VigilAnses

THE BULLETIN OF VIGILANCE

No 15 - November 2021

Keep magnetic balls out of the reach of children!

Cases of young children accidentally swallowing magnetic balls have recently been reported. These balls, from stress-relief objects intended for adults, have a strong magnetic force and can lead to very serious digestive complications. These items are not intended for children and should be kept out of their reach. In June 2021, the French health authorities issued a press release to warn parents and carers of young children about these risks.

Serious risks from accidental ingestion

In the summer of 2021, a hospital department notified the French health authorities of two serious cases of accidental ingestion of 3 to 5 mm diameter magnetic balls. They concerned young children (aged three years or younger), and the magnetic balls in question came from "stress-relief" objects intended for adults. Other cases of ingestion of magnetic balls, involving children's toys this time, have also been reported to the French health authorities by hospital departments.

Ingestion of magnets, especially if they have a strong magnetic induction (force of attraction), can lead to very serious complications. Several magnets swallowed at the same time or with ferromagnetic objects can clump together, obstructing the digestive tract and tearing the intestinal walls, causing intestinal blockage or perforation. The most serious cases require major surgery and can be life-threatening.

Magnetic balls in toys...

Some toys contain magnets that can become accidentally detached. A child can then swallow or choke on one of them.

These toys, like all others, must comply with European Directive 2009/48/EC and the NF EN 71-1 standard on toy safety [1,2]. According to this regulation, a toy is an item intended for children up to the age of 14. The European directive requires manufacturers to carry out several tests, defined by the NF EN 71-1 standard, to ensure that accessible magnets cannot be swallowed by children over the age of three[1] (resistance tests after toys have been dropped or twisted, for example). In addition, the regulation stipulate that magnetic experiment kits should only be used by children over the age of eight (a warning message must be clearly displayed on the packaging). Tests on the magnetic induction flux[2] must also be carried out to ensure that the force of attraction is low and that the magnet cannot become detached through the attraction of a stronger magnet.

...but also in objects for adults

So-called "stress-relief" objects, building blocks or decorative objects containing magnets are also available on the market. They consist of magnetic bars or balls, sometimes small and with a high magnetic flux (neodymium-iron-boron magnets, for example, are stronger).

These items are not intended for children under 14 years of age and are subject to the General Safety Requirement defined in Article L. 421-3 of the French Consumer Code. In this case, manufacturers must inform consumers that these magnetic products are not intended for children and should be kept out of their reach.

1. Directive 2009/48/EC specifies that toys intended for children under three years of age may only contain components of such dimensions as to prevent their being swallowed or inhaled.
2. The magnetic induction flux is calculated from the density of the flux passing through a given surface, and is used to assess a magnet's strength.

A warning issued by the French authorities

In June 2021, ANSES, *Santé Publique France*, the Ministry of Health and the Directorate General for Competition, Consumer Affairs and Fraud Control (DGCCRF) issued a joint press release to warn parents and carers of young children about the risks of swallowing magnetic balls from objects intended for adults [3], and remind them to keep any object containing magnetic balls out of the reach of children, who could mistake them for sweets and swallow them.

The DGCCRF takes action to recall/withdraw any magnetic items declared dangerous under either the general safety requirement or the Toy Safety Directive. Elsewhere in Europe and across the Atlantic, magnetic items for adults are also regularly withdrawn from the market [4, 5, 6].

Cécilia SOLAL (ANSES)

Références bibliographiques

[1] Directive 2009/48/CE du Parlement européen et du Conseil du 18 juin 2009 relative à la sécurité des jouets : https://eur-lex.europa.eu/legal-content/FR/TXT/HTML/?uri=CELEX:32009L0048

[2] Norme NF EN 71-1. 2018. Sécurité des jouets – Partie 1 : propriétés mécaniques et physiques

[3] https://www.economie.gouv.fr/dgccrf/objets-contenant-des-billes-aimantees-tenir-hors-de-portee-des-enfants

