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VETERINARY PHARMACOVIGILANCE

NUTRIVIGILANCE

anses

Never use a mixture of bleach and vinegar for weed control

Faced with bans on the sale of numerous plant protection products to private individuals, more and more people have been choosing to make their own herbicides by mixing together bleach and vinegar. However, this combination releases toxic chlorine gas, which can cause irritation of the respiratory tract and asthma attacks, sometimes requiring hospitalisation. In view of an increase in poisoning cases, ANSES and French poison control centres warned the general public about this dangerous practice and recommended using only products bearing the words "Authorised for use in gardens" for weed control.

From a ban on pesticides for the general public...

The aim of the Labbé Act of 6 February 2014 is to protect people and the environment from the toxic effects of certain plant protection products, commonly referred to as pesticides.

These products, which target species of pests (plant or animal) that threaten cultivated plants, are not without risk and require certain precautions to be taken. In addition, their use on a massive scale can lead to resistance in the organisms they are intended to destroy. The legislator therefore deemed it necessary to restrict their use by non-professionals in order to reduce poorly controlled exposure of the public and the environment. Some products therefore disappeared from retail outlets in 2019. Public policy-makers also introduced a ban on professionals using them to treat public gardens, parks and forests, i.e. any green space open to the public.

The only options now available to private individuals are so-called biocontrol products, products described as low-risk (such as iron phosphate against slugs), and products that can be used in organic farming. These bear the words "Authorised for use in gardens". The term biocontrol encompasses macro-organisms (invertebrates, insects, mites, nematodes), plant protection products containing micro-organisms (fungi, bacteria, viruses), chemical mediators such as sex pheromones (chemical substances produced by insects that play a role in sexual attraction) and natural substances of vegetable, animal or mineral origin.

ANSES is responsible for assessing the risks, particularly for health, and the agronomic benefits of biocontrol products.

... to the use of dangerous "home-made" recipes

Deprived of the products they were accustomed to using, certain amateur gardeners have been turning to potentially hazardous alternatives. Some of these, mainly ones found on websites or gardening forums, recommend the use of bleach, vinegar or hydrochloric acid, which are all inexpensive, everyday products. Unfortunately, often as a result of following the instructions on these sites, some people mix these products together before spraying them. This mixture produces a chemical reaction that suddenly releases chlorine gas, which causes major irritation of the airways and can lead to acute respiratory distress syndrome, a very serious, life-threatening form of respiratory failure. Respiratory sequelae such as asthma may persist. There is also a risk of explosion if the products are mixed in a pressurised sprayer.

An exponential increase in chlorine poisoning from mixing bleach and vinegar or another acid

Between 1 January 2001 and 31 October 2022, poison control centres observed an exponential increase in calls following exposure to chlorine after mixing bleach and vinegar, or another acid, for weed control purposes. During this period, they counted 204 patients who had inhaled chlorine in this context (Figure 1).

While only one case of exposure was recorded from 2002 to 2013, almost 80% of the reported cases have occurred since the date of the ban on the use of herbicides by the general public (2019).

As expected, there is a strong seasonal pattern to these exposures, with a peak in late spring and early summer when most weeding takes place (Figure 2).

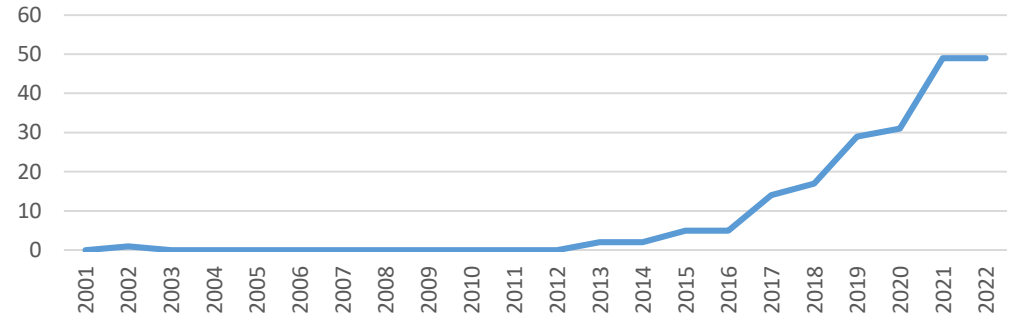

Figure 1: Annual number of cases of exposure to chlorine from mixing bleach and vinegar or acid for weed control, reported to PCCs from 01/01/2001 to 31/10/2022 (Source SICAP).

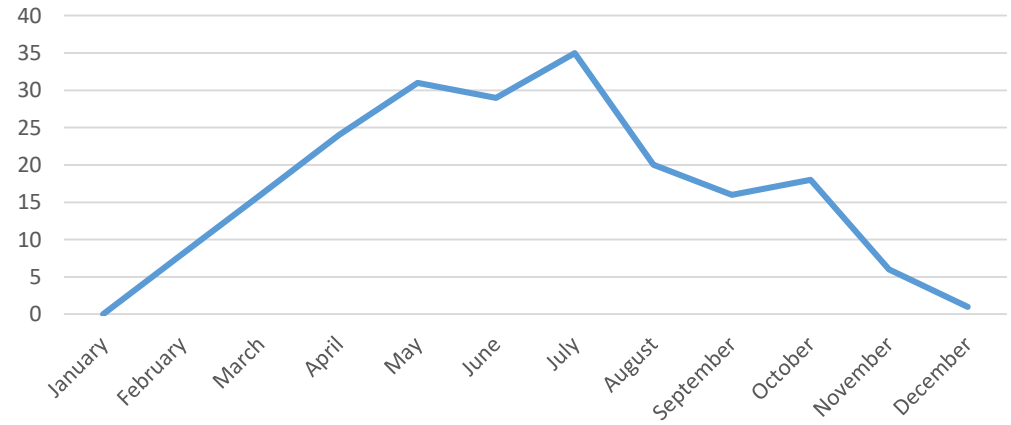

Figure 2: Monthly number of cases of exposure to chlorine from mixing bleach and vinegar or acid for weed control, reported to PCCs from 01/01/2001 to 31/10/2022 (Source SICAP).

