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Consume drinks, sweets and other foods containing liquorice in moderation

Chronic consumption of large amounts of foods containing liquorice can lead to serious poisoning, in particular a drop in blood potassium levels and hypertension, even in people who have never suffered from high blood pressure. French Poison control centres and ANSES studied the 64 cases of poisoning recorded in the Poison control centres' database from 2012 to 2021. Just under one in two cases were severe, and one death was reported. Here is a reminder of the regulations on maximum intake of liquorice. Prevention measures are based on moderate and occasional consumption.

Liquorice: a plant used in many food products

Liquorice extract is obtained from the roots of the liquorice plant which, when dried, can be chewed as a treat. Glycyrrhizin is the most abundant compound in the root. It has considerable sweetening power, as well as salt-softening and flavour-enhancing properties. It is used in many sweet products (confectionery, chewing gum, snacks, bakery products, ice creams and sorbets) to reinforce their sweetness, as well as in savoury products (as a softener), cocoa-based products (as a flavour enhancer), soft drinks and syrups, alcoholic drinks based on liquorice extracts (pastis, ouzo, raki, sambuca, etc.), non-alcoholic pastis, beers and food supplements.

Toxicity of glycyrrhizin

Adverse effects due to liquorice are far from uncommon. A literature review compiling 402 scientific papers, published in 2015, showed that liquorice was responsible for more than 12% of adverse effects associated with the consumption of herbal food supplements or traditional herbal products [1]. In a retrospective study of data from European and Brazilian poison control centres, liquorice was among the ten plants consumed in the diet and most frequently reported as causing adverse effects [2].

Glycyrrhizin induces pseudohyperaldosteronism[1]. It causes the loss of potassium in urine leading to hypokalaemia, water and sodium retention, and elevated blood pressure.

This is mainly due to inhibition in the kidney of an enzyme (11β-hydroxysteroid dehydrogenase type 2 isozyme) that plays an important role in regulating the receptors for aldosterone, a hormone that helps maintain normal blood pressure. After consumption of liquorice ceases, this enzyme's activity continues to be inhibited for about two weeks, and the body's return to a normal physiological state requires two to six months. All adults are at risk of pseudohyperaldosteronism, not just those who already have high blood pressure.

This risk increases with age because this enzyme's activity decreases with age. No cases of pseudohyperaldosteronism from liquorice poisoning have been described in children.

Liquorice poisoning mainly occurs in the event of prolonged consumption (several weeks) of high doses. A regular intake of 100 mg glycyrrhizin/day has been established as the threshold for the lowest observed adverse effect level (LOAEL). For example, depending on the concentration in the product, 100 mg of glycyrrhizin corresponds to about five 15-drop doses of Antésite™ liquorice concentrate, 4 to 50 2 cl doses of non-alcoholic pastis, 25 to 70 2 cl doses of pastis with alcohol, or 60 to 100% of a 6 g tin of confectionery made from pure liquorice extracts.

Some authors have suggested that dividing this dose by ten – daily ingestion of 10 mg of glycyrrhizin – would not have any health consequences for most healthy adults [3].

What the regulations say

In the European Union, glycyrrhizin is listed as a flavouring substance. Regulation (EU) No 1169/2011 on the provision of food information to consumers imposes specific labelling requirements. The statement "contains liquorice" must be added for confectionery or beverages containing glycyrrhizin at a concentration of 100 mg/kg or 10 mg/l or above, unless the term "liquorice" is already included in the list of ingredients or in the name of the food. The statement "contains liquorice – people suffering from hypertension should avoid excessive consumption" must be added for confectionery with concentrations at 4 mg/g or above and for beverages at concentrations of 50 mg/l or above (or 300 mg/l or above in the case of beverages containing more than 1.2% by volume of alcohol). This statement implies that healthy people are not at risk from excessive consumption, whereas in fact they are.

1. Hyperaldosteronism is a condition caused by the excess production of aldosterone. This hormone produced by the adrenal glands helps maintain normal blood pressure by allowing sodium to be reabsorbed by the kidneys

In France, according to the Ministerial Order of 24 June 2014 establishing the list of plants other than fungi authorised in food supplements, as well as the conditions of their use, the recommended daily serving of liquorice-based products must not lead to glycyrrhizin ingestion exceeding 100 mg and the labelling must include the statement "not to be used for more than six weeks without medical advice" along with a warning advising against use in children.

A first French retrospective study

Considering all the calls and reports of serious poisonings received by poison control centres and the nutrivigilance scheme [4], ANSES conducted a retrospective study of poisoning cases occurring after liquorice consumption that were recorded by poison control centres between 2012 and 2021. During this ten-year period, 64 people presented with clinical or biological signs related to the consumption of liquorice-based beverages or foods. The median age was 55 years (range 10–77 years), and 53% of the poisonings concerned men.

