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Over-the-counter food supplements are becoming increasingly popular in France, even though some of them contain substances that may pose a major health risk. Even when they are banned in our country, they remain available on the internet. Others, although authorised, may nevertheless be dangerous for some people, who may not even be aware of the risk.

This first 2020 issue of Vigil'Anses therefore presents a case of fatal hepatitis that occurred following the intake of a food supplement for weight loss, Slim Metabol®, which contains Garcinia Cambogia, a plant most likely responsible for the product’s toxicity.

The potassium salts used as a substitute for table salt in sodium "salt-free" diets can be sold over the counter, yet can be hazardous in some situations. ANSES reiterates the importance of seeking medical advice before using these products, as low-salt diets are often indicated for people for whom potassium salts can lead to hyperkalaemia and heart problems.

Another article in this issue looks back at an alert issued a year ago about an abnormally high level of opioids found in sandwiches made from poppy seed bread, which resulted in positive screening tests for commercial drivers. It presents the findings of the investigations carried out and an update on the regulations in this area.

When you want to protect your children from insect bites, the last thing you expect is for their skin to be burned by the liquid in the mosquito-repellent wrist band you put on them. Based on a study of cases reported to poison control centres, we provide an update on these devices and the hazards to which they expose younger children.

Lastly, the final article in this issue explains the hazards to food-processing workers of certain flavourings inhaled during manufacturing. While severe respiratory diseases were initially described in the United States in contexts of high exposure, less pronounced forms have also been observed in France, and reported to the National Network for Monitoring and Prevention of Occupational Diseases (RNV3P). This has led to a call for preventive measures to be reinforced.

Juliette Bloch, Vigil'Anses chief editor
Positive opioid tests due to consumption of poppy-seed bread sandwiches

In early 2019, consumption of sandwiches made from poppy-seed bread was linked to positive results from urine opioid screening tests. Although the offending foods were promptly removed from the market, the fact remains that depending on the type of poppy seeds used, the cleaning process applied to those seeds and the bakery product recipes and manufacturing processes, the alkaloid content of the poppy may remain high enough to yield a positive test result or, more rarely, to cause clinical signs. Discussions are under way at EU level to amend the regulations.

The alert

In late February 2019, the poison control centres (CAPs) alerted ANSES because commercial drivers had tested positive for alkaloids (morphine and codeine) even though they denied taking any illegal products, or pain or cough medication containing opioids. The toxicology laboratory at the Garches University Hospital, whose expertise had been sought by the company employing the drivers, linked these results to the fact that they had consumed sandwiches made from poppy-seed bread. It alerted the CAPs to the abnormally high alkaloid content (morphine, codeine and thebaine) in 50 g of poppy seeds scraped off these sandwiches. Analyses showed that a baguette sandwich containing about 15 g of seeds yielded about 4 mg of morphine (a dose higher than 1.9 mg for a 60-70 kg subject is considered as potentially having a clinical effect).

To confirm the veracity of the positive test results leading to the alert, ten people from the Garches laboratory consumed poppy-seed bread sandwiches from the incriminated brand, purchased in two départements of the Ile-de-France region. For all of them, morphine was detectable in their urine for up to 18 hours after consumption, and for 50% of them it was detectable for up to 48 hours.

The saliva test was positive until 10 hours after ingestion. One subject agreed to give blood samples 1, 2 and 3 hours after consumption: all were significantly positive for morphine. Poppy-seed bread sandwiches from other brands were studied, and the people who consumed them also tested positive in urine tests [1].

ANSES promptly alerted the health authorities and the Directorate General for Competition, Consumer Affairs and Fraud Control (DGCCRF). The foods concerned were immediately recalled and withdrawn from the market. A press release of 1 March 2019 called on consumers to avoid consumption of bakery products containing significant quantities of poppy seeds, especially before engaging in any activity requiring special attention (e.g. driving) or for populations most at risk (pregnant or breastfeeding women, children, and people with urinary retention or respiratory risk factors²).

The DGCCRF issued a European alert under the "Rapid Alert System for Food and Feed" (RASFF) on 21 March 2019, enabling the withdrawal of all products from the incriminated brand that may have been placed on the market in other EU Member States or other countries.

1. Determination by liquid chromatography coupled with mass spectrometry (LC-MS/MS)
Another case of poppy seed poisoning was reported by the Paris CAP on 6 May 2019. A woman in her fifties had eaten a 300 g poppy seed loaf purchased from a bakery in the Paris region every day for the previous three years. She had been experiencing clinical signs of opioid contamination such as a dry mouth, tachycardia, dizziness, drowsiness and nausea for several months. Informed of the alert issued by the health authorities, she contacted the Paris CAP. Blood and urine tests showed the presence of thebaine, characteristic of opioid contamination associated with the consumption of poppy seeds. After stopping consumption, she experienced sweating and tremor, symptoms consistent with a withdrawal syndrome. In addition, the other signs, mainly the dizziness she had complained about and for which she had undergone a number of additional tests – all negative – disappeared. The urine test was then negative. Although it was not possible to analyse the bread consumed, the chronology of events and the dosages involved very much supported a causal link.