A mixture of bleach and vinegar, two of the most accessible products on the market, accounted for two thirds of the cases (74%). The next most common combination was bleach/hydrochloric acid (23%), followed by bleach and another acid (2.9%). Lastly, two people had mixed bleach, vinegar and hydrochloric acid (Table 1).

In addition to these mixtures, some patients had added coarse salt (53 cases), washing-up liquid or detergent (10 cases), sodium bicarbonate (7 cases), a small quantity of leftover weedkiller (4 cases), a hydrocarbon (diesel, dearomatised petroleum in 2 cases), caustic soda (1 case) or a swimming pool chlorine tablet (1 case).

Respiratory signs were rarely serious...

Two-thirds of the patients were adult males (68% aged 18-64 years) (Table 2).

The most frequently observed symptom was coughing (81% of patients), most often combined with breathing difficulties (50%) or irritation of the ear, nose and throat (ENT) or respiratory tract (46%). Of the 95 patients seen by a doctor[1], almost one third (N=27) presented with signs of bronchospasm, i.e. constriction of the bronchi as in an asthma attack. Hypoxia (reduced blood oxygen concentration) was found in 29% (N=22) of the 76 patients treated in hospital, and respiratory distress in 5% (N=4). Of the 204 cases in the study, 21% (N=42) were moderately or severely poisoned, with no difference in severity according to the mixture used.

In contrast, a history of respiratory conditions, such as smoking, asthma, chronic obstructive pulmonary disease or emphysema, constitutes a risk factor for moderate or severe poisoning.

1. People who called a poison control centre about a poisoning case were sometimes able to stay at home if their condition warranted it. These were of course the mildest cases.

Table 1: Number (percentage) of cases of exposure to chlorine according to the mixture, reported to PCCs from 01/01/2001 to 31/10/2022 (Source: SICAP).

Agents	n (%)
Bleach + vinegar	149 (74.0)
Bleach + hydrochloric acid	47 (23.0)
Bleach + other acid (sulphuric or phosphoric)	6 (2.9)
Bleach + vinegar + hydrochloric acid	2 (0.1)

... but sequelae were observed in the most severe forms

Almost half of the exposed patients required medical treatment, mainly oxygen therapy (12.7%). After going to the emergency department, 2.5% – or five patients – were admitted to hospital, three of whom were in intensive care.

The outcome, known for three quarters of the patients, showed that a total of four patients had persistent after-effects following this poisoning, with difficulty breathing, shortness of breath or a reduction in respiratory capacity lasting from one to six months after exposure. Three of them were monitored by a pulmonologist.

Never mix bleach with vinegar or acid

While chlorine exposure due to cleaning and swimming pool maintenance activities has already been described [2], weed control using a "home-made" mixture of bleach/vinegar or another acid is a new practice that is growing significantly. ANSES and the poison control centres wished to warn the public about this dangerous practice and recommend using only products bearing the words "Authorised for use in gardens" for weed control.

Marie DEGUIGNE (Angers poison control centre and Juliette BLOCH (ANSES)

References

[1] Labbé Act of 6 February 2014 https://www.assemblee-nationale.fr/14/ta/ta0280.asp

[2] Disinfection products for swimming pools and spas: comply with the precautions for use to avoid any accident – Vigil'Anses 9, November 2019 – https://vigilanses.anses.fr

Table 2: Age, sex, clinical symptoms and outcome of cases of exposure to chlorine from mixing bleach and vinegar or acid for weed control, reported to PCCs from 01/01/2001 to 31/10/2022 (Source SICAP).

Patients	n (%)
Sex	
Female	54 (26.5)
Male	150 (73.5)
Age group	
< 3 years	2 (1.0)
3 - 17 years	4 (2.0)
18-64 years	138 (67.6)
65 - 75 years	41 (20.1)
> 75 years	24 (11.8)
Symptoms	
Cough	165 (80.9)
Respiratory discomfort	102 (50.0)
ENT or respiratory irritant pain	94 (46.1)
Asthma attack	27 (13.2)
Headaches	9 (4.4)
Respiratory distress	4 (2.0)
None	5 (2.5)
Severity	
Zero (no symptoms)	5 (2.4)
Low	157 (77.0)
Moderate	38 (18.6)
High	4 (2.0)
Place where medical care received	
Home	99 (48.5)
Doctor's surgery	19 (9.3)
Hospital emergency department	71 (34.8)
Emergency department then hospitalisation in a medical department	2 (1.0)
Resuscitation/intensive care	3 (1.5)
Unknown	10 (5.0)
Outcome	
Recovery	150 (72.5)
Sequelae	4 (2.0)
Death	0 (0)
Unknown (no follow-up or failure to follow through to final outcome)	50 (24.5)

TO FIND OUT MORE:

- **How to garden without pesticides ?** https://www.ecologie.gouv.fr/comment-jardiner-sans-pesticides
- **What are the alternatives to the use of synthetic plant protection products?** https://www.jardiner-autrement.fr/

Fuel shortages at the pump and increased risk of siphoning accidents

In October 2022, against the backdrop of a national fuel shortage, poison control centres recorded five times as many accidents involving petroleum fuel siphoning as in normal times. Using your mouth to siphon fuels is dangerous and carries a risk of inhalation pneumonia and significant after-effects. While fuel siphoning accidents occur on a regular basis, an increase is seen every time there is a fuel shortage.