The annual number of cases ranged from three to nine, with no significant variation over the period.

The products consumed were soft drinks such as non-alcoholic pastis, Antésite™ with liquorice, and liquorice syrup (50%), alcoholic beverages such as pastis (11%), confectionery containing liquorice (13%), confectionery made from pure liquorice extract (9%), herbal infusions (13%) and food supplements (5%).

Only two poisonings were reported in children, aged 10 and 12 years, and only after consumption of Antésite™ with liquorice. The first child had an allergic-type reaction within two hours of consumption, which resolved quickly after emergency treatment. The second child developed muscle pain, possibly reflecting hypokalaemia, within two weeks of beginning repeated consumption of the drink, but there was no follow-up information to document the outcome.

Most consumption among adults was chronic (for more than three months in 67% of cases). Most people (70%) reported use exceeding the maximum recommended intake, i.e. estimated consumption of more than 100 mg per day of glycyrrhizin. For chronic consumption, the presentation was typical, with symptoms of pseudohyperaldosteronism whose severity appeared to be correlated with the amount of glycyrrhizin ingested. With acute poisoning, rare cases of allergic-type reactions were observed.

In 42.2% of poisoning cases, severity was high with life-threatening prognosis and one death was reported in a person with severe liver damage. Serious cases were observed with all types of products, except for liquorice syrup and food supplements, and were more common with beverages (pastis with or without alcohol, Antésite™ and large quantities of herbal infusions).

When the outcome was specified (57.8%), it was favourable in almost all cases (91.9%), often after hospital care and sometimes in an intensive care unit. Only one patient had sequelae, following a stroke complicating a hypertensive crisis.

How can liquorice poisoning be prevented?

Liquorice is found in many everyday products (food, cosmetics, medicines, tobacco products) in many forms: plant, liquorice extract, purified glycyrrhizin, solid or liquid.

The risk of toxicity depends on the product consumed (type and quantity) and the person exposed. Indeed, the body's reaction to glycyrrhizin varies greatly from person to person: absorption in the intestine, circulating glycyrrhizin levels, enzymatic activity.

Moreover, some medicines increase the risk of toxicity. This is the case with some diuretics causing a loss of potassium in urine, which is compounded by the glycyrrhizin.

Consumers cannot necessarily tell whether or not their consumption is excessive. The presence of liquorice is specified in the ingredients and/or in a statement, but the maximum recommended daily amount is not always given.

On the basis of current knowledge, it seems reasonable to propose daily consumption of no more than 10 mg/d of glycyrrhizin in the event of chronic consumption, taking care not to multiply the sources of intake through food, medication and tobacco products. Lastly, continuous consumption of products containing liquorice should be avoided.

Weniko CARÉ (Paris Poison control centre) and

Sandra SINNO-TELLIER (ANSES)

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Exercise caution with the products used to eradicate bed bugs

Besides the physical and psychological consequences of bed bug bites, the products used to eradicate them can cause poisoning! A case study conducted by poison control centres between 2007 and 2021 found 1056 cases of exposure to bed bug control products, including 12 cases of severe poisoning. Serious cases were more common with banned substances and included the death of a child. Here is a reminder on the recommendations in the event of infestation.

Bed bugs are small insects that live on blood and bite humans during the night, causing itching and local allergic reactions, not to mention the psychological consequences of this infestation of the home.

Bed bugs are transmitted through clothing, luggage or furniture when travelling or buying items second-hand. They are most often found in mattresses and bed frames, but also in skirting boards, electrical sockets, cracks, etc. [1].

An Ipsos study[1] estimated that 7% of the French population may have been affected between 2016 and 2020. All socio-professional categories seem to be almost equally concerned.

Bed bugs are particularly tenacious as their life expectancy, even without feeding, can exceed one year. In addition, a female lays five to fifteen eggs per day, resulting in very rapid multiplication when no action is taken [2].

Eradicating these pests can therefore be particularly difficult and victims may resort to all sorts of methods, some of which are ineffective or even dangerous.

To better understand the circumstances leading to poisoning, cases of exposure to products used to control bed bugs, recorded in French poison control centres from 1999 to 2021, were analysed.

A steady rise in exposure from 2010, halted by the COVID-19 pandemic

The first case of exposure to a bed bug control product identified in the poison control centres' database (SICAP) dates from 2007. Then from 2007 to 2021, the database recorded 1056 people exposed to such products.