[4] https://ec.europa.eu/safety-gate-alerts/screen/webReport/alertDetail/10004158

[5] https://canadiensensante.gc.ca/recall-alert-rappel-avis/hc-sc/2021/76391r-fra.php

Nitrous oxide: increasing misuse associated with serious neurological consequences

Although nitrous oxide has long been misused due to the fact that it is freely available via cartridges for whipped cream dispensers, the number of such misuses has increased sharply since 2019. French poison control centres had issued an alert regarding the increase in the number of calls between 2017 and 2019 and the serious neurological symptoms observed in some people. An analysis of the cases from 2020 confirmed this increase as well as the occurrence of persistent neurological consequences, especially in users who regularly inhale large amounts. It also showed the growing use of (larger capacity) cylinders instead of cartridges. A legislative framework has now been established in France, with an act designed to prevent this misuse being adopted on 1 June 2021. At the same time, consumers and healthcare professionals need to be better informed of the risks involved.

Tank of nitrous oxide. Photo credit : C. Greillet

An alert already issued in 2019

The inhalation of nitrous oxide is a "recreational" practice that has been known to the vigilance networks for about a decade, due to the availability of cartridges for whipped cream dispensers in shops and on the internet. Indeed, as a food additive under Regulation (EC) No 1333/2008, nitrous oxide is freely available for sale to consumers [1].

Several alerts regarding the misuse of this food gas have recently been issued by the health authorities: in late 2019, the French Interministerial Mission for the Fight against Drugs and Addictive Behaviour (Mildeca) published a press release confirming an increase in serious cases reported to the centres for evaluation and information on drug dependence and addiction monitoring (CEIP-A) [2]; in June 2020, messages targeting young consumers and their families and friends were posted by Mildeca on social media [3]; in July 2020, ANSES and the French Health Products Safety Agency (ANSM) simultaneously published two reports on cases reported to Poison Control Centres (PCCs) [4] and to the CEIP-A [5] between 2017 and 2019.

Data from poison control centres, presented in Issue 11 of Vigil'Anses [6], showed an increase in cases of recreational inhalation of nitrous oxide from whipped cream cartridges in 2019 (46 cases compared to 20 between 2017 and 2018). The consumers, mostly young adult men, inhaled this gas at evening social events (festivals and student parties, for example) but also at private parties. Consumption was mainly from cartridges, with several hundred sometimes being consumed in a day. In this study, only two out of 66 people had consumed nitrous oxide from a cylinder (containing the equivalent of about 100 cartridges). The mildest symptoms reported were nausea and headaches, while the most severe were neurological disorders including peripheral neuropathy[1].

Worrying results that justified further monitoring during 2020

Because of these worrying results, the decision was taken to continue identifying cases reported to poison control centres in 2020. Indeed, it was thought that the pandemic context and the successive periods of lockdown and curfew could favour the inhalation of nitrous oxide at home.

1. Peripheral nerve damage, most frequently resulting in paraesthesia and hypoaesthesia of the lower limbs, night-time pain and muscle weakness.

Compared to the previous report, the number of calls to poison control centres concerning recreational nitrous oxide use more than doubled in 2020. Between 1 January and 31 December 2020, a total of 134 people called poison control centres concerning a case of nitrous oxide exposure (canisters for whipped cream dispensers or any other packaging containing nitrous oxide), compared to 20 cases between 2017 and 2018, and 46 cases in 2019.

Of these 134 cases, 126 were symptomatic. With 83 men and 51 women, the sex ratio of 1.6 confirmed the male preponderance that had already been noted in the previous study. Users were young, ranging from 13 to 42 years old, with a median age of 20.

Ile-de-France was the most commonly affected region with a quarter of the cases for only 18% of the French population, followed by Hauts-de-France. These two regions were already the most represented in 2017-2019.

Furthermore, the 2020 data confirmed the occurrence of serious neurological disorders, especially among regular consumers. At least one neurological and/or neuromuscular symptom was reported in 76.2% of cases. Of these cases, three quarters had at least one motor and/or sensory sign such as paraesthesia[2], hypoaesthesia[3], motor deficit, tremor of the extremities or muscle pain.