Changing European regulations

Poppy seeds are oil seeds derived from the plant *Papaver somniferum* L. These plants can be grown for food or pharmaceutical purposes. In the latter case, the varieties are selected for their high opium alkaloid content, concentrated in the plant capsule.

In the natural state, poppy seeds contain few or no opium alkaloids. However, they can become contaminated as a result of insect damage or during harvesting, when dust from the capsule adheres to the seeds. Food processing steps such as washing, soaking, grinding and cooking can reduce the alkaloid content of poppy seeds by 25-100%.

In a report published in November 2011 [2], the European Food Safety Authority (EFSA) assessed the health risks associated with exposure to opium alkaloids in poppy seeds. In this first report, it acknowledged that consumption of poppy products could lead to the pharmacological effects of morphine. However, EFSA only considered morphine in this assessment. Based on this substance’s pharmacological properties, the acute reference dose (ARfD) was estimated at 10 μg of morphine per kg of body weight.

In 2014, the European Commission published Recommendation 2014/662/EU on good practices to prevent and to reduce the presence of opium alkaloids in poppy seeds and poppy seed products [3]. These recommendations relate to harvesting, post-harvest cleaning, and specific labelling for seeds that need to undergo further physical treatment to reduce the opium alkaloid content before human consumption or use as an ingredient in foodstuffs. Treatments such as washing, soaking, grinding and cooking at a temperature of at least 135°C but preferably above 200°C can potentially reduce the alkaloid content of poppy seeds by 25-100%.

A target level of 10 mg of morphine per kg of poppy seeds was accepted by Member States on 25 November 2016. This applies to seeds intended to be sold to the final consumer or to food sector operators, without any indication of the need to subject these poppy seeds to further physical treatment. If this target value is exceeded, producers are encouraged by the competent authorities in each Member State to comply with guides to good practice, in order to reduce the opium alkaloid content. Discussions are under way to establish restrictive regulations, i.e. with maximum authorised values in morphine equivalent for seeds sold to the consumer.

The European Commission asked EFSA to update its scientific opinion in the light of new data on the alkaloid content of poppy seeds. A new opinion [4] published in May 2018 confirmed “the safe level of 10 μg of morphine equivalent per kg of body weight, i.e. a "group ARfD" that, in addition to morphine, takes codeine content into account when calculating dietary exposure. This is because the new data show that in some samples of poppy seeds on the European market, the codeine concentration may be higher than that of morphine”. A full assessment of the risks of other poppy alkaloids (thebaine, oripavine, noscapine and papaverine) could not be carried out due to a lack of available data, but according to EFSA’s experts, dietary exposure to thebaine might pose a health risk. Additional data, in particular on the toxicity of thebaine, are needed to clarify this issue”.

There is currently no European or French legislation setting a maximum alkaloid content for poppy seeds used for food purposes. Such a value would enable foods placed on the market to be withdrawn if testing found that the limit had been exceeded.

3. The acute reference dose (ARfD) is an estimate of the amount of a substance in food — normally expressed in terms of body weight (mg per kg or μg per kg of body weight) — that can be ingested in a period of 24 hours or less without appreciable health risk to the consumer.
**DGCCRF surveys of French products**

The DGCCRF obtained full traceability of the seeds used for the sandwiches incriminated in the first alert: they had a high morphine content (80 mg/kg). Two factors combined to lead to a high alkaloid content in the bakery products: (i) the large quantity of seeds used and (ii) insufficient cleaning of the seeds along with a manufacturing process that led to a fairly small reduction in the amount of morphine compared to that usually found in the literature.

In March 2019, the DGCCRF launched a national survey. Thirty-one samples were taken from eight regions (15 départements) and were analysed by the SCL (Joint Laboratories Service) laboratory in Strasbourg (six samples of seeds, two of biscuits, one of brioche, three of crackers, five of bagels and 14 of bread loaves or baguettes).

- Seven samples of foodstuffs containing poppy seeds (one brioche, two bagels and four bread samples) were declared "unfit for consumption", as eating them could lead to EFSA's ARfD being exceeded, at least for certain categories of the population. The operators concerned were asked to put in place the necessary corrective measures, in conjunction with their poppy seed suppliers. These exceedances were moderate for all samples except the brioche, whose consumption could lead to the ARfD being exceeded for all consumer categories considered.
- One poppy seed sample was declared "unsatisfactory" because it exceeded the target value for morphine.

The survey also found that manufacturers of foodstuffs containing poppy seeds and their poppy seed suppliers had little or no awareness of this health risk.

A new survey was undertaken in early 2020 to verify the effectiveness of the measures taken.

In Luxembourg, in 2016 and 2017, the Food Safety Unit tested about 20 samples of raw poppy seeds from different origins for opium alkaloids [5], with results similar to those of the DGCCRF survey.

