of serious and potentially fatal adverse effects in treated animals. In 2012 (shown by a red arrow in Figure 1), therefore, it was decided that these medicines would only be available on prescription after a consultation with a veterinarian. Despite the introduction of this measure and the fall in the use of these products, the incidence of serious adverse effects has continued to rise (Figure 1).

An increased risk of developing serious uterine or mammary gland diseases

The use of these medicines, which have a progestational effect, can cause numerous adverse effects in female cats and dogs. These have been documented in the scientific literature and reported in the many adverse effect reports received each year by the French Agency for Veterinary Medicinal Products (ANSES-ANMV). Behavioural or dietary changes (polyphagia) have mainly been described. However, more serious disorders are regularly observed, particularly in the reproductive system (inflammation of the uterus, uterine infections and tumours, ovarian cysts, vaginitis) and the mammary glands (mammary hyperplasia, tumours).

Cases of diabetes mellitus have also been reported. These side effects require prompt action and surgical and/or medical treatment.

A retrospective review of pharmacovigilance reports received by ANSES-ANMV between 2016 and 2019 found that the treated cat died in 20% of the 80 cases reporting the occurrence of reproductive tract and/or mammary gland disorders following administration of a contraceptive containing megestrol acetate. The number of animals and their mortality according to the observed disorder are shown in Figure 2.

Seven cases of adverse effects in bitches on contraceptives were also reported, including one death.

Adverse effects sometimes after several administrations

Depending on the effect sought (prevention or interruption of oestrus), megestrol acetate pills are administered every one to two weeks during the desired prevention period, or daily for a few days. The analysis of pharmacovigilance cases showed an increased risk of side effects with a longer duration of treatment. However, some adverse effects were also observed after less than 3 months of use (Figure 3).

Figure 3 details the adverse effects in female cats treated with megestrol acetate pills for preventing oestrus (76 animals), according to the time to onset of clinical signs.

Lastly, the analysis found that the risk of serious adverse effects increased in the event of overdose.

Precautions to be taken to limit adverse effects

The administration of oral contraceptives to female cats and dogs is far from innocuous. While they remain rare, their adverse effects concern healthy animals, meaning that the benefit/risk ratio of such treatments needs to be assessed on a case-by-case basis.

In order to prevent or interrupt oestrus in female cats and dogs and avoid unwanted pregnancies, a consultation with a veterinarian is therefore necessary. Faced with all the different possible methods of birth control, veterinarians are best placed to suggest the most appropriate solution according to the profile of the animal in question: either surgical sterilisation, which is the only definitive (irreversible) method, or medicated contraception, either in the form of injections (which can only be carried out by the veterinarian), or pills as described in this article (which can be administered by the owner).

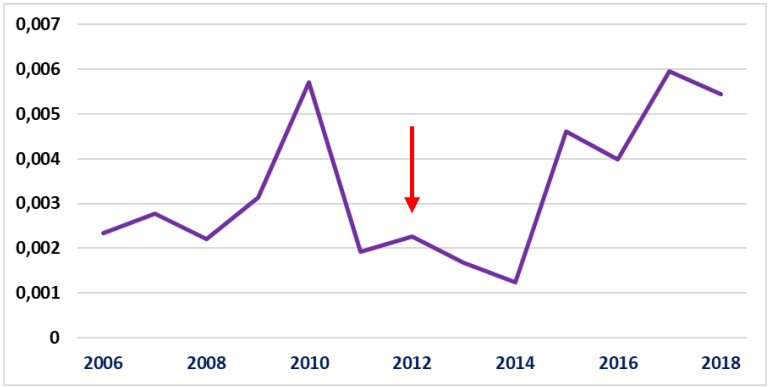

Figure 1: Change in the incidence of adverse effects occurring in female cats (% of treated animals) following the administration of megestrol acetate pills between 2006 and 2018. Source: ANSES-ANMV veterinary pharmacovigilance network.