The number of cases started to increase from 2010, even more sharply from 2016 onwards, before falling in 2020 and 2021 (see Figure 1). This decline could be linked to the COVID-19 pandemic, which led to a slowdown or even a complete halt in national and international tourist travel, which is a vector for the spread of bed bugs. The majority of cases occurred in the summer and concerned mainly women. The median age was 35 years.

Following exposure to these bed bug control products, 75.5% of people who called a poison control centre (n=797) experienced symptoms. These were mainly ENT and respiratory symptoms (breathing difficulties, coughing, oropharyngeal pain or irritation), skin symptoms (itching, skin irritation), headache, dizziness and abdominal pain.

The products involved

People who contacted a poison control centre were mainly exposed via insecticides of the pyrethrin or pyrethroid classes (53.5%). In 27% of cases, the type of insecticide was not specified, half the time because the insecticide had been applied by a professional and the exposed people did not know the product reference used.

Massive (clearly greater than recommended) or repeated use was reported in 10.8% of cases.

The study also revealed the use of substances that have been banned for this purpose in 4.2% of cases (n=44). These were, from most to least common, dichlorvos, malathion, aluminium phosphide and rotenone. The products containing these substances had been imported from abroad, purchased on the internet or from street vendors.

1.https://badbugs.cdn.prismic.io/badbugs/708ae86d-9406-495f-a4c1-9e21c3612346_Les+Franc%CC%A7ais+face+aux+nuisibles+-+Ipsos+pour+Badbugs.fr+-+Aout+2022.pdf

2.The re-entry time is the period between application of a product and the return to the treated area. It is very important to comply with this period, in order to avoid the risk of poisoning.

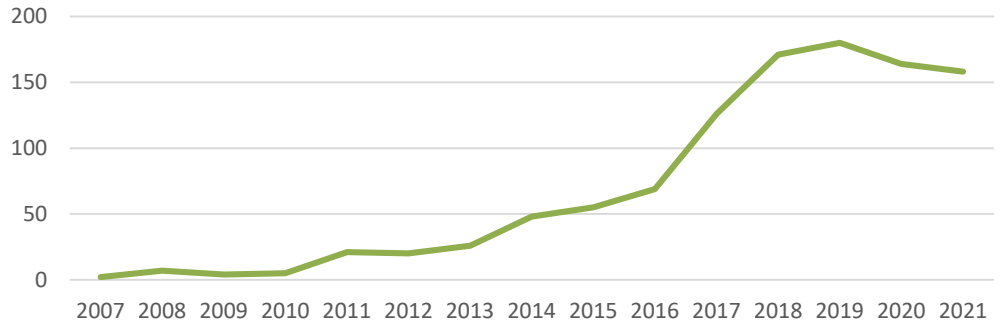

Figure 1 : Number of exposures to products used to control bed bugs per year. (Source: SICAP 2007-2021).

Exposure mainly during application of the product

Exposure was either "direct", i.e. occurring at the time the product was applied in 51% of cases, or "indirect", occurring when the person returned to the treated premises in 39% of cases (the type of exposure – direct or indirect – was undetermined in 10% of cases).

With the poisoning on return to the treated area ("indirect"), 46% of victims said they had complied with the prescribed re-entry time[2]. Conversely, 11% admitted that they had not observed this interval. Information was missing in 43% of cases.

When the re-entry time was not observed, the reasons given were as follows:

- lack of information about the treatment of premises: employees not informed about the treatment of their workplace, people staying in collective accommodation (hostels, student rooms, hotels) unaware that the rooms had been treated;
- urgent need to return during treatment due to something being left behind in the premises (keys, another object, pet), or due to an alarm or smoke detector being triggered;
- wilful or forced (in the case of occupational exposure) non-compliance with instructions.

Some serious and even fatal poisoning cases

Products used to control bed bugs were responsible for 12 serious cases: nine cases of moderate severity, two high-severity cases and one death. These serious cases (moderate or high severity) and the one death accounted for 1.1% of all cases (n=12).

Exposure was respiratory and/or dermal. Respiratory, digestive, neurological and/or cardiac symptoms were observed. Some people had a history of respiratory disease that may have aggravated their symptoms.

Of the 12 people who were seriously poisoned, five were children. One of these children died as a result of inhaling phosphine released by a product containing aluminium phosphide (CELPHOS®), which is banned in France. This illegally imported product had been sprinkled in a bedroom occupied by two children and a young woman. All three presented with digestive symptoms, complicated by myocardial damage in the two children, causing the death of one of them.

Lastly, serious cases were more common with substances that have been banned for this use. Thus, 9.1% of serious cases or deaths (4/44) involved prohibited substances, compared with 0.8% (8/1012) involving non-prohibited or unspecified substances.