**Prospects**

To ensure that consumers are not wrongly accused of consuming illicit substances in the event of a positive opioid screening test, prosecutors will be informed that screening tests may be declared positive after consumption of bakery products containing poppy seeds and that, by using more complex toxicological tests, it is possible to differentiate between a food origin and a medicinal or illicit origin by identifying the presence of thebaine, which is specifically associated with the consumption of poppy seeds.

**What can be done in the meantime?**

Pending the entry into force of the new European regulations and full awareness in the profession of the manufacturing processes leading to a reduction in the alkaloid content of poppy seeds and products containing them, ANSES recommends limiting their consumption and avoiding them completely when driving a vehicle or when an activity requires full alertness. These measures especially concern children, pregnant women and people at risk of urinary retention or interrupted breathing.

In the event of a positive test leading to legal proceedings, it is possible, with analyses carried out in toxicology laboratories such as that of the Garches University Hospital, to prove the food origin of the alkaloids by the presence of thebaine among the alkaloids assayed. Even when the urine or blood tests have not been carried out within 48 hours, thebaine can still be found in hair.

It is important for consumers, police officers, lawyers and magistrates to be informed.

Jujette BLOCH

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4. Full results in the DGCCRF’s 2020 annual report (publication pending).
Références bibliographiques
The signal
In recent years in France, an occupational disease consultation centre (CCPP) and an occupational health service (SST) have been working together to investigate clustered cases of bronchiolar-type respiratory disorders occurring in a food processing plant making sweet cereal products. This signal was forwarded to the National Network for the Monitoring and Prevention of Occupational Diseases (RNV3P), coordinated by the French Agency for Food, Environmental and Occupational Health & Safety (ANSES).

What we know already
In the United States, clustered cases of severe bronchiolitis obliterans, resulting in progressive irreversible respiratory failure, have been attributed to food professionals inhaling flavourings with a buttery, creamy taste and aroma, which were initially thought to be harmless. In particular, eight cases were described among the 130 employees of a single popcorn manufacturing company, leading to the first real investigations in 2002 [1]. Four of the patients in these cases had severe forms and were awaiting lung transplants.

Due to the context in which they occurred, these occupational conditions were initially described as "popcorn workers' lung disease" (or simply "popcorn lung") and then more correctly as "flavouring-induced lung disease", given the wide range of circumstances in which people can be exposed to these flavourings.

The alpha-diketone- or alpha-dicarbonyl-based flavourings incriminated, are mainly diacetyl (or 2,3-butanedione) but also 2,3-pentanedione, initially used as a substitute for diacetyl, but ultimately found to have similar toxicity.

These substances' mechanism of action on the bronchioles is now well understood. In 2016, the US National Institute of Occupational Safety & Health (NIOSH) published a major reference document on the topic, providing an exhaustive overview of knowledge on hazards, exposures and risks, and setting occupational exposure limits (OELs) [2].

Since then, new publications have regularly corroborated the toxicity of these flavourings [3], and similar occupational cases have been described in the Netherlands and England, as well as a few domestic cases in individuals consuming microwave popcorn on a daily basis [4]. It then became apparent that these flavourings could be found in other occupational contexts, for example in the manufacture of dry biscuits, cereals, chocolate and coffee, and could even be generated by certain industrial processes such as coffee roasting [5, 7]. New cases have been described in these occupational contexts [6].

Investigation and management
When the signal was presented to the Working Group on Emerging Risks, no serious cases of bronchiolitis obliterans related to these flavourings had been reported in France. However, the cases involved raise the issue of the effect that these flavourings may have at much lower concentrations than those found in the index cases published in the United States.

As part of the investigation into these clustered cases, a retrospective longitudinal follow-up of 200 employees from the plants concerned and their pulmonary function tests (PFTs) was carried out, including information on tobacco consumption.

Flavourings to avoid inhaling

Certain flavourings used in cereal product manufacturing processes to give a "buttery" and "creamy" taste can cause severe respiratory illness in workers inhaling them over the long term. Preventive measures and respiratory monitoring of exposed employees are recommended, and the French companies potentially concerned – along with their occupational health services – are asked to exercise vigilance.
Concerning the occupational factors associated with the results of the PFTs, working in a sector exposed only to raw materials (cereals, flours, and their biological contaminants) was associated with an excess of obstructive ventilatory disorders of the large bronchi, as is typically observed with this type of exposure. However, working in the processed products manufacturing sector was associated with an excess risk of bronchiolar damage, as seen with the flavourings mentioned above. In both cases, tobacco consumption was taken into account. In view of the knowledge of this potential risk from the flavourings, the composition of the ingredients used in the recipe for the products manufactured in these plants was analysed and measurements were taken from the air inside the plants. The latter revealed the presence of diacetyl, which was not mentioned in the product safety data sheets (SDSs) detailing all the substances present in a product and their hazards, and 2,3-pentanedione, which was reported in only one SDS.