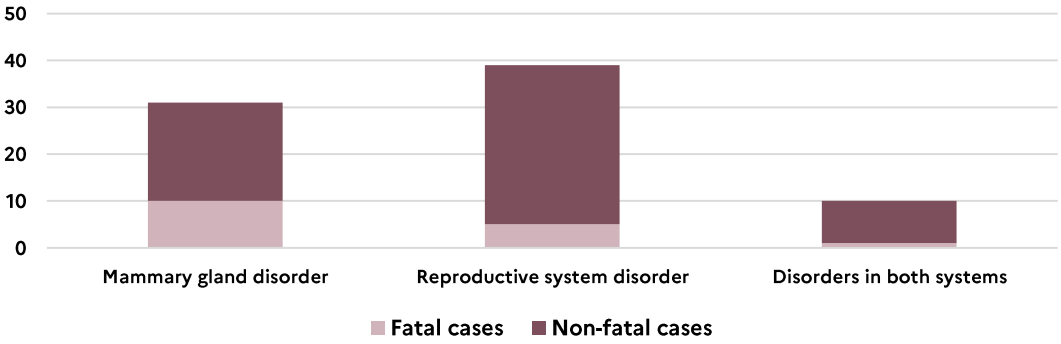

Figure 2: Number of reports of adverse effects in female cats treated with megestrol acetate pills between 2016 and 2019, according to the affected system (n=80). Source: ANSES-ANMV veterinary pharmacovigilance network.

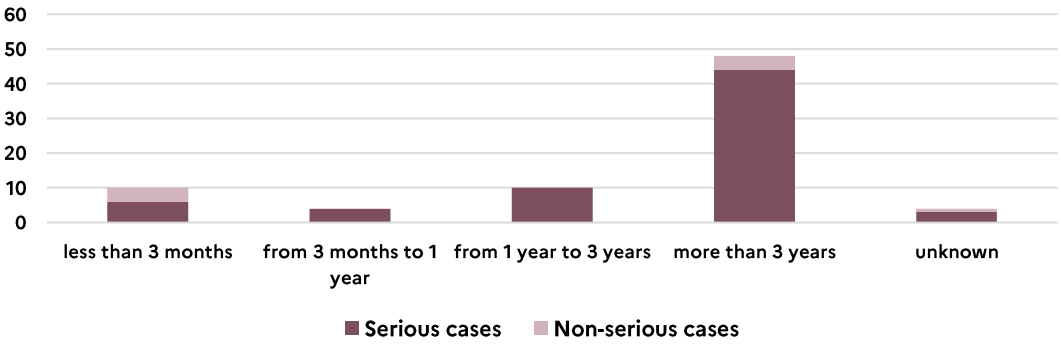

Figure 3: Number of reports of adverse effects in female cats treated with megestrol acetate pills between 2016 and 2019, according to the duration of treatment (n=76). Source: ANSES-ANMV veterinary pharmacovigilance network.

If pills are the chosen method, the following precautions must be taken:

- It is essential to consult a veterinarian to determine the most appropriate treatment and limit the risk of adverse effects,
- Treatment should cease immediately and a veterinarian should be contacted if any adverse effects occur,
- As the risk of serious adverse effects increases with the duration of treatment, administration should be limited to what is strictly necessary and, for the longer term, sterilisation should be considered,
- As the risk of serious adverse effects increases in the event of overdose, the animal should be weighed before each treatment and the dose adjusted to its weight,
- In the event of prolonged treatment (more than three months), the veterinarian should organise regular visits.

At ANSES-ANMV's request, these recommendations will soon be included in the package leaflets and summaries of product characteristics of oral contraceptives.

New risk minimisation measures

New measures to minimise the risk to treated animals are also planned:

- Reduction in pack size so that the permitted treatment period after a box of medicine has been dispensed does not exceed three months for the prevention of oestrus in a 5 kg cat.
- Increase in surveillance of the reported adverse effects.