On 13 October 2022, a poison control centre alerted ANSES to an increase in siphoning accidents: 42 petroleum fuel siphoning accidents had been reported to all poison control centres between 1 and 12 October, compared to the usual 20 or so accidents per month.

A strike in several refineries had begun on 27 September and then gradually spread throughout the country, causing a fuel shortage. On 12 October, according to the Ministry of Energy Transition, supply difficulties for at least one type of fuel were reported in more than 30% of service stations in Ile-de-France, Bourgogne-Franche-Comté and Auvergne-Rhône-Alpes, in 15% to 30% of stations in seven other metropolitan regions, and in less than 15% for the rest of the country. Prefectoral decrees prohibiting the sale and purchase of fuel in jerry cans were issued in all *départements*.

The strike lasted up to five weeks in some refineries, and was followed by a week of gradual restoration of service. The shortage therefore lasted all of October and the first week of November, and this period coincided with a sharp increase in siphoning accidents recorded by poison control centres (Figure 1).

On 28 October 2022, ANSES and the poison control centres published an alert on the risks of poisoning in the event of siphoning fuel by mouth [1].

Siphoning of petroleum fuels: a practice that could lead to serious poisoning

Fuel siphoning consists in emptying a vehicle's tank by sucking up the fuel and transferring it to another container (jerry can, petrol can, etc.). While several techniques are possible, the principle is the same: one end of a hose is immersed in the tank to be siphoned and the other end – or the end of a second hose to which the first hose is indirectly connected – is placed in the container into which the fuel is decanted.

Priming the siphon by sucking in fuel draws the liquid from the tank into the pipe so that it then flows spontaneously out of the other end, according to the principle of communicating vessels[1]. Doing this with the mouth is dangerous, as it can result in the person sucking on the hose getting fuel inside their mouth and ingesting it. To avoid this risk, there are siphon pumps that enable fuel to be sucked into the hose without any contact with the mouth.

Ingesting a small amount of fuel is enough to cause poisoning, regardless of the type of fuel siphoned (petrol, diesel, etc.). In addition, sucking by mouth runs the risk of ingesting large volumes.

Petroleum fuels are highly fluid, volatile and irritating, which stimulates the cough reflex if ingested. This causes fuel to enter the bronchi instead of being swallowed.

Vomiting must then not be induced as this could cause some of the fuel to enter the lungs.

The onset of fever or coughing a few hours after ingestion is the first sign of possible aspiration pneumonia. This chemical lung disease can also be manifested by chest pain, respiratory discomfort and shortness of breath.

Poisoning is also indicated by the occurrence of digestive symptoms, characterised by belching with a smell of fuel in the mouth, gastric reflux, abdominal pain, diarrhoea with irritating stools, nausea and vomiting. More rarely, neurological signs such as a feeling of inebriation, headache, dizziness or drowsiness are observed.

1. A mechanism for balancing the pressures of the liquid between the petrol tank at a higher level and the container at a lower level, usually on the ground.

To a lesser extent, the fuel vapours released during siphoning may cause eye and upper airway irritation, and neurological or digestive signs as described above.

A fivefold increase in poisoning in October 2022

The poison control centres' information system (SICAP) lists 4094 cases of exposure from siphoning petroleum fuels between 1 January 2008 and 31 December 2022, an average of 22.7 cases per month. In October 2022, 114 cases were recorded, five times the usual monthly number.

The Ile-de-France (39% of cases), Auvergne-Rhône-Alpes (12% of cases) and Provence-Alpes-Côte d'Azur (11% of cases) regions were the most affected. The other regions each accounted for less than 10% of cases.

Most of the people exposed were men (96%), with an average age of 36 years (median 33 years).

The fuel had been siphoned from the tanks of road vehicles (motorbikes, scooters, mopeds), and even agricultural vehicles (tractors) and petrol-driven machinery such as lawnmowers.

Exposure in these accidents was mainly oral/buccal (111 out of 114 cases), with or without inhalation of fuel vapours; three people had inhaled without ingesting.

Eighty-eight percent of people (101 cases) were symptomatic, with digestive signs in three-quarters of these cases (Figure 2). These digestive symptoms were mainly belching with a petrol smell in one third of cases, vomiting in 20%, and abdominal, epigastric and/or oesophageal pain in 19% of cases.

One third of people reported respiratory signs, mainly coughing (29%), while 4% complained of respiratory pain or discomfort. Neurological signs were observed in almost one in five people, mainly dizziness (9%), headache (6%) or a feeling of inebriation (2%). Lastly, cardiovascular signs, mainly tachycardia or hot flush, were present in 5% of the poisoning victims.

While the vast majority of poisoning cases were mild, four patients had moderate or persistent symptoms of moderate severity. The first of these involved a 45-year-old man who briefly lost consciousness after ingesting a few gulps of petrol while siphoning from the tank of his motorbike.

He regained consciousness spontaneously and was given oxygen by the fire brigade. The progression of his symptoms was unknown.

A 16-year-old boy vomited and experienced chest pain after siphoning off-road diesel. He went to the hospital emergency department the next day with persistent respiratory pain and was placed on antibiotics. His symptoms regressed within three days.

An 18-year-old man experienced a "burning sensation in his lungs" 17 hours after ingesting two to three gulps of petrol siphoned from the tank of his moped. His symptoms regressed three days after treatment with antibiotics and a bronchodilator.

Lastly, a 25-year-old man presented with persistent vomiting and a temperature of 38°C without respiratory signs, 48 hours after ingesting a gulp of diesel fuel. The progression of his symptoms was unknown.

Although there were no serious or life-threatening cases in October 2022, several cases of poisoning requiring a stay in intensive care due to petroleum fuel siphoning accidents have been recorded in the past by the poison control centres.