Four cases of subacute combined degeneration of the spinal cord[4] were confirmed by MRI. In addition, three cases of myelitis[5] and peripheral neuropathy were diagnosed.

In this report, 61.1% of cases were of low severity, 26.2% of moderate severity and 12.7% of high severity.

In 19.4% of cases, nitrous oxide consumption occurred alongside the use of psychoactive substances (compared to 30.3% in the previous study). Alcohol was involved in 10.4% of cases, cannabis, amphetamines or "poppers" in 10.4% of cases, and medicines in 3.0% of cases, with some users having consumed several psychoactive substances at the same time.

Lastly, in 76.1% of cases, the nitrous oxide was inhaled in the home of the exposed person or their family or friends (compared with 47% between 2017 and 2019).

These trends in the number of cases and practices most certainly reflect an increase in the number of young people inhaling nitrous oxide during this unusual year, but above all, an intensification of practices among certain consumers who have been using nitrous oxide sometimes for more than two years.

The 2020 study showed a higher proportion of calls involving regular consumption for over a year, of several dozen or even hundreds of cartridges per day, with this chronic consumption increasing the occurrence of severe neurological damage over time.

Increased use of cylinders

While nitrous oxide was almost exclusively consumed from cartridges and inhaled via balloons, the study highlighted a much higher share of nitrous oxide consumption from cylinders. Twenty-six people had inhaled nitrous oxide via a cylinder, a much higher proportion than in previous years (19.4% versus 3.0% between 2017 and 2019).

These cylinders are only available via the internet as their sale is restricted to professionals (e.g. caterers). Nevertheless, they are freely available for sale on many websites, with the option of ordering large quantities or requesting rapid home delivery for a party. This makes it dangerously easy to consume nitrous oxide, since a "cracker" or bottle opener to empty the gas into a balloon is no longer necessary. These cylinders allow one user to consume considerable amounts of nitrous oxide over a short period of time.

Much awaited legislation adopted in 2021

Until very recently, only a few municipal by-laws had been passed to ban the consumption of nitrous oxide in public places or to restrict its sale in shops.

On 1 June 2021, the French Senate definitively adopted the Act on preventing dangerous uses of nitrous oxide [7].

This Act applies to adults as well as minors, and recommends a ban on the sale or offer of nitrous oxide to any person (minor or not) in licensed premises (drinking establishments and tobacconists).

2. Tingling, numbness, prickling.
3. Decreased sensitivity.
4. Simultaneous damage to two areas of white matter in the spinal cord (posterior column carrying sensation and lateral column carrying motor function). It causes sensory disorders associated with involuntary muscle contractions, especially in the lower limbs.
5. Inflammation of the spinal cord causing motor and sensory impairment. Symptoms set in within a few hours to a few days, initially affecting the legs. Partial or complete loss of strength in the limbs, numbness and bladder-sphincter problems are observed.

The law provides for a fine of 15,000 euros for "causing a minor to misuse an everyday consumer product to obtain psychoactive effects". This offence is mainly intended for nitrous oxide but will be able to cover the misuse of everyday consumer products in other contexts. It prohibits "selling or offering nitrous oxide in any form to a minor". This will allow sellers to require proof of age from purchasers of nitrous oxide cartridges. Regarding online sales, websites will also have to mention this ban on sales to minors before allowing the purchase of nitrous oxide "in any form".

A "maximum quantity authorised for sale to private individuals" will be set by ministerial order.

Lastly, the Act "prohibits the sale and distribution of any product specifically designed to facilitate the extraction of nitrous oxide in order to achieve its psychoactive effects", i.e. "crackers" or any other device that may become available in the future.

With regard to information, a statement on the packaging indicating that "the misuse of nitrous oxide is dangerous to one's health" will be mandatory for sale.