To make pet owners aware of the inherent risks of administering these treatments and the resulting precautions for use, ANSES-ANMV published an alert[1] on anses.fr. Communications informing veterinarians and pharmacists of the new measures were also published in the trade press.

Corinne PIQUEMAL
and Sylviane LAURENTIE (ANSES-ANMV)

1. https://www.anses.fr/en/content/birth-control-pills-female-cats-and-dogs-must-be-prescribed-veterinarian

Cases of adverse liver effects due to turmeric or curcumin in food supplements

Numerous food supplements containing turmeric or its active substance curcumin are available on the French market. In ten years, the French and Italian vigilance systems have recorded over 40 cases of hepatitis that occurred following consumption of this type of food supplement. Consumers, healthcare professionals and the companies marketing these products need to be made aware of the risk, so that in the event of a liver disorder, a link can be sought between its occurrence and the turmeric, and consumption of the food supplement containing it can rapidly be stopped. Moreover, when they occur, these adverse effects should be reported to the nutrivigilance scheme in order to improve knowledge on this topic.

Turmeric rhizomes have historically been used in powder form as a spice (curry, ras-el-hanout, etc.) in various cuisines, but also in traditional Indian and Chinese medicine, mainly for their digestive (stimulation of bile secretion), antioxidant and anti-inflammatory properties. There are also many food supplements on the French market containing turmeric, or its active compound curcumin. In the past five years, more than 1600 products containing turmeric or curcumin have been notified to the Directorate General for Competition, Consumer Affairs and Fraud Control (DGCCRF) with a view to placing them on the French market.

Since the nutrivigilance scheme was established in 2009, 15 cases of adverse liver effects potentially associated with the consumption of food supplements containing turmeric or curcumin have been reported to and analysed by ANSES. In one of these cases, the consumer's symptoms were life-threatening. Italy, meanwhile, also reported around 20 cases of hepatitis involving turmeric in food supplements between November 2018 and June 2019 [1,2].

ANSES therefore decided to conduct a review of knowledge on this plant, estimate the exposure of the French population to curcumin present in food and, if necessary, take action to protect the most exposed and vulnerable populations [3].

The various adverse effects reported

From January 2009 to August 2021, ANSES was made aware of 120 cases of adverse effects of all types potentially associated with the consumption of food supplements containing turmeric or curcumin. Of these 120 cases, 67 were sufficiently well documented to be analysed for their causality[1]. The most commonly reported adverse events were hepatitis, headache, dizziness and digestive disorders such as diarrhoea or nausea.

The food supplement's causality in the occurrence of these effects was considered "very likely" for one case, "likely" for 31 cases, "possible" for 24 cases and "unlikely" for 10 cases. The severity[2] of the adverse events was low (Level 1) in 28 cases and moderate (Level 2) in 25 cases. Fifteen cases were of high severity (Level 3), four of which were life-threatening (Level 3 with life-threatening prognosis). These involved acute lung oedema, a recurrence of myocardial infarction and mixed hepatitis[3] (in these three cases causality was considered "likely"), as well as cardiorespiratory arrest in which causality was "possible". No deaths were reported.

This article reviews the adverse liver effects of greatest concern, which led to an in-depth expert appraisal by ANSES.

Focus on adverse liver effects

- **Data from the nutrivigilance system**

Among the 120 cases reported to the nutrivigilance scheme, 15 cases of hepatitis were identified. The food supplement's causality was "very likely" for two cases, "likely" for seven, "possible" for four and "unlikely" for two cases. Three cases were of high severity (Level 3), one of which was life-threatening (Level 3 with LTP). The distribution of these cases according to causality and severity is shown in Figure 1.

The consumers' ages ranged from 22 to 74 years old, with a median age of 56. Almost 75% of the cases involved women. The adverse liver effects occurred within three days to one year of the start of consumption, with a median time to onset of two months. The consumers all had a history of liver or biliary disease.