A practice accentuated during periods of fuel shortage

According to the analysis of poison control centre data from 2008 to 2022, petroleum fuel siphoning accidents occur routinely and relatively constantly (Figure 3). On the other hand, each of the peaks in siphoning accidents in October 2010, May 2016 and October 2022 corresponded to a period of fuel shortage.

In October 2010, against the backdrop of opposition to pension reform, all French refineries were shut down for more than three weeks, with the result that service stations ran out of fuel, a situation unseen in France since May 1968. An increase of up to 75 fuel siphoning accidents per month was recorded by the poison control centres. Similarly, in May 2016, half of France's refineries were blockaded due to industrial action, and 55 petroleum fuel siphoning accidents were recorded during that month.

In contrast, in late December 2013, a strike at several French refineries had had no impact on fuel distribution or siphoning accidents, with 21 and 23 accidents respectively in December 2013 and January 2014.

More generally, there is an increase in fuel siphoning accidents in industrialised countries when the distribution of fuel to users is affected. For example, Hurricane Sandy, which hit the north-east coast of the United States in October 2012, caused severe damage to oil refineries, resulting in fuel shortages and rationing not seen in the country since the 1970s. The regional poison control centre recorded 283 cases of exposure to fuel in the month following the hurricane, an 18 to 283-fold increase over the previous four years [2]. More than 80% of the exposure cases were due to ingestion of fuel through reported or suspected siphoning.

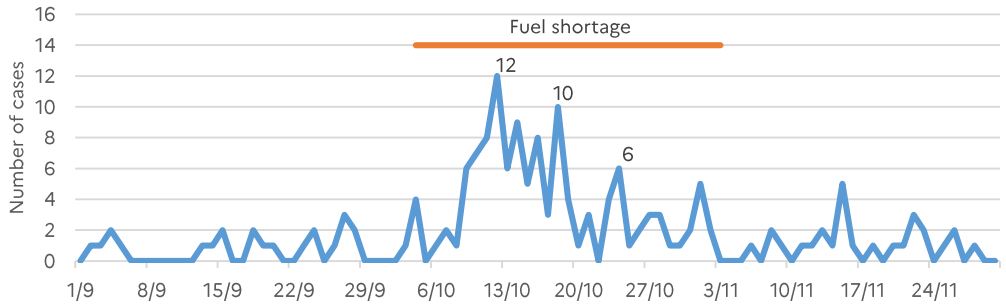

Figure 1: Daily number of petroleum fuel siphoning accidents recorded by PCCs between 01/09/2022 and 30/11/2022 (Source: SICAP)

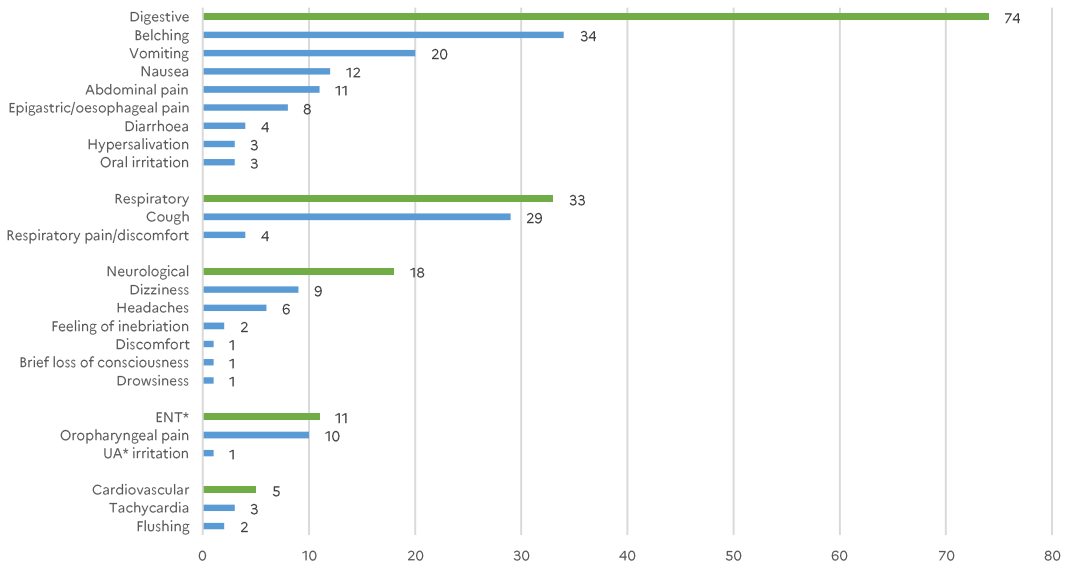

Figure 2: Petrol fuel siphoning accidents recorded by PCCs in October 2022. Symptoms presented and percentages of cases presenting with the symptom (N=101). (Source: SICAP). *ENT: Ear-nose-throat; UA: Upper airways.

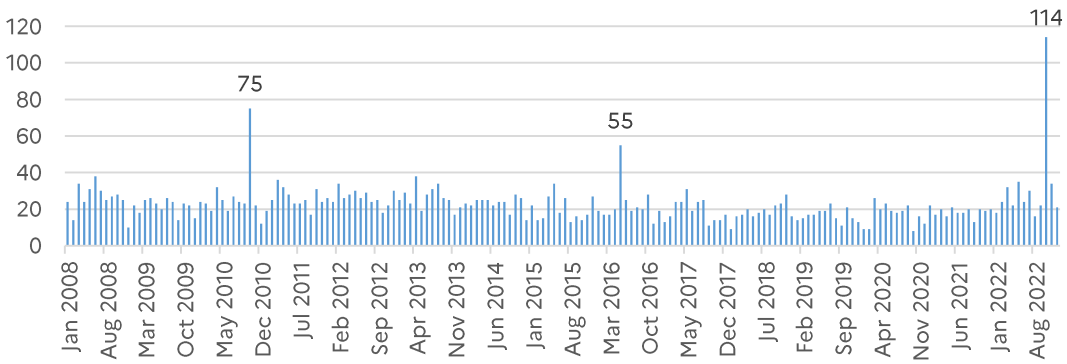

Figure 3: Monthly number of petroleum fuel siphoning accidents recorded by PCCs between 01/01/2008 and 31/12/2022 (Source: SICAP)

Monitor siphoning accidents during shortage situations

Although they are not necessarily predictable, changes in the social, economic or environmental context could lead to new episodes of fuel shortages and consequently to an increase in siphoning accidents over time.