This Act will be notified to the European Commission in the coming months to ensure its compliance with European law, in particular Regulation (EC) No 1907/2006 (REACH), which defines restrictions on the use and sale of chemicals [8].

Targeting young people with the appropriate tools

This awaited legislative development and its forthcoming notification at European level come at a time when young people are continuing to misuse nitrous oxide. Poison control centres are receiving increasing numbers of calls: in the first five months of 2021, the number of calls equalled that of the whole of 2020, with the use of cylinders and massive consumption practices being confirmed.

It is therefore still essential to provide consumers and their families with more information on the risks associated with this practice, which is still too often considered to be a harmless use of "laughing gas". The 2020 case report indicated that severe and long-lasting neurological damage appears to be associated with heavy or chronic consumption of nitrous oxide. This damage requires prolonged medical monitoring in a neurology department, or even functional re-education with the complete interruption of work, ongoing training or studies. The data currently available provide no assurance that patients will fully recover after ceasing consumption of nitrous oxide or that the lesions will not worsen if use resumes. These patients are often reluctant to seek medical care, which implies regular multidisciplinary follow-up to assess the progression of the neurological damage. The risks continue to be underestimated by these users, in terms of both short-term problems such as asphyxiation and longer-term disorders such as neurological deficit complicated by gait and balance disorders. Media targeting young people, particularly social networks, and risk prevention associations working in universities, secondary schools and at student parties are the best channels for relaying public health messages.

The other driver for action already mentioned in the first toxicovigilance study remains information to healthcare professionals: general practitioners, hospital emergency workers, neurologists, paediatricians, and school doctors and nurses. For example, in April 2021, the CEIP-A in Lyon, France published a checklist informing healthcare professionals about the very real risks of massive or long-term consumption of nitrous oxide [9]. This checklist describes the symptoms observed in the event of neurological or haematological damage, as well as the biological and radiological examinations recommended for establishing a diagnosis. It also insists on multidisciplinary care between hospital emergency workers, general practitioners and neurologists, as well as addictologists, to help the patient stop using nitrous oxide.

Jean-Marc SAPORI (Nord-Ouest Hospital, Villefranche sur Saône), Chloé GREILLET (ANSES), Cécilia SOLAL (ANSES)

In case of unusual symptoms after use, contact a Poison Control Centres. In case of emergency, call the emergency services (15 or 112).

If you have difficulty controlling and stopping your consumption, consult a doctor or a structure specializing in the treatment of addictions, such as a young consumers' consultation, which offers a free and confidential service to receive, listen to, advise and, if necessary, provide guidance (www.drogues-info-service.fr).

TO FIND OUT MORE :

Rapport d'étude de toxicovigilance. Protoxyde d'azote. Bilan des cas rapportés aux Centres antipoison en 2020

References

[1] Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32008R1333&from=EN

[2] French Interministerial Mission for the Fight against Drugs and Addictive Behaviour (Mildeca). 2019. Press release. https://www.drogues.gouv.fr/presse/augmentation-cas-graves-lien-lusage-detourne-de-protoxyde-dazote-gaz-hilarant-autorites

[3] Mildeca. 2020. https://www.drogues.gouv.fr/actualites/lusage-detourne-protoxyde-dazote-une-pratique-risques-de-plus-plus-repandue

[4] French Agency for Food, Environmental and Occupational Health & Safety (ANSES) 2020. Nitrous oxide. Study of cases reported to poison control centres between 1 January 2017 and 31 December 2019. https://www.anses.fr/fr/system/files/Toxicovigilance2019SA0216Ra.pdf

[5] French Health Products Safety Agency https://ansm.sante.fr/actualites/de-nouveaux-chiffres-sur-lusage-detourne-de-protoxyde-dazote-gaz-hilarant-pour-eclairer-les-autorites-sanitaires-communique

[6] Vigil'Anses. 2020. https://www.anses.fr/fr/system/files/VigilAnsesN11_Juin2020_VPC_Proto.pdf