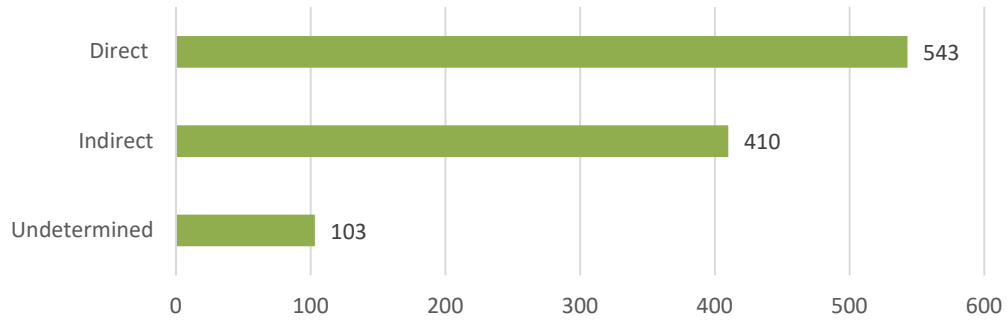

Figure 2: Distribution of cases by type of exposure (all agents combined). (Source: SICAP 2007-2021).

In addition to bites and acute poisoning…

Bites and poisoning from bed bug control products are not the only consequences of an infestation [3]. In some patients who visited an occupational and environmental disease consultation centre after their call to the poison control centre, major psychological consequences were observed. Some of these manifestations, such as sleep disturbances, a permanent state of alertness sometimes amplified by the persistent smell of the product used, and an obsessive fear of re-infestation, can be likened to post-traumatic stress.

Avoidable accidents

To eradicate bed bugs, it is advisable to begin with mechanical and thermal control. All surfaces should be meticulously vacuumed and the vacuum bag disposed of, and clothes and linen should be machine washed at temperatures above 55°C or placed in a freezer at a temperature below -17°C for 72 hours. Chemical control should only be used if these other methods fail.

Recommendations in the event of infestation [1]:

- favour non-chemical means initially; these are listed on the Ministry of Health's website;
- limit the insecticide products you apply yourself. Inexperienced people find it very difficult to resolve their bed bug problem and tend to repeat the use of insecticides, which increases their exposure;
- if you choose to use chemicals yourself, ensure that you comply with the recommended conditions of use (product quantity, number of applications, re-entry time);
- never use products that are banned in France: only buy products through conventional channels and not on the internet or from clandestine markets that sell products illegally imported from abroad;
- if you call on professionals, follow their instructions regarding the re-entry time.

Jérôme LANGRAND (Paris poison control centre) and Rachel PAGES (ANSES)

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[2] https://www.sentiweb.fr/document/5008

[3] https://www.anses.fr/fr/system/files/CNEV-Ft-Sept2015-Rapport_Punaises_de_lits_en_France.pdf

Biocidal products should be used with caution

The Ministry of Ecology is currently considering which biocidal products should no longer be available for self-service sales to non-professional users. ANSES has been helping by analysing data from poison control centres over the period 2015-2019. It identified 51 serious accidents caused by biocidal products, including 12 deaths. Most of these accidents were due to surface disinfectants. The cause was often a lack of awareness of the risk or the decanting of these products into another container.

What is a biocide?

What do surface disinfectants, insecticides and construction material preservatives have in common? They all belong to the category of **biocidal products**. They are classified by product type, "PT", according to their uses. There are 22 PTs[1], divided into four groups: disinfectants (PT1 to 5); preservatives, such as for wood (PT6 to 13); pest control products (PT14 to 20) and other biocidal products (PT21 and 22).

Etymologically, the term means "destruction of living things" *("bio-" = living, "-cide" = that kills)*. In a broader sense, a biocide is a product intended to destroy, deter or render harmless a harmful organism by any means other than simple physical or mechanical action. Biocidal products and the active substances they contain are covered by a European regulation governing their marketing and use (Regulation (EU) No 528/2012). Its main objective is to ensure a high level of protection for humans, animals and the environment by only placing on the market those biocidal products that are effective and do not present unacceptable risks relative to their benefits. Some of these are sold freely to private individuals, while others are reserved for professional use (more concentrated products, for example).

What types of access to biocidal products should be restricted?

In 2018, three measures were added to the French Environmental Code[2] to better prevent and reduce exposure of the population and the environment to biocidal products.

The advertising of certain biocides is therefore now prohibited and promotional offers[3] are no longer authorised.