Monitoring of these accidents could be set up quickly in the event of a shortage, to raise the alert without delay and prevent the occurrence of potentially serious accidents.

Sandra SINNO-TELLIER (ANSES) and Dominique VODOVAR (Paris poison control centre)

Recommendations

ANSES and the French poison control centres strongly discourage you from using your mouth to siphon fuel, and make the following recommendations.

If you have swallowed fuel:

- **Do not make yourself vomit**, to prevent the fuel from entering your bronchi and then your lungs;
- **Do not drink anything**, to avoid the risk of vomiting;
- Rinse your mouth with water;
- Do not engage in any high-risk activity, such as driving a car or using machinery or tools, because your vigilance may be impaired;
- Watch out for respiratory symptoms (cough, fever, shortness of breath), which may be delayed;
- If any fuel comes into contact with your skin, wash your hands with soap and rinse your skin;
- Take off any fuel-soaked clothing.

In the event of a life-threatening emergency (respiratory distress, loss of consciousness, etc.): dial 15 (in France), 112 or 114 (for the deaf and hard of hearing).

Otherwise, for any medical advice after swallowing fuel: call a poison control centre or see a doctor.

References

[1] News from ANSES Daily Life – 28/10/2022. "Fuel siphoning: watch out for the risk of poisoning" https://www.anses.fr/en/fuel-siphoning-watch-out-risk-poisoning

[2] KimH, TakematsuM, BiaryR, WilliamsN, HoffmanR, SmithS. Epidemic Gasoline Exposures Following Hurricane Sandy. Prehosp Disaster Med. 2013;28(6):1-6.

Exposure to psyllium: an emerging risk for food industry workers

Gluten-free and vegan products may include psyllium powder as an additive. While it is known to trigger allergic reactions in pharmaceutical workers and healthcare professionals, little is known about such reactions in food industry workers. However, a clinical case was recently described in the literature, and a French case was identified by the National Network for Monitoring and Prevention of Occupational Diseases (RNV3P).

Gluten-free food has become very popular in France in recent years, as shown by the steady growth rate of the French market for gluten-free products, which increased by around 20% between 2016 and 2020 [1].

Gluten is the insoluble protein fraction of cereal grains such as wheat, rye, oats, spelt or barley. This protein mixture gives the flour viscoelastic properties which are responsible for the elasticity of the kneaded dough and the chewability of baked cereal products. However, gluten consumption can have harmful effects on some people, especially those with allergies or coeliac disease[1], who are advised to avoid gluten completely in their diet. Some people are also said to be "gluten hypersensitive", a disorder with a poorly understood pathophysiology that manifests as non-specific digestive or non-digestive symptoms after ingesting gluten. These symptoms improve when gluten is excluded from the diet and reappear with its reintroduction.

At the same time, more and more consumers are embracing a vegan diet. This involves eliminating all foods of animal origin including eggs, dairy products and honey.

In order to meet the demand for gluten-free and vegan products, the food industry has therefore adapted by introducing ingredients such as psyllium powder into recipes.

The hydrocolloid properties of this powder give elasticity and viscosity to gluten-free doughs. In vegan products, psyllium is used as an egg substitute [2]. This introduction of new ingredients then leads to changes in the occupational exposure of workers in the food industry, with potential new health risk situations.

Psyllium plants have long been used for their seeds high in fibre and mucilage

The term psyllium is used to refer to several different species of plants belonging to the Plantaginaceae botanical family: *Plantago ovata* (*P. ovata*) known as blond psyllium or ispaghul, and *Plantago afra*, or black psyllium.

The seed coat of these psyllium plants is very high in fibre and, in particular, in mucilage[2] (especially blond psyllium). This explains why psyllium has long been used as a laxative.

Allergic symptoms from occupational exposure to psyllium

In the past, numerous cases of occupational allergy to psyllium have been described in the scientific literature: the individuals concerned were employees in the pharmaceutical industry or healthcare professionals who had handled *P. ovata* seed powder during the manufacture or preparation of laxatives.

The death of a nurse from a severe asthma attack after handling a laxative made from *P. ovata* seeds has even been described, due to an anaphylactic reaction[3] caused by psyllium inhalation [3].

In 2021, the first case of occupational allergy to psyllium was reported in a female baker who had been diluting psyllium powder in a liquid before incorporating it into a bread dough made of a gluten-free flour mixture [2].

1. A chronic, autoimmune intestinal disease related to the ingestion of gluten, occurring in genetically predisposed individuals.
2. Plant substance capable of absorbing a large volume of water, taking on a viscous consistency.
3. Sudden allergic reaction, potentially serious or even fatal.

After one year of exposure, the patient began suffering from rhino-conjunctivitis, which was triggered at work, as well as coughing and dyspnoea. After two years of exposure, she developed contact urticaria on her wrists. Prick tests[4] revealed sensitisation to wheat, rye and buckwheat flours, but also to psyllium. A nasal provocation test[5] confirmed the diagnosis of allergic rhinitis to psyllium.