[7] Act No. 2021-695 of 1 June 2021 on preventing dangerous uses of nitrous oxide https://www.legifrance.gouv.fr/jorf/id/JORFTEXT000043575111

[8] Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02006R1907-20140410&from=EN

[9] Centre for evaluation and information on drug dependence and addiction monitoring (CEIP-A Lyon). 2021. Usage détourné de protoxyde d'azote (N_2O): mémo sur l'atteinte neurologique et hématologique [Misuse of nitrous oxide (N_2O): memo on neurological and haematological damage]. Addict'o'News No. 4. https://www.addictolyon.fr/post/addict-o-news-protoxyde-d-azote

Banned rat poison causing death and serious poisoning in children in France

ANSES was recently alerted to the death of two very young children after they ingested an imported Chinese rat poison that is prohibited in France, yet seems to be widely used in French Guiana. Analysis of the product found a substance that has never been authorised in France: sodium monofluoroacetate, and not bromadiolone as indicated on the packaging. Other cases of poisoning with rat poison sold in the same packaging have been reported to poison control centres over the past five years, including two severe cases in young children. This is not the first time that deaths have been caused by banned products. ANSES and the poison control centres are therefore alerting consumers to the hazards of these products, and recommending they use only products authorised in France and comply with their conditions of use.

The alert

In April 2021, ANSES was informed by the network of poison control centres of the death of two one-year-old children in metropolitan France after they ingested rat poison brought back from French Guiana. The children had swallowed food impregnated with the product that they had found on the floor.

The product in question was a rat poison manufactured in China and smuggled from Suriname into French Guiana. The information on the packaging was written in Chinese and required a translator to confirm that the product was a rat poison and that the packaging indicated the presence of bromadiolone only, at a concentration of 0.5%. Bromadiolone is an anticoagulant whose use is strictly regulated in France. Presentations in the form of 0.5% concentrated liquids (as in this case) are now prohibited and were, even before their ban, reserved for professional rat controllers. However, poisoning by bromadiolone, a substance with delayed toxicity, could not explain the rapid deaths in these cases. Analysis of the product by an expert laboratory found no bromadiolone or other anti-vitamin K (AVK)[1] rat poison, but rather the presence of sodium monofluoroacetate, a substance that is not authorised in France.

It has severe acute toxicity: ingestion of even a small quantity can cause the death of an adult, let alone a low-weight person such as a child.

In French Guiana, over the period from 1 January 2017 to 30 August 2021, 32 cases of exposure to rat poison with packaging similar to that of the product that caused the two above-mentioned deaths were reported to poison control centres. The victims were mainly young children (median 2.4 years). In several cases the user had impregnated foodstuffs with the product. These included two high-severity cases (PSS3[2]) in two-year-old children suggestive of neurological and cardiac toxicity, four cases of moderate severity (PSS2), three of low severity (PSS1) and 24 asymptomatic cases (PSS0).

This suggests that these rat poisons manufactured in China may contain active substances different from those mentioned on the packaging. Some of them probably contained an AVK because some patients had a decrease in prothrombin levels, a characteristic marker of the action of this anticoagulant. Poisonings with neurological signs (mainly convulsions) were instead suggestive of the presence of a neurotoxic substance (strychnine, fluoroacetate, alphachloralose).

1. Substance with anticoagulant properties.
2. Clinical severity was assessed using the method for calculating severity in toxicovigilance, adapted from the "Poisoning Severity Score (PSS)" for acute poisoning. Persson HE, Sjöberg GK, Haines JA, Pronczuk de Garbino J. Poisoning severity score. Grading of acute poisoning. J Toxicol Clin Toxicol. 1998;36(3):205-13.

Products containing AVKs in concentrated liquid form are banned for sale to the public (access is restricted to professionals), and the only bromadiolone products intended for the public are solid baits containing a maximum of 25 ppm of active substance (i.e. a concentration of 25 mg/kg) and a bittering agent[3]. Similarly, the various neurotoxic rodenticides potentially causing some of these poisonings are highly regulated because they can cause severe accidental poisoning in children and adults, even if only small quantities are ingested. Only baits containing alphachloralose and a bittering agent are allowed to be sold to the general public.