The concentrations measured when the products came out of the oven were sometimes higher than those stipulated in the regulations: respectively 3% and 15% of the European (2017) and French (October 2019) OELs.

These flavourings were also detected in the control room, but at lower concentrations, resulting in less intense but longer-lasting operator exposure. This seems to corroborate the results of a cross-sectional study, published in 2014, of 367 employees in a flavouring manufacturing plant that had replaced diacetyl by 2,3-pentanedione [8].

Results showed a doubling of respiratory symptoms and decreased respiratory function in participants who spent at least one hour per day in production areas where the exposure level was twice as high as the US reference values.

Following these results, preventive measures were taken concerning ventilation and employee protection during work on the production line.

Lessons to be learned from this signal
Aside from the severe clinical pictures for high exposures found in the literature, the long-term effects of prolonged inhalation of these flavourings at low concentrations are not yet fully known.

The situation reported here illustrates several key elements in the detection and investigation of new occupational diseases. Firstly, it shows that in the context of a very progressive disease, the link with work is often ignored because there is no improvement to patient complaints during weekly rest days or even holidays (unlike allergic diseases for example). It is therefore necessary to rely on a collective analysis of respiratory function parameters to detect any deterioration in them among certain subgroups of workers. It is then essential to correlate these results with measurements made at the various work stations: concentrations of potentially incriminating substances in the air and in the components handled, even if they are not mentioned in the SDSs. This situation also illustrates the importance of monitoring emerging toxic risks described at the international level, in order to be able to identify them within companies. When investigating this type of situation, the cooperation of SSTs and CCPPs adds real value; in this case relating to all three of the points mentioned above.

Lastly, it should be remembered that when clusters of identical diseases are observed, occupational physicians, employers, staff representatives or employees may refer the matter to the Occupational Health Alert Groups (GASTs), managed by Santé Publique France, which will also seek the expertise of the CCPP(s) in the region concerned.

Moreover, a high-severity signal due to occupational exposure (in this case, from a high-temperature flavouring processing method) raises questions about whether there are any similar situations in other uses. For example, tobacco products and e-liquids designed for vaping often contain flavourings, and are heated during consumption. In recent years, this topic has been addressed in several publications. Researchers have found that a compound in the e-liquids that is chemically similar to diacetyl (2,3-butanolone or acteoin) degrades to diacetyl within the cartridge, whose contents are then inhaled [5,6].

Is it safe to use such ingredients in these tobacco and vaping products? Diacetyl is not currently included in the list of ingredients prohibited in e-liquids. It is the responsibility of the companies marketing the products to ensure that the ingredients they use do not pose a risk to human health. As part of its roadmap on substances of interest, ANSES will examine how to take into account this feedback from a context outside that of tobacco products and vaping.

Vincent BONNETERRE

1. In France, the regulations stipulate taking 10% of the OEL as a reference value that can be used to consider that the OEL has been complied with. This approach enables the variability of occupational exposure to be taken into account, in particular on the basis of a small number of measurements. https://www.legifrance.gouv.fr/affichTexte.do?idTexte=JORFTEXT000021487566.
References

To find out more, visit:

Occupational exposure limit values (OELs) for diacetyl
- France: Ministerial Order of 27/09/2019 setting indicative occupational exposure limits for certain chemical agents. The 8-hour OEL for diacetyl is set at 0.07 mg/m3 (0.02 ppm); the 15-minute OEL is set at 0.36 m3 (0.1 ppm)
- Europe: EU Directive 2017/164, the 8h OEL is set at 0.02 ppm or 20 ppb
- US-NIOSH 2016, the 8h OEL (8h TWA) is set at 5 ppb (this NIOSH limit value is based on human data and corresponds to an estimated excess risk of bronchiolitis of 1/1000 in the event of lifetime exposure to diacetyl (8h/d, 40h/week, for 45 years); Park JOEM 2018.

Occupational exposure limit values (OELs) for 2,3-pentanedione
- The MAK value (Germany) is set at 0.02 ppm, i.e. 20 ppb
- US-NIOSH (2016) a TWA of 5 ppb as for diacetyl was desired, but was increased to 9.3 ppb due to the limit of quantification
Skin and eye reactions caused by insect-repellent wrist bands

ANSES has issued a warning about the risks of wrist bands worn by children and adults to repel insects. Reactions such as burns as a result of accidental contact of the skin or mucous membranes with the chemicals contained in these bands have been recorded by poison control centres. Through its vigilance scheme, ANSES has been able to evaluate the 12 cases collected by the poison control centres since 2012. Following its analysis, the Agency recommends prohibiting the wearing of repellent wrist bands by infants and young children. Furthermore, it recommends manufacturers to include instructions on the packaging to ensure that users avoid direct skin contact with the side of the band containing the active substances.