The third measure introduces a ban on self-service sales to non-professional users: sales will have to take place through an intermediary, who will provide advice and recommendations on the precautions to be taken.

This includes products for which emerging pest resistance is known or suspected, those for which cases of unintentional poisoning have been reported, and products that are frequently "misused" (i.e. in disregard of the rules to protect human health or the environment, as stated in their marketing authorisation or in the package leaflet prepared by the manufacturer).

ANSES was asked to make recommendations on which products should be concerned by this third measure. In order to draw up its proposal, the Agency relied in particular on an analysis of data from poison control centres, to identify biocidal products that had caused poisoning in humans.

The analysis focused on cases of serious poisoning and death registered between 2015 and 2019, where the causality of a biocidal product was at least "likely". One hundred and twenty-five cases were recorded, including 109 serious cases and 16 deaths. Forty per cent were accidental and involved private individuals (n=51, 39 serious cases and 12 deaths) (see Table 1).

Occupational accidents (19 serious cases), deliberate poisoning (50 serious cases and 4 deaths), and one case where the circumstances were not determined are not addressed in the remainder of this article.

Surface disinfectants responsible most of the time

In almost three quarters of cases, the accidental poisonings (outside occupational settings) involved a surface disinfectant (Figure 1). This product category caused all 12 deaths.

1.The PTs are defined in Regulation (EU) No 528/2012.
2.EGALIM Act No. 2018-938 of 30 October 2018 on the balance of commercial relations in the agricultural and food sector and healthy, sustainable and accessible food for all – Article 76.
3.Discounts, rebates, reductions, differentiation of general and specific conditions of sale within the meaning of Article L. 441-6 of the French Commercial Code, or the giving of free units and all equivalent practices are prohibited.

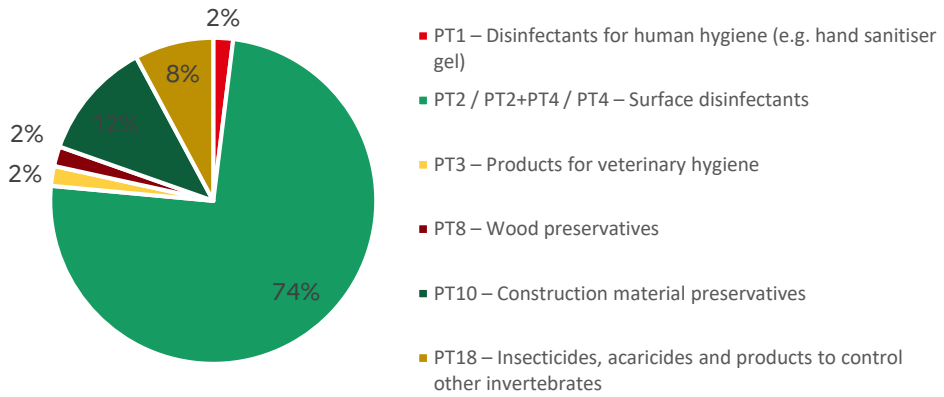

Figure 1 : Number of cases of high severity poisonings or accidental deaths with biocidal products recorded by Poison Control Centers (2015-2019) by PT. (source: SICAP)

Surface disinfectants are the most common biocidal products on the market, in terms of both the number of different products and the quantities sold.

Accidents mainly due to a lack of awareness of the risk

Two broad categories of accidental poisoning circumstances warrant attention, as they are easily avoidable:

- accidents involving young children and elderly people with cognitive disorders who are unable to see the risk (a circumstance known as "risk perception failure"), or following decanting of the product into a container other than the original one, generally a food container (water or soft drink bottle), which then leads to accidental ingestion.

These circumstances accounted for 33 cases or 65% of accidental poisonings. The vast majority involved oral exposure. The 12 accidental deaths all occurred in these circumstances (11 due to a risk perception failure and one due to decanting), in people over 70 years of age who were mainly residents in nursing homes. The products used in nursing homes may be designed for professional use. These products are generally more concentrated than domestic biocides. It was therefore probably a combination of these two factors that led to these deaths: more dangerous professional products made easily accessible to vulnerable individuals, who may have ingested the products in large quantities due to cognitive disorders.

- DIY or domestic accidents, or due to swimming pool maintenance. These circumstances accounted for 18 poisoning cases, or 35%. These accidents are particularly interesting with regard to the issue of restricting self-service sales to the general public, because the individuals involved knew they were using a biocidal product but may not have been aware of the hazard or the conditions of use (advice at the time of sale could rectify this).

The majority of people were exposed by the respiratory route. Some accidents had occurred with chlorine-based products for disinfecting swimming pool water, as inhalation exposure when opening the container can cause respiratory tract irritation. There was already a warning about this in a previous Vigil'ANSES article [1].