The Paris Poison Control Centre[4] reported these cases to the Central Office for Combating Damage to the Environment and Public Health (OCLAESP), the French Guiana Regional Health Agency (ARS), and the Suriname Ministry of Health to alert them to the danger posed by this product and the associated risk of severe accidental poisoning.

Similar cases already reported to poison control centres

Unfortunately, this is not the first time that such a tragedy has occurred in France. A few years ago, two young children and a 20-year-old woman inhaled the fumes of CELPHOS®, a banned product, after it had been applied in their bedroom to control bedbugs. One of the children died as a result. The illegally-imported product had been purchased from a French market and contained aluminium phosphide, which caused the poisoning.

Controlling pests such as rodents, insects, bedbugs, etc. is generally difficult, especially since resistance to conventional products is developing. Powerless consumers then turn to parallel markets (on the internet or from street vendors) to purchase banned products containing particularly hazardous substances, without being informed of the danger.

A persistent risk of poisoning by banned products that has already been identified

A toxicovigilance study on reports to Poison Control Centres of cases of poisoning by plant protection products[5] containing active substances banned in France had shown that these products were nevertheless still in use. This could be due either to storage of old products at home after their ban came into effect, or fraudulent use through illegal importation from the border countries where they were sold (such as the introduction of products from Suriname into French Guiana).

A total of 408 cases of exposure (symptomatic or not) were recorded by the network of poison control centres over the period 2012 to 2016, 62% of which were accidental. The substances most often incriminated were dichlorvos, paraquat and aldicarb. The origin of the products was obtained for 60 cases (14.7%): 30 indicated home storage of old products and 30 came from illegal importation. Of the 408 identified exposure cases, 21 patients had died (all in a context of suicidal behaviour) and 51 patients experienced severe or life-threatening symptoms [1][2].

The results of the Pesti'home study [3] on the use of pesticides in the home, published by ANSES in 2019, showed that more than a quarter of households was still storing at least one plant protection product banned from sale. ANSES recommended that old, used or banned plant protection products should not be thrown in the bin or poured down the sink, but taken to a waste disposal centre or similar facility provided by the local municipal authorities.

Conclusion and recommendations

These tragedies illustrate the highly dangerous nature of products that may be effective in controlling pests but are banned in France because of their toxicity.

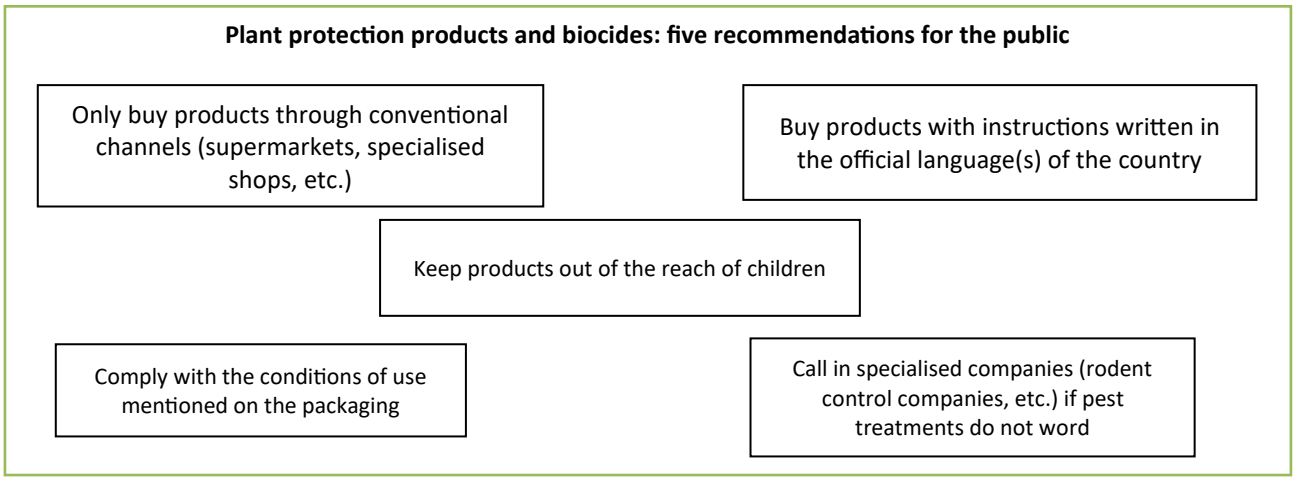
The regulations and controls put in place in Europe ensure the safety of the biocidal and plant protection products on the market and their use. On the other hand, banned products are either products that were never placed on the market because their safe use could not be guaranteed, or products that were withdrawn from the market due to new scientific data on their toxicity.