Insect-repellent wrist bands come in the form of a bracelet, usually made of plastic, to which is attached a small plate or capsule that releases an odorous mixture of essential oils extracted from plants. Volatile chemicals can also be included in the mixture. After a certain period of use, the repellent system must either be replaced (interchangeable clip) or recharged using the solution provided with the wrist band or purchased separately.

The alert
The poison control centres (PCCs) alerted ANSES to a case of skin burns that occurred in a small child wearing an anti-mosquito wrist band that had come into contact with his cheek during naptime (see below). ANSES then identified all the cases that had occurred since 2012.

A non-isolated case
Over the period from 01/01/2012 to 31/08/2019, 12 cases of exposure to these wrist bands were recorded by the PCCs. In two cases, the individuals involved were adults and in nine cases children, including a 4-month-old infant (the age in the other case was not specified). In seven cases, the route of exposure was exclusively or predominantly dermal and resulted in local irritation-type reactions or general reactions of varying severity. In one of these, a 3-year-old child whose wrist band had remained in contact with his cheek during his nap woke up with redness corresponding to the imprint of the wrist band, which progressed over 24 hours into a second-degree burn. These injuries disappeared with supportive treatment after five days. In another case, an infant had several convulsive episodes after wearing an ankle band for one month; here, it is possible that the substances contained in the wrist band had penetrated the body through the skin and caused the symptoms, as the device contained a mixture of essential oils and plant extracts, some with neurotoxic properties. Lastly, a case of generalised rash appearing in a child immediately after oral contact with a small plate was most likely an allergic reaction. This allergic-like reaction is consistent with the sensitising properties of geraniol (in particular), contained in the device. Moreover, of the five cases involving contact with the eyes, four were due to splashing after the capsule ruptured when handled (possibly during play) by young children, raising questions about the robustness of this type of device.

Where does the risk come from?
The vast majority of the substances used in these devices are potential skin and eye irritants, which explains the type of reactions—such as burns or erythema—observed after accidental direct contact between liquid from the device and the skin or mucous membranes. The intensity of these reactions seems to be greater in the event of prolonged contact with the capsule or small plate and contact with particularly fragile areas such as a young child’s face.

In addition, it is not possible to rule out a mechanical phenomenon due to the wrist band’s plastic composition, which can aggravate local irritation, as with the two adult subjects developing reactions described as abrasive during “normal” use.
Geraniol is a constituent frequently found in these devices; it is a fragrance also used in a multitude of household products (cleaning products), cosmetics (soaps, shampoos), perfumes, etc. These other sources of contact may therefore promote the development of sensitisation to this substance.

Although most manufacturers advise against the wearing of these wrist bands by anyone under 3 years of age, the case of an infant experiencing convulsions as a result of prolonged wear raises the question of an absolute contraindication of these wrist bands in very young children.

In addition, most packagings lack instructions on the maximum duration of use by older children.

**ANSES’s recommendations**

Due to the claimed properties of some of the substances they contain, these wrist bands come under the regulations on biocides. As some active substances are still currently being assessed, wrist bands are not yet subject to marketing authorisation and may be sold during this transitional period. In light of these observations, based on the hazards related to certain constituents and in the absence of any assessment of the safety and efficacy of these devices, ANSES recommends prohibiting their use in infants and young children. Moreover, the instruction to avoid direct skin contact with the "active" side of the wrist band should also appear on the packaging.

Marie-Odile RAMBOURG

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**To find out more, visit:**

Skin and eye reactions to insect-repellent wrist bands. Retrospective study of observations recorded by the French Poison Control and Toxicovigilance Centres from 01/01/2012 to 31/08/2019 (in French)
Fatal fulminant hepatitis associated with consumption of a food supplement

As part of its nutrivigilance scheme set up in 2009, ANSES received a report of fatal fulminant hepatitis likely to be associated with consumption of the food supplement Slim Metabol® marketed by Zuccari. The Agency felt it necessary to bring this case to the attention of the general public and health professionals, and strongly advises against consumption of this food supplement.

**Case description**
This involved a 71-year-old woman with high blood pressure, treated with antihypertensive drugs. She had no other known medical conditions. She started taking the food supplement Slim Metabol® in January 2019. Three months later, she “felt unwell” and consulted her general practitioner. The biological examinations carried out then revealed major abnormalities in liver biology, requiring the patient to be hospitalised. The biological abnormalities indicated acute hepatitis with predominant cytolysis (i.e. corresponding to liver cell destruction), while the liver biopsy performed suggested autoimmune hepatitis, a diagnosis that was initially accepted. Despite appropriate treatment, the situation deteriorated and the patient died of fulminant hepatitis three weeks later.

Doctors concluded as to fulminant hepatitis of autoimmune and toxic origin, complicated by sepsis and multiple organ failure.

The product Slim Metabol® was also analysed. This analysis found lovastatin and hydroxycitric acid, confirming the presence in the product of red yeast rice and *Garcinia cambogia*. No adulteration\(^1\) with any active medicinal substance was found.