Avoidable accidents

These results are a reminder of the importance of storing biocidal products – and more generally all hazardous products – out of the reach of children and adults with cognitive impairment, especially products used for cleaning surfaces in medico-social establishments.

The practice of decanting should be avoided, regardless of the product, as it is responsible for many potentially fatal accidents.

Lastly, a ban on self-service access to certain biocidal products for the general public could help raise awareness of the danger posed by these products, by emphasising that they should only be used when necessary and strictly in accordance with the recommended conditions of use (compliance with doses, use in a ventilated space, etc.). This could potentially reduce poisoning cases.

The results of this study were taken into account to establish criteria for identifying product categories or products for which a ban on self-service access for private individuals would be appropriate.

Gaëlle CREUSAT (Nancy poison control centre),
Rachel PAGES (ANSES)

Table 1 : Number of high severity poisoning cases and accidental deaths with biocidal products recorded by Poison Control Centers (2015-2019) according to the exposure circumstance. (source: SICAP)

	Accident circumstances	Number of cases	%	%
1	Risk perception failure (related accident)	18	35	65
	Decanting (related accident)	15	29	
2	DIY/domestic	12	24	35
	Other accident	6	18	
	Total	51	100	100

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[1] https://vigilanses.anses.fr/sites/default/files/VigilAnsesN9_Novembre2019_Vigilanceintrantsvegetal_Chlore.pdf

TO FIND OUT MORE:

ANSES TOXICOVIGILANCE REPORT on the study of serious cases associated with biocidal products – Retrospective study of observations recorded by the French poison control and toxicovigilance centres from 1 January 2015 to 31 December 2019: https://www.anses.fr/fr/content/rapport-toxicovigilance-2020-sa-0008

ANSES OPINION on the ban on self-service sales of certain categories of biocidal products: https://www.anses.fr/fr/content/avis-2020-sa-0008

Decorative "cake design" dust is not always edible

More and more individuals are taking up "cake design", a practice that consists in decorating cakes as if they were works of art, with *trompe l'œil* patterns, shimmering colours, etc. Products from specialised shops or the Internet can be purchased to add a "metallic" visual touch to these cakes or the stands on which they are displayed. Sold as gold, silver or copper "lustre" dust or powder, these metallic colourings need to be diluted and then applied with a brush or spray gun. However, this metallic dust can be unsafe.

An alert issued by poison control centres in France

In 2021, French poison control centres reported three cases of accidental inhalation of this decorative dust [1]. Two women inhaled a large amount of gold metallic dust while preparing a cake, after opening the bottle. They quickly developed a cough, difficulty breathing and fever, which was short-lived and had a favourable outcome. The third case involved a healthy child under three years of age, who inhaled gold metallic dust poured into a glass by his mother. This young boy also rapidly developed a cough, polypnoea[1] and fever. He was taken to the hospital emergency department, where biological tests revealed a pulmonary inflammatory syndrome, which resolved within 48 hours.

All three cases involved the same product, a decorative gold dust.

Composition data on the dust obtained by poison control centres showed the presence of 30% zinc and 70% copper, in the form of very fine particles that are able to penetrate deep into the lungs. Inhalation of these metal particles, especially zinc oxides, caused a syndrome similar to "metal fume fever", a manifestation that has been described in welding and metal assembly workplaces.

Confusing labelling for consumers

The packaging for this gold dust stated that it was "non-toxic", wrongly suggesting that there was no risk. However, these three cases prove that accidental inhalation of this metallic dust can cause adverse effects. The packaging also stated that the product was "non-edible". Nevertheless, other types of metallic dust available on the market are in fact edible. The similarity of the packaging and the barely visible information on whether this decorative dust is edible or inedible could lead to confusion among consumers.

This confusion may lead to inedible decorative dust being used on cakes and a risk of ingesting non-food-grade metallic colourings. This was demonstrated in 2021 by the Centers for Disease Control and Prevention[2] in the United States, which revealed cases of heavy metal poisoning in children having eaten cakes decorated with this type of inedible metallic dust.

They identified copper poisoning in children aged 1–11 years with high biological concentrations of barium, chromium and lead, and lead poisoning in a one-year-old child related to the use of a dust containing 250 g/kg lead [2].

The US Food and Drug Administration[2] also issued a warning in 2021 about possible confusion between edible and non-edible decorative metallic dust, and about the risk of metal poisoning [3].

What the regulations say

If a decorative dust is designed to be applied to cakes, then it must be edible and comply with the European regulations governing assessment of the efficacy and safety of food additives, and their authorisation (Regulations (EC) No 1331/2008[3] and (EC) No 1333/2008[4]).