To avoid this type of accident, consumers should be reminded not to use banned products, whether they are brought in from abroad, or purchased on the internet or from street vendors. To avoid the risk of unwittingly buying a product containing a banned substance, consumers should preferably buy this type of product through conventional channels (shops, supermarkets, specialised shops). The exact ingredients, indications and safety information must appear on the box and must be written in the official language(s) of the country (in this case French). Any other situation should alert the consumer to the risk that the product is not authorised and is therefore dangerous.

3. Bittering agents are substances added to a product to give it a bitter taste and prevent ingestion.
4. The emergency telephone hotline for French Guiana is operated by the Paris poison control centre.
5. Plant protection products are designed to protect plants and crops and include insecticides and herbicides.

Moreover, even for products authorised in France, it is still essential to comply with the conditions of use mentioned on the packaging. Lastly, children are particularly vulnerable because of their low weight (they reach the toxic doses more easily even after ingesting just a small amount), their inability to perceive the risk and their propensity to put everything in their mouths. This is why it is essential to prevent them from accessing toxic products (not just rat poison and insecticides, but also household products, detergent tablets, etc.).

Magali LABADIE (Bordeaux Poison Control Centre), Jérôme LANGRAND (Paris Poison Control Centre) and Rachel PAGES (Anses)



References

[1] Rambourg M-O. 2019. Quand des produits phytopharmaceutiques non autorisés restent en circulation [When unauthorised plant protection products remain in circulation]. *Vigil'Anses 7*, p.8-10.

https://vigilanses.anses.fr/sites/default/files/VigilansesN7_PPPinterdits_0.pdf

[2] ANSES. 2019. Study report: Exposure to plant protection products containing unauthorised active substances in metropolitan France and the overseas territories. Maisons-Alfort, 52p.

https://www.anses.fr/fr/system/files/Toxicovigilance2019SA0027Ra.pdf

[3] ANSES 2019. Study report. ANSES's recommendations. Pesti'Home studies: National survey on domestic uses of pesticides. Maisons-Alfort, 282p.

PRASCEND® tablets for horses: be aware of the risk of accidental ingestion and the steps to take in the event of an accident

Accidental ingestion of PRASCEND® (pergolide) tablets, a drug for horses with equine Cushing's disease, poses a significant risk to human health. Accidents occur when the product, often hidden in fruit and prepared well before administration, ends up being eaten by a person. ANSES-ANMV has identified 37 cases of accidental ingestion since the drug was first placed on the market in 2012. As a result, the Agency has asked for the summary of product characteristics to be updated and reminds horse owners and keepers of the risks inherent in preparing this medicine in advance of administration. If someone accidentally swallows PRASCEND®, they should seek prompt medical attention, while avoiding driving due to its potential neurological effects. Preventive measures should be taken to avoid such accidents occurring.