**Nutrivigilance causality score**
The method for determining causality in nutrivigilance [2] was applied to establish the plausibility of a causal link between consumption of the food supplement and fulminant hepatitis. In this case, the time to onset of the adverse effect was deemed “compatible” and the progression was described as “suggestive”. Given the clinical findings, the hypothesis of an autoimmune type hepatitis induced or facilitated by the toxin was a possibility. The responsibility of the food supplement in the occurrence of fatal fulminant hepatitis was therefore considered likely, especially since the patient had no history of immune disease.

**Literature data**

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1. Adulteration is a fraudulent practice that involves adding a product of inferior quality to another product, which is then sold or given away as something that it is not.
"Red yeast rice" is a red mould grown on white rice. It contains monacolin K, also called lovastatin, which has the chemical characteristics and pharmacological activity of statins. In February 2014, ANSES published an opinion on the risks associated with the presence of red yeast rice in food supplements [3]. In order to supplement the data in this opinion and identify new clinical cases, a literature search was conducted. Two articles of interest were identified, including one from the Italian natural health product surveillance scheme, which between 2002 and 2015 recorded ten reports of adverse liver effects following consumption of food supplements containing red yeast rice [4-5].

_Garcinia cambogia_ (GC) extracts or products containing this plant are among the most popular food supplements on the weight-loss market. Its supposed properties are attributed to the hydroxycitric acid found in the pericarp of the fruit. According to the French National Agency for Medicines and Health Products Safety (ANSM), GC meets the definition of a medicinal product by function, because of its glucose-lowering and lipid-lowering properties. This plant is also monitored under the pharmacovigilance scheme. This led to a ban on the importation, preparation, prescription and dispensing of magistral, officinal and hospital preparations consisting of GC, as well as the prescription, dispensing and administration to humans of the GC plant as of 12 April 2012, following a decision by the Director General of the ANSM.

Four cases of severe acute hepatitis in women who used this plant for weight loss purposes were identified by the Italian natural health product surveillance scheme[6]. Seventeen articles also reported acute liver damage observed in 50 patients who had consumed food supplements containing GC or pure GC extracts. It is important to stress the major role of GC in the occurrence of fulminant hepatitis, similar to the clinical case reported above (see first paragraph), with eleven cases collected. Only two involved another factor potentially responsible for hepatitis (hepatitis B for one, and use of montelukast – a drug known for its hepatotoxicity – for the other). In the remaining cases, no differential diagnosis other than that of GC-induced hepatitis could be suggested, even though most of them involved a histological study of the liver. Eight cases had a context of autoimmune hepatitis but very atypical for this disease. It is therefore possible that the GC hepatotoxicity may involve an autoimmune mechanism, at least in some cases.

A systematic review of the literature on plants causing liver damage was published in 2019. The authors pinpointed 334 cases of liver damage where a plant was identified. Rhubarb (_Rheum officinale_) was responsible for 24 of these [7]. Experimental studies in rats have also shown the hepatotoxic potential of rhubarb [8-9]. A few clinical cases of hepatitis involving the consumption of products containing rhodiola, guggul, green coffee, _Orthosiphon stamineus_ and cassia nomame have been published [6, 10, 11, 12, 13, 14]. Some of these products also contained GC [6, 10, 13].

The literature search did not identify any cases of liver damage for olive, hibiscus, cola, moringa, nopal, coleus, shiitake, hawthorn, Siberian ginseng, caigua, maqui, blackcurrant, zinc gluconate or chromium picolinate.

**Search for similar cases in the nutrivigilance database**

To date, no other reports concerning the food supplement Slim Metabol® have been recorded by the nutrivigilance scheme. However, cases of liver damage likely to be associated with the consumption of other food supplements containing at least one of the components of Slim Metabol® – Siberian ginseng, cassia nomame, caigua, maqui, blackcurrant and marine collagen – have been recorded in the nutrivigilance database [1] since its creation in 2009.

**Conclusion and recommendations**

Given all this evidence, the causality of consumption of this product in the occurrence of the serious adverse event – in this case death – was considered likely (I3, on a scale from I0 = excluded to I4 = very likely). This food supplement contains numerous ingredients: mainly plants including _Garcinia cambogia_, and red yeast rice. Other reports of liver damage associated with the consumption of _Garcinia cambogia_, some of them severe, have been identified in the literature and observed in other countries. This led the experts to consider the link between this consumption and the liver effects as well documented. In addition, red yeast rice, which is another ingredient in this supplement, has a similar literature score for liver damage. Moreover, ANSES noted that _Garcinia cambogia_ is the subject of an ANSM decision prohibiting the importation, preparation, prescription and dispensing of magistral, officinal and hospital preparations, as well as the prescription, dispensing or administration to humans of this same plant.