If it is only intended for colouring inedible decorative items, then it is not a food additive, but it can be brought into contact with food and in this case, it must comply with the European regulation on food contact materials (Regulation (EC) No 1935/2004[5]). Considered as a coating applied to a cake stand or to decorative elements placed on cake, the dust must not leach any substances that could present a hazard to human health into the food.

1. Increased respiratory rate associated with a decrease in the volume of air inhaled and exhaled.
2. US public health agencies that analyse and manage health alerts.
3.https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX%3A32008R1331
4.https://eur-lex.europa.eu/legal-content/en/TXT/?uri=CELEX:32008R1333
5.https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=celex%3A32004R1935

Be careful when buying… and using this dust!

ANSES therefore called for vigilance before the year-end celebrations by warning of this risk of confusion [4]. When purchasing or using decorative dust, check whether it is edible before applying it to a cake or cake stand. Moreover, whether or not it is edible, this dust is very fine and light, and easily dispersed in the air, so it should be used in a well-ventilated room and kept out of the reach of children.

Cécilia SOLAL (ANSES)

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[4] ANSES. 2021. https://twitter.com/Anses_fr/status/1471829028223033344

Severe allergic reaction following consumption of a food supplement

ANSES received a report of life-threatening anaphylaxis after consumption of the food supplement Actirub® by a woman with an allergic predisposition. Causality of the product was deemed to be very likely in this case. Given the severity of the adverse effect described, ANSES is bringing this case to the attention of the general public and healthcare professionals. It warns people with allergies of the risk of severe allergic reactions from consuming purple coneflower and green chiretta. In addition, if adverse effects do occur, they should be reported to the national nutrivigilance scheme.

As part of the nutrivigilance scheme it has been running since 2009, ANSES received a report of anaphylaxis[1] potentially associated with consumption of the food supplement Actirub® marketed by Santé Verte. This product is presented as helping to support the immune system.

The alert

The report concerned a 49-year-old woman with an allergic predisposition, mainly skin allergies, with a diagnosis of sensitisation to cat and dog hair.

In January 2022, after waking up in the morning and on an empty stomach, she took a tablet of the food supplement Actirub® because of rhinitis.

Immediately afterwards, she suffered heartburn followed by itching hands. She also experienced sweats and hot flashes. After vomiting intentionally, she experienced hot and cold temperature swings. This was followed by generalised urticaria with facial oedema and difficulty swallowing, without respiratory discomfort.

When the emergency services arrived, she had major hypotension with a systolic reading of 60 mmHg (normal: 100–145 mmHg) and a temperature of 34.5°C. She was taken into care and lost consciousness in the ambulance.

The biological test results showed an elevated histamine level[2] (more than 100 µg/l, whereas normal levels are below 50 µg/l).

The other test results were normal. Grade 3[3] anaphylaxis was diagnosed.

Subsequently, on an unspecified date, a prick test[4] carried out with an Actirub® tablet crushed in water for injection was positive, with a 5 mm wheal and 9 mm rash showing sensitisation of the patient to one or more ingredients of Actirub®.

The consumer had previously taken the same product in 2019, without any associated food intake, and had immediately experienced a grade 1 reaction with rash and oedema of the hands, which resolved after she took an antihistamine.

What is the link with use of the food supplement?

The causality of the food supplement in the occurrence of the anaphylaxis was assessed using the method developed for the nutrivigilance scheme [1].

Causality takes four components into account: the onset time, the outcome after discontinuing the product, whether or not the effect reappears upon reintroduction, and the absence of any other possible explanation for the observed adverse effect. For the food supplement Actirub®, the time to onset of the effect was considered "compatible". The outcome was described as "suggestive". The reintroduction was considered "positive" due to the first episode in 2019. The aetiological investigation led to the food supplement being formally incriminated, since a prick test was carried out with this product and proved positive. The Actirub® product was therefore deemed very likely responsible for the occurrence of the anaphylaxis, i.e. I4 on a scale ranging from I0 (excluded) to I4 (very likely).

1.Anaphylaxis is an acute, life-threatening, IgE-mediated allergic reaction that occurs in a previously sensitised patient when re-exposed to the sensitising antigen.
2.Histamine is a chemical compound whose levels increase in the event of an allergy.
3.Anaphylaxis severity grades range from 1 (low severity) to 4 (cardiac arrest) according to the Ring classification (Ring and Behrendt, 1999).
4.The prick test is used to explore an allergic reaction involving immunoglobulin E (Hayamizu et al.). It is an epidermal micro-puncture performed with a lancet or needle through an allergenic extract or suspect product.