1.Causality enables a causal relationship to be defined. It has five levels: excluded, unlikely, possible, likely and very likely.
2.The scale of severity in nutrivigilance goes from Level 1 (low severity) to Level 4 (death).
3.Hepatitis in which transaminases (ASTs and ALTs), alkaline phosphatases and GGTs are increased.

Twelve cases involved concomitant consumption of at least one other food supplement or medicine. In 14 other cases, the food supplements involved were multi-ingredient, i.e. turmeric or curcumin was combined with other ingredients. Some of these ingredients, such as green tea, *Garcinia cambogia* and Chinese cinnamon, are described as hepatotoxic. In eight cases the dose of curcumin consumed was known. It ranged from 10 mg per day to 1.2 g per day with a median dose of 186 mg per day.

- **Data from the literature**

In addition to these vigilance data, eight cases of hepatitis involving the consumption of food supplements containing turmeric have been published in the literature. All of these patients recovered upon cessation of use. Only one patient had a history of liver disease and all of them were taking one or more medicines in parallel. In four cases the dose of curcumin consumed was known: it ranged from 50 mg to 1 g per day [3].

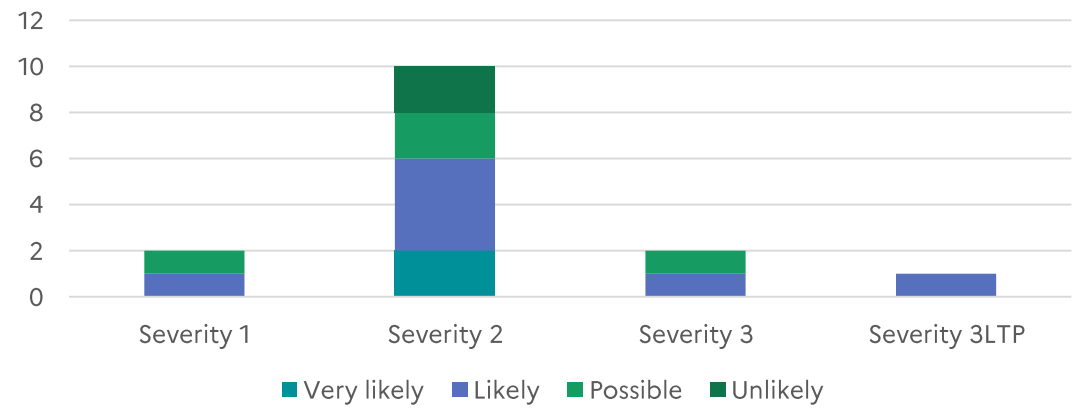

Figure 1: Distribution of cases of hepatotoxicity from food supplements containing turmeric according to their causality and severity (N=15)

Conclusions and recommendations

Hepatotoxicity associated with the consumption of food supplements containing turmeric or curcumin was therefore identified by the nutrivigilance scheme, by the reports received, and from the analysis of the literature. No risk factors specific to the consumers were found; in particular the majority of these turmeric consumers had no history of liver disease. At present, therefore, there are no special warnings for people with prior liver damage. This finding will nevertheless need to be confirmed through increased vigilance. Consumers of food supplements, healthcare professionals and the companies marketing these products are invited to pay closer attention to any possible link between turmeric consumption and the occurrence of this hepatitis, in order to take prompt action to cease consumption. These adverse effects should also be reported to the nutrivigilance scheme.

In addition, anyone being treated with medication is advised to seek the opinion of their doctor or pharmacist before taking food supplements in general, and in particular if they contain turmeric or curcumin.

Lastly, because turmeric promotes bile secretion, consumption of turmeric is not recommended for anyone with biliary tract disease.

Fanny HURET (ANSES)

To report an adverse effect following the consumption of a food supplement: https://www.nutrivigilance-anses.fr/nutri#

FIND OUT MORE:

ANSES opinion on the assessment of risks associated with the consumption of food supplements containing turmeric.

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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 adedicated 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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