Lastly, from a regulatory point of view, ANSES notes on the one hand that the product Slim Metabol® is not among the food supplements declared in France, and on the other hand that the plant _Garcinia cambogia_ is not listed in the 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. However, it does appear under the name _Garcinia gummi-gutta_ (L.) Roxb in the January 2019 version of the list of plants that can be used in food supplements, published by the DGCCRF on its website (commonly known as the "Plant List"), without any health recommendation or restriction.
In view of all these points, and although this is the first report to the nutrivigilance scheme of a case associated with this food supplement, ANSES strongly advises against consumption of the food supplement Slim Metabol® marketed outside France.

Since *Garcinia cambogia* appears to be a common ingredient in food supplements on the weight-loss market, ANSES also reiterates that according to its expert appraisal published in 2010, seeking to lose weight without a formal medical indication involves risks and requires support from a health professional (ANSES 2010).

Lastly, ANSES has issued an internal request to determine whether safe conditions for the use of food supplements containing *Garcinia cambogia* can be identified.

ANSES reiterates its usual recommendations concerning food supplements:

- Consumers should:
  - notify a healthcare professional of any adverse effect occurring after consumption of a food supplement;
  - comply with the conditions of use specified by the manufacturer;
  - avoid taking food supplements on a multiple, prolonged or repeated basis throughout the year without having sought the advice of a healthcare professional (doctor, dietician, etc.);
  - exercise great vigilance with regard to improper claims;
  - exercise great vigilance regarding the purchase of products sold through alternative channels (internet, gyms, etc.) and without personalised advice from a health professional.

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

Fanny HURET

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

To find out more, visit:

Opinion of the French Agency for Food, Environmental and Occupational Health & Safety on a case of fatal fulminant hepatitis associated with consumption of the food supplement Slim Metabol®
References


Potassium-based salt substitutes are not without health risks

Potassium chloride (KCl) products used as a substitute for sodium chloride or table salt (NaCl) are intended for patients requiring a low-salt or "salt-free" diet. However, their consumption may not always be safe for this population, because these individuals often suffer from high blood pressure, heart failure, kidney failure or diabetes, all of which are risk factors for abnormal serum potassium levels, either directly (due to the disease itself or its complications) or indirectly (side effects of treatments). For this population, therefore, consuming these substitute salts can aggravate a situation of hyperkalaemia, with potentially high health risks.

The alert
In October 2018, a cardiologist alerted ANSES to a risk of severe or even fatal hyperkalaemia associated with the consumption of potassium chloride (KCl) as a substitute for sodium chloride or table salt (NaCl), as advocated with a low-salt diet. The cardiologist believed that these salt substitutes currently on sale over the counter, sometimes without any precautionary statement for the consumer, should at least be sold in pharmacies where advice can be obtained from the pharmacist, or even be dispensed on medical prescription. ANSES immediately undertook an expert appraisal to assess the risks associated with the consumption of these products.

Causes and risks of hypokalaemia and hyperkalaemia
Potassium is an essential mineral for the body, found in all our cells. In particular, it plays a fundamental role in nerve transmission, muscle contraction and heart function. It is also involved in insulin secretion, carbohydrate and protein metabolism and the body’s acid-base balance.

Hypokalaemia (a serum or plasma potassium concentration of less than 3.5 mmol/L) is characterised by heart rhythm disorders, cramps and asthenia (severe fatigue). It can be caused by increased potassium loss, due for example to diarrhoea or vomiting, or to excessive loss from the kidneys. Hypokalaemia resulting from inadequate dietary intake is unusual and is only rarely encountered in the context of very low-calorie diets or malnutrition.

The clinical manifestations of mild to moderate hyperkalaemia (serum or plasma potassium concentration greater than 5.5 mmol/L in adults) are generally non-specific (fatigue, decreased strength of certain muscles, paraesthesia, nausea, vomiting, even diarrhoea). When the concentration is greater than 6.5 mmol/L, hyperkalaemia can lead to variable clinical signs depending on the cause and the patient’s condition: the most dangerous are potentially fatal heart rhythm disorders.

Sources of potassium in the diet and recommended intakes
According to data from EFSA [1] and the French Information Centre on Food Quality (CIQUAL) – which is part of ANSES – chocolate, bananas, vegetables and dairy products are the common foods with the highest potassium content.

In a 2016 opinion [2], ANSES estimated that a potassium intake of 3500 mg/d had a beneficial effect on blood pressure in adults and that potassium intakes below 3500 mg/d were associated with an increased risk of stroke.

1. https://ciqual.anses.fr/
The data available at the time were insufficient for determining an average requirement (AR) for potassium, but were sufficient for defining an adequate intake (AI) of 3500 mg/d for both men and women.

On the other hand, like EFSA [3], ANSES considered that there were insufficient data to propose a tolerable upper intake level (UL) for potassium.