Following this publication, ANSES and its expert group on "Emerging issues in Occupational Health" searched for similar cases in the database of the National Network for Monitoring and Prevention of Occupational Diseases (RNV3P), which records summaries of consultations carried out in the 28 occupational and/or environmental disease centres (CCPPEs) in France. A case of allergic rhinitis in a production worker in the industrial food manufacturing sector was identified.

A French case in the food industry identified by the RNV3P

This patient, who had been working in an industrial cake manufacturing company since 2015, consulted a CCPPE in 2019 for clinical manifestations possibly related to his work. He was required to manually load the various recipe ingredients into the production tank, mainly in powder form. He was thus constantly and significantly subject to respiratory exposure to flour and other components of the recipes. This was compounded by exposure to resuspended dust when the workstation was cleaned, once or twice a week.

According to the patient, symptoms of rhinitis with nasal obstruction, severe rhinorrhoea, sneezing and conjunctivitis had appeared as early as 2017.

These symptoms were work-related, i.e. they appeared after one hour of work, regressed in the evening after stopping work and disappeared completely during the holidays.Then respiratory symptoms such as nocturnal wheezing and dyspnoea on exertion appeared. Respiratory function tests, carried out three weeks after stopping work, were within normal limits, with no non-specific bronchial hyperresponsiveness from a methacholine test[6].

In order to check whether certain substances used by the patient at his workplace could be the cause of the clinical condition, prick tests were carried out with the different ingredients handled. The results showed sensitisation to wheat and rye flour, but also to psyllium. The CCPPE doctor diagnosed occupational allergic rhinitis with sensitisation to various allergens, particularly psyllium. This diagnosis enabled the patient to apply for its recognition as an occupational disease under Table 66 of the General Regime, relating to occupational rhinitis and asthma.

An emerging occupational disease in a new occupational context

Faced with the possible increase in occupational exposure to psyllium in the food industry and the consequent increase in the risk of sensitisation to psyllium, an information message was sent to all CCPPEs, inviting doctors to watch out for exposure and sensitisation to this allergen in patients working in the manufacture of food products.

Eva OUGIER (ANSES), Pascal ANDUJAR and Marie-Thérèse LECAM (Créteil CCPPE)

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[1]. Survey on gluten-free products by the Directorate General for Competition, Consumer Affairs and Fraud Control; sans_gluten.pdf (economie.gouv.fr)

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6. The methacholine challenge test is used to diagnose bronchial hyperresponsiveness, a characteristic of asthma.

Beware of the risks of poisoning when self-medicating your pet

Administering medicines to a pet without consulting a veterinarian can lead to serious poisoning. Adverse effects due to the misuse of veterinary medicines, or animals being given medicines originally intended for their owners, are regularly reported. To minimise this risk, a veterinary medicinal product should only be administered after the owner has read the package insert or prescription. Furthermore, medicines intended for humans should only be administered to animals if they have been prescribed by a veterinarian.

Self-medicating your pet is tempting...

It may seem like a good idea to treat your pet without consulting a veterinarian, but only the administration of non-prescription medicines such as certain antiparasitics, or drugs to relieve minor illnesses (e.g. digestive powders for occasional vomiting without any other symptoms), should be considered without systematic medical advice.

Pet owners can buy veterinary medicines from:

- pharmacists, who can sell all types of veterinary medicines, although prescription medicines require a veterinary prescription
- veterinarians, who can sell all types of veterinary medicines for animals they treat or whose supervision and care they are regularly entrusted with
- supermarkets, pet shops and garden centres, which can sell antiparasitics for external treatment, provided that they are not on prescription

However, if they are misused, medicines can be dangerous and poison the treated animal. An analysis of animal poisoning cases reported in the literature [1] or in the veterinary pharmacovigilance database of the French Agency for Veterinary Medicinal Products (ANMV) showed that they often result from improper administration of veterinary medicines, but are also sometimes due to pets being given human medicines initially intended for their owners.

Poisoning by administration of a medicinal product intended for another animal species

Numerous cases of poisoning due to errors in the administration of veterinary medicines are recorded in the ANMV database. ANSES has already warned about the most common poisonings, in particular, giving cats antiparasitic products containing permethrin, as this species is unable to eliminate this compound from its body. These products are reserved for dogs and just a few drops applied to a cat's skin can be enough to induce serious effects or even death in the most sensitive animals [2,3]. Similarly, antiparasitics containing fipronil intended for dogs and cats should not be given to rabbits, which are highly sensitive to them [4, 5].

As marketing authorisations for veterinary medicinal products are issued for one or more specific animal species, it is important to comply with the instructions regarding the target species. Moreover, genetic mutations within the same animal species mean that some breeds may have a particular sensitivity to certain medicinal products. For example, some collies and related breeds (Shelties, Australian shepherds, Border collies) may be poisoned by the administration of substances belonging to, among others, certain classes of antiparasitics, antidiarrhoeals, antiemetics and tranquillisers, even those intended for dogs. A veterinarian's advice is therefore essential.

Administration of medicinal products intended for humans: the classic case of paracetamol

The human formulations available in pharmacies are generally unsuitable for treating animals, whose weight is often far less than that of a human being. This can lead to administration of a dose that is toxic or even fatal for the animal. Poisoning is therefore often due to overdose.

In addition, the recommended human dose per kilogram of body weight cannot always be directly transposed to animals, as they may absorb the medicine in a different way. Poisoning is also sometimes due to a lack of awareness of the side effects of certain substances, which can vary depending on the species treated, but also on the breed, age, or any illnesses the animals may be suffering from.

As in humans, analgesics, and in particular paracetamol (the most widely sold active ingredient in French pharmacies), are the products most often used by owners for self-medicating their pets, especially since some commercial paracetamol products for humans are sold without a prescription. However, owners are often unaware of their adverse effects in animals.