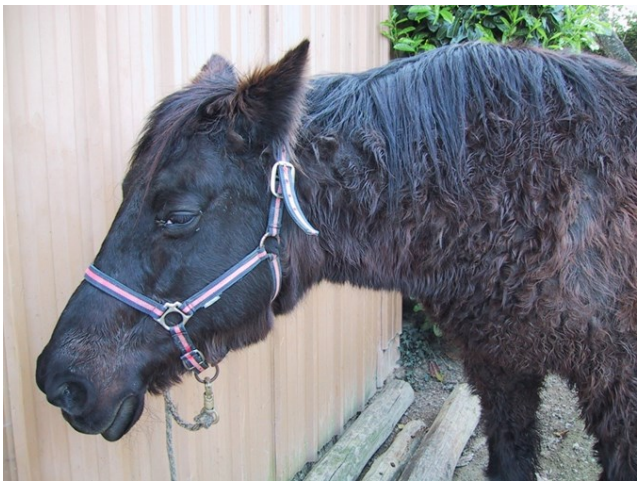


Photo credit : Eric Fresnay

Background

PRASCEND® (pergolide) is a veterinary medicinal product indicated for the treatment of clinical signs associated with pituitary *pars intermedia* dysfunction in horses, a condition better known as equine Cushing's disease (see photo). It is an endocrine disease that mainly affects older subjects: at least 15% of horses over 15 years old are thought to be affected [1]. This syndrome is linked to dopaminergic neurodegeneration in the hypothalamus, leading to disrupted functioning of the pituitary gland, the brain gland responsible for the synthesis of many hormones. The pituitary gland then increases in size, inducing an overproduction of steroid hormones by the adrenal glands, which results in symptoms that are highly suggestive of the disease such as lethargy, emaciation, polyuria-polydipsia, hirsutism, excessive sweating and laminitis [2]. Once the diagnosis has been made, Cushing's disease requires daily treatment throughout the animal's life.

PRASCEND® has been considered the reference treatment for this syndrome for some years. However, horses are distrustful and difficult when it comes to food. Giving the horse a substance it does not know is often a source of conflict and risk, both for the horse itself and anyone around it. Long-term administration of this drug therefore requires ploys to maintain good compliance. This is often done by mixing the drug with food that the horse likes. However, once it has been prepared, administration can then be delayed, leaving time for an uninformed third party to accidentally ingest it.

The effects of pergolide, the active substance in PRASCEND®

Pergolide is a synthetic derivative of rye ergot. It stimulates dopamine receptors by mimicking the effects of dopamine (i.e. it is a dopamine agonist).

Dopamine plays a complex role in the central nervous system and is involved in various key functions such as behaviour, cognition, motor functions, motivation, reward, sleep and memory.

Pergolide was used in humans in some countries for treating Parkinson's disease at doses of 1 to 3 mg/day, but due to serious adverse effects — particularly cardiac problems [3] — it is no longer used in human medicine. It is generally well tolerated in Equidae, however. PRASCEND®, available in 1 mg tablets, is used in horses at an average dose of 2 µg/kg.

1. Syndrome combining intense thirst with large urine volumes.
2. Metabolic disorder leading to inflammation of the horse's foot.

Cases regularly reported

Since it was placed on the market in 2012, 37 human cases of accidental ingestion of PRASCEND tablets have been reported to the French Agency for Veterinary Medicinal Products (ANMV). The annual number of reports increased from 2018 onwards. However, this increase is biased: starting from this date, poisonings recorded by poison control centres were added to the reports transmitted directly to the ANMV via the veterinary pharmacovigilance network. Since 2018, there have been six or more reports involving PRASCEND® every year (Figure 1).

A study carried out on all human reports of adverse events notified in France in 2018 following the use of a veterinary drug [4] showed that with 11 cases over the year, PRASCEND® was the veterinary drug most frequently involved in human poisonings, just behind external antiparasitics.

The main clinical signs, reported at least twice to the ANMV, are listed in Figure 2. These signs, observed following ingestion, can be explained by the dopaminergic properties of pergolide. The main symptoms are nausea and/or vomiting, fatigue, malaise or asthenia, sometimes mental confusion, dizziness, headaches, and/or cardiovascular disorders such as hypotension, bradycardia or palpitations. The first signs appear quickly, usually within an hour of ingestion.