Have similar cases been described in the scientific literature?

The literature search focused on possible human cases of anaphylaxis associated with the active ingredients of the food supplement Actirub®, which according to the manufacturer's website are purple coneflower (*Echinacea purpurea,* 300 mg/tablet), green chiretta (*Andrographis paniculata,* 150 mg/tablet), astragalus (*Astragalus propinquus,* 150 mg/tablet), white willow (*Salix alba,* 20 mg/tablet), N-acetyl-L-cysteine (118 mg/tablet), vitamin C (ascorbic acid, 80 mg/tablet), common mullein (*Verbascum thapsus* L., 75 mg/tablet.), common thyme (*Thymus vulgaris,* 70 mg/tablet), feverfew (*Tanacetum parthenium* L., 16.5 mg/tablet), black elder (*Sambucus nigra,* 10 mg/tablet), essential oil of narrow-leaved peppermint (*Eucalyptus radiata*, 5 mg /tablet) and zinc (5 mg/tablet).

This search showed that according to the literature, several ingredients, including purple coneflower and green chiretta, have been associated with the occurrence of anaphylaxis. White willow and astragalus may also play a role in the onset of this effect.

The scientific literature therefore showed that the observed anaphylaxis may have been due to several of the ingredients in the food supplement Actirub®, acting through a combination of mechanisms, some of which are dependent on immunoglobulin E (or IgE[5]). The combination of purple coneflower and green chiretta in the product may have increased the intensity of the allergic reaction.

Moreover, in the event of respiratory sensitisation to Asteraceae pollen, an allergic reaction to purple coneflower is possible from the very first ingestion.

Have similar cases been reported to the nutrivigilance scheme?

While no other cases of grade 3 anaphylaxis have been notified to the nutrivigilance scheme for the food supplement Actirub®, three cases of immediate hypersensitivity reactions following consumption of this food supplement have been reported: one case of grade 2 anaphylaxis, one case of palpebral angioedema (swelling of the eyelid) and one case of angioedema of the face and lips. The causality of Actirub® was deemed possible for these three cases.

There have also been reports of cases of immediate hypersensitivity reactions[6] with other products containing the same ingredients as Actirub®, mainly purple coneflower, green chiretta, black elder, common mullein or common thyme. In five of these, the causality of the product was either possible or likely. However, some of the products involved contained other known allergenic ingredients such as honey or propolis.

Conclusions and recommendations

The causality of the food supplement Actirub® in the occurrence of anaphylaxis in an allergic individual was deemed to be very likely. This product contains several ingredients, including purple coneflower and green chiretta, whose link with the occurrence of anaphylaxis has been documented in the literature.

ANSES recommends informing people with allergies about the risk of severe allergic reaction associated with the consumption of these two plants. They should carefully read the composition of the food supplements they plan to take, and ask their pharmacist for advice if they are in any doubt about one or more ingredients.

In addition, people with allergies should be particularly wary of products with multiple ingredients, because this increases the risk of cross-reaction with other allergens previously encountered (including by other routes of exposure, such as airborne pollen via the respiratory tract), and the risk of stronger allergic reactions occurring due to the simultaneous triggering of different mechanisms (allergic, mechanical or sensitisation).

In general, ANSES recommends that consumers of food supplements:

- notify a healthcare professional of any adverse effect occurring after consumption of a food supplement;
- comply with the conditions of use specified by the manufacturer;
- avoid taking food supplements on a multiple, prolonged or repeated basis throughout the year without having sought the advice of a healthcare professional (doctor, pharmacist, etc.);
- be wary of products claiming "miracle" properties;
- avoid the purchase of products sold through alternative channels (internet) and without personalised advice from a healthcare professional.

ANSES also reminds healthcare professionals that they must report to its nutrivigilance scheme any cases of adverse effects they suspect are associated with the consumption of food supplements. The analysis of these reports helps identify products or ingredients posing a risk, thereby protecting consumer health.

Gwenn VO VAN REGNAULT and Claire MATHIOT (ANSES)

TO FIND OUT MORE:

ANSES OPINION on a case of grade 3 anaphylaxis associated with consumption of the food supplement Actirub

5.IgE are the main antibodies responsible for immediate hypersensitivity reactions
6.Reaction occurring within a few minutes and a few hours of consumption.

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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FRENCH AGENCY FOR FOOD, ENVIRONMENTAL
AND OCCUPATIONAL, HEALTH & SAFETY
14 rue Pierre et Marie Curie
94 701 Maisons-Alfort Cedex

www.anse.fr / **@Anses_fr**

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