Giving paracetamol to a dog or cat can lead to serious poisoning or even death. Paracetamol's toxicity is linked to the inability of these animals to eliminate the compound,
because they do not have (cats) or have very few of (dogs and exotic pets such as dwarf rabbits, ferrets or pet birds) the enzymes needed to break it down.

The active ingredient then accumulates in the blood, leading to the onset of adverse effects, mainly anaemia in cats and liver disorders in dogs. In cats, even a very small dose can be fatal.

Other poisonings are linked to an overdose of anti-inflammatory drugs (ibuprofen, ketoprofen, aspirin, diclofenac), which cause digestive, renal and neurological disorders that can lead to coma and death of the animal.

In addition, there have been a few cases of poisoning following the administration of benzodiazepine anxiolytics and tricyclic antidepressants intended for humans, by owners wishing to reduce their pets' anxiety.

Furthermore, some people are tempted to give their pets medicines containing loperamide intended for humans, as this compound is sometimes prescribed for the treatment of diarrhoea in dogs. Nevertheless, great care should be taken when administering loperamide, particularly to collies and related breeds, some of whom carry a genetic mutation that makes them unable to metabolise this substance.

Lastly, the administration of drugs containing vitamin D – which pets rarely need – has also led to cases of poisoning. This administration should be avoided without a veterinary prescription, as an overdose can have dramatic consequences for the animal.

Precautions to be taken before administering medicinal products to animals

In order to avoid any risk of poisoning, ANSES reiterates that:

• a veterinary medicine should only be given to an animal after the owner has read the package leaflet or prescription, when the medicine has been prescribed by a veterinarian, and this information should be strictly followed, in particular the administration conditions such as the dose, when and how often it should be taken, the route of administration, as well as any contraindications and precautions for use,

• a medicinal product intended for humans may only be given to an animal if prescribed by a veterinarian, in compliance with the details of this prescription, in particular the adjustment of the dosage.

In the event of a suspected error in administering a veterinary or human medicine to an animal, contact a veterinarian or veterinary poison control centre[1] as soon as possible, to enable the risk to the animal to be assessed and determine the action to be taken.

In addition, if an adverse effect is observed following the administration of a veterinary or human medicinal product, it must be reported to the ANMV or the Lyon Pharmacovigilance Centre (https://pharmacovigilance-anmv.anses.fr/). This will help improve knowledge of veterinary pharmacovigilance and if necessary will enable preventive measures to be taken to avoid further accidents.

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Cases of chronic vitamin D poisoning in infants caused by the misuse of food supplements

Last year, ANSES received three new reports of chronic vitamin D poisoning in infants most likely due to misuse of food supplements marketed by Sunday Natural. Given the severity of the adverse effects reported, ANSES again wishes to remind the general public and healthcare professionals to avoid substituting vitamin D in medicinal form by a food supplement, as the dose administered per drop will not necessarily correspond to the one prescribed.

As part of the nutrivigilance scheme it has been running since 2009, ANSES received three new reports in 2022 of severe hypercalcaemia[1] potentially associated with consumption of food supplements containing vitamin D marketed by Sunday Natural.

These products are sold in bottles with a dropper and contain between 5000 IU and 10,000 IU of vitamin D per drop depending on the formulation. One of the products also contains vitamin K2.

As stated by the manufacturer on its website, these products should not be given to children under the age of seven. Furthermore, the dose recommended by the manufacturer for these products is 1000 IU per day, whereas in 2021 ANSES had selected an intake of 400 IU/day as adequate for infants under six months of age. In its 2022 update, the French Paediatric Society recommended daily supplementation of 400-800 IU of vitamin D2 or D3 for children aged 0-2 years (whether or not they are at risk of deficiency) [1].

In addition, EFSA has set a tolerable upper intake level of 1000 IU/day for infants under six months and 1400 IU/day for children aged six months to one year [2] .

The three cases that triggered the alert

The first case involved an infant who, two weeks after birth, began receiving four drops per day of a Sunday Natural food supplement containing 10,000 IU of vitamin D per drop and vitamin K2, making a total of 40,000 IU of vitamin D per day.

This product was purchased on the internet on the initiative of the parents, who were looking for a more natural alternative to a synthetic medicine for vitamin D supplementation.

Two months later, the infant stopped gaining weight and was taken to the paediatric emergency department. The clinical assessment was normal but the blood test revealed hypercalcaemia at 5.46 mmol/L (upper limit of the norm: 2.6 mmol/L). The food supplement was discontinued following these results. An ultrasound scan of the kidneys showed nephrocalcinosis[2] although there was no impairment of kidney function. At the age of three months, the infant's blood calcium levels had returned to normal and vitamin D supplementation had not yet been reinstated.

The second case involved an infant who was prescribed vitamin D supplementation with the medicinal product ZymaD on discharge from the maternity ward. The mother purchased a Sunday Natural food supplement on the internet containing 10,000 IU per drop, and gave her child four drops, this time again equivalent to 40,000 IU of vitamin D per day.

Four months later, the infant developed a fever of 39.1°C, with reduced appetite, and was taken to the hospital emergency department. The blood test showed hypercalcaemia at 3.7 mmol/L. An electrocardiogram[3] also showed an abnormality, a shortened QT interval[4], which indicates a risk of serious heart rhythm disorders. An ultrasound detected nephrocalcinosis in both kidneys. Following these results, the vitamin D was discontinued. Ten days later, after hyperhydration, administration of diuretics and initiation of corticosteroid therapy[5], the infant's condition returned to normal.

1. Too much calcium in the blood.
2. Presence of calcium deposits in the kidney.
3. A test that studies heart function by measuring its electrical activity.
4. A life-threatening abnormality of ventricular repolarisation.
5. Treatment with corticosteroids, natural hormones that can increase calcium excretion in the urine.