**Risk factors for hyperkalaemia**

EFSA [3] pointed out that adverse effects, particularly on heart function, have been observed in patients with impaired renal function and reduced urinary potassium excretion when the intake of potassium salts was equivalent to 1 g/d in addition to normal dietary intake. It considered that the risk of adverse effects was low with dietary intakes of the order of those observed in European countries (5-6 g/d in adults) but indicated that gastrointestinal effects had been seen in healthy adults taking potassium supplements at doses of 1-5 g/d. It also identified individuals engaging in activities leading to dehydration (sports, working in hot conditions, etc.), diabetic patients, people suffering from impaired kidney function, undergoing cardiovascular treatment, or suffering from metabolic disorders affecting potassium balance, as being at greater risk of hyperkalaemia, as well as the elderly, due to reduced kidney function.

In the United States, the National Kidney Foundation (NKF) recommends limiting the daily dietary intake of potassium to no more than 2 to 4 g in patients with mild to moderate kidney failure. A lower intake (< 2 g/day) is recommended in the event of end-stage renal disease. These situations concern 4% of the American population, and this prevalence can be extrapolated to France. In addition, in 2005 and 2006 [3-4], ANSES considered that the consumer should be informed, when purchasing food supplements containing potassium or salt substitutes, that they are contraindicated in cases of kidney failure or a low-potassium diet.

An international database (Vigilyze) has recorded all cases of hyperkalaemia worldwide since 1986. Out of more than 23,000 cases (including about 1000 with a fatal outcome), just under 3000 were recorded in France. The cause was mainly medication-related, especially in patients with diabetes (type 2), heart failure or kidney failure treated with drugs that decrease renal excretion of potassium (e.g. ACE inhibitors, ARBs, NSAIDs, anti-aldosterone, etc.) or are sources of potassium (e.g. Diffu-K®).

Based on these observations and all the data in the literature, it therefore appears that the people most at risk of hyperkalaemia if potassium salts are used inappropriately are:

- patients with stage IV kidney failure, known as end-stage renal disease;
- diabetic patients;
- heart failure patients;
- hypertensive patients;
- elderly subjects, who are more frequently treated for high blood pressure, diabetes, heart failure or decreased kidney function.

**ANSES’s recommendations**

Populations with one or other of these risk situations form a non-negligible part of the French population. Because of their health status, they should undergo rigorous and regular medical monitoring. If this is not the case, or if the individuals are unaware of their condition, the risk of hyperkalaemia is increased.

Faced with public health recommendations that encourage a reduction in sodium intakes and scientific organisations advocating an increase in potassium intakes, consumers may turn to products with a reduced salt content or replace traditional salt with potassium salts. However, KCl is already used in many food products as an additive and as a replacement for NaCl without this being clearly indicated on these products. As a result, total KCl intakes are difficult to determine and their estimation cannot be based solely on intakes resulting from the substitution of traditional salt by KCl.

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2. The average requirement (AR) is the average daily need within the population, as estimated from individual intake data in relation to a criterion of nutritional adequacy in experimental studies. It is used to calculate a population reference intake (PRI), which expresses the daily intake that meets the nutritional needs of almost all (97.5%) the population.

3. The adequate intake (AI) is the average daily intake of a population or subgroup whose nutritional status is considered adequate. It constitutes a nutritional reference when an AR and therefore a PRI cannot be estimated.

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**Where should reports be sent?**

Adverse effects can be reported on the [Adverse Health Event Reporting Portal](#) of the Ministry of Social Affairs and Health or directly by completing the [online reporting form](#).
ANSES therefore recommends that people who need to reduce their sodium intake or increase their potassium intake should be informed of the risks of hyperkalaemia due to drug interactions with KCl-based substitutes.

It alerts the public authorities to the hazards incurred by consumers due to a lack of information on labels concerning the use of potassium salts. This is especially true for people with one of the conditions that increase the risk and who are receiving inadequate or no medical attention.

ANSES also draws the attention of the public authorities to the existence of three health claims authorised by Regulation EC 1924/2006 for potassium, one of which states that "potassium helps to maintain normal blood pressure". This claim could encourage hypertensive individuals to turn to foods offering KCl and thus expose themselves to a health risk.

In addition, ANSES notes that dietary potassium intakes are difficult to quantify due to food manufacturing processes (sodium salt substitutes, potassium enrichment of foodstuffs, additives and processing aids). It recommends conducting a study to quantify the potassium intakes of the vulnerable populations mentioned in its latest opinion, in order to refine the assessment of their risk of hyperkalaemia.

Lastly, ANSES stresses the importance of rigorous and regular medical monitoring of people at risk, in order to significantly reduce their risk of hyperkalaemia.

Fanny HURET

References
Editorial board

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ANSES in charge of several health vigilance systems (pharmacovigilance for veterinary medicinal products, nutrivigilance, phytopharmacovigilance, toxicovigilance and vigilance for occupational diseases), has decided to make its work more visible, through the creation of a dedicated newsletter entitled Vigil’Ansès.

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, institutions and expert bodies that are partners of ANSES, prevention policy managers, the scientific community, professionals, associations and users. Vigil’Ansès also invites the interested reader to delve deeper and discover publications, opinions and reports available online that will further their knowledge.