The third case concerned an infant who, since leaving the maternity ward, had been treated with the medicinal product ZymaD at a rate of two drops per day, i.e. 600 IU. At the age of one month, his doctor increased the dosage to four drops per day. A month later, the parents replaced the ZymaD with a Sunday Natural food supplement containing 1000 IU of vitamin D per drop. He continued to be given four drops per day, i.e. an increase from 1200 IU to 4000 IU per day. A month later, the parents renewed their purchase of the food supplement, but due to an error, the purchased product contained 5000 IU per drop. With four drops, the infant was now being supplemented with 20,000 IU per day. At eight months of age, he was found to be losing weight. He was taken to the hospital emergency department and the supplement was discontinued. The clinical assessment found hypercalcaemia at 4.89 mmol/L and hypokalaemia[6]. The ultrasound showed nephrocalcinosis. He was treated with hyperhydration, diuretics and corticosteroids. Blood calcium levels returned to normal after four days in hospital.

Were the observed signs related to the use of these food supplements?

The food supplements' causality in the occurrence of these three cases of hypercalcaemia was assessed using the method developed for the nutrivigilance scheme [3]. As a reminder, causality is calculated from two parameters: the chronological concordance of the adverse events with the intake of the food supplement, and the search for another possible cause that would explain the adverse effects (aetiology).

To determine the chronology, the onset time of the effects, their progression and, in the event of reintroduction of the product, the reappearance or not of the undesirable effects, were analysed.

In the first case, the onset time for the adverse effect was found to be "compatible". Progression was described as "suggestive" in view of the regression of the adverse effect when the food supplement was discontinued. The product was not reintroduced. The aetiological investigation identified the infant's exposure to doses 50 times higher than those recommended by the French Paediatric Society as the cause of the observed symptoms.

In the second and third cases, the time to onset of the adverse effect was deemed "compatible" and the progression was described as "suggestive". The product was not reintroduced. The aetiological investigation pointed to the infants' exposure to doses more than 30 times higher than the prescribed dose as the cause of the observed symptoms.

For all three cases, the food supplement was therefore deemed very likely responsible for the occurrence of the hypercalcaemia and associated complications, i.e. I4 on a scale ranging from I0 (excluded) to I4 (very likely).

Have similar cases been described in the scientific literature?

The symptoms of vitamin D poisoning have been extensively described in the literature: hypercalcaemia, dehydration, anorexia, transit disorders, cardiac disorders, hypokalaemia, nephrocalcinosis. A previous ANSES opinion published in 2021 [4] contained a non-exhaustive list of 54 cases of hypercalcaemia related to vitamin D poisoning in infants and children, from seven weeks to four years of age. In 2021, the case of a four-month-old girl receiving 15,000 IU of vitamin D per day was published. She was brought to the hospital emergency department because of lethargy, decreased food intake and constipation that had lasted for over a month. Examinations showed hypercalcaemia and nephrocalcinosis. Instead of giving her three drops per day (400 IU) of over-the-counter vitamin D, the parents had administered three 1 mL vials per day for one month, equating to 5000 IU.

Opt for vitamin D in medicinal form and check the amount of vitamin D per drop

In order to prevent further vitamin D poisoning, ANSES, together with the French National Agency for Medicines and Health Products Safety (ANSM), paediatric scientific societies[7], the National College of Midwives and poison control centres published explicit recommendations[8] in January 2021 for healthcare professionals and parents, mainly to:

- opt for medicines rather than food supplements;

- check the doses administered (verify the amount of vitamin D per drop);

- avoid combining consumption of several products containing vitamin D.

The occurrence of three new cases since this publication shows that these strong recommendations are not sufficient to protect children.

In the six cases recorded by the ANSES nutrivigilance scheme, poisoning followed the substitution of vitamin D in medicinal form by a food supplement. This substitution resulted from a decision of the parents or inaccurate advice from a healthcare professional.

6. Too little potassium in the blood
7. SFP: French Paediatric Society, SFN: French Society of Neonatology, SFMP: French Society of Perinatal Medicine, FFRSP: French Federation of Perinatal Health Networks, SFEDP: French Society of Paediatric Endocrinology and Diabetology, SNP: French Society of Paediatric Nephrology, AFPA: French Association of Ambulatory Paediatrics, the OSCAR network and the Reference centre for rare diseases of the metabolism of calcium and phosphate.
8. Press release available at: https://www.anses.fr/en/content/vitamin-d-children-use-medicines-and-not-food-supplements-prevent-risk-overdose

The dosing error was due to confusion between the different ways in which the vitamin D doses were expressed. The concentration of vitamin D in a medicinal product is expressed per mL, whereas in the food supplements consumed it was expressed per drop. This disparity in the definition of a concentration was clearly responsible for the overdose cases. ANSES therefore recommends that it be prohibited.

Furthermore, ANSES notes that these products were purchased on the Internet, which increases the risk of dosage errors due to a lack of guidance.

Lastly, the availability of food supplements containing very high concentrations of vitamin D is another risk factor for overdose. ANSES believes that adequate oversight of formulation practices would help limit the risks of poisoning.

In addition, the Agency wishes to reiterate its usual advice concerning food supplements, namely:

Consumers should:

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

- comply with the conditions of use determined by the manufacturer, to the extent that they are present and understandable;

- avoid taking food supplements on a multiple, prolonged or repeated basis throughout the year without having sought the advice of a healthcare professional (doctor, dietician, pharmacist, etc.);

- exercise great vigilance with regard to improper health claims;

- exercise great vigilance regarding the purchase of products via alternative channels (internet, for example) and without personalised advice from a healthcare professional.

Healthcare professionals should report to the nutrivigilance scheme any cases of adverse effects they suspect are associated with the consumption of food supplements.

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TO FIND OUT MORE:

ANSES Opinion on new cases of vitamin D poisoning in infants due to the misuse of food supplements

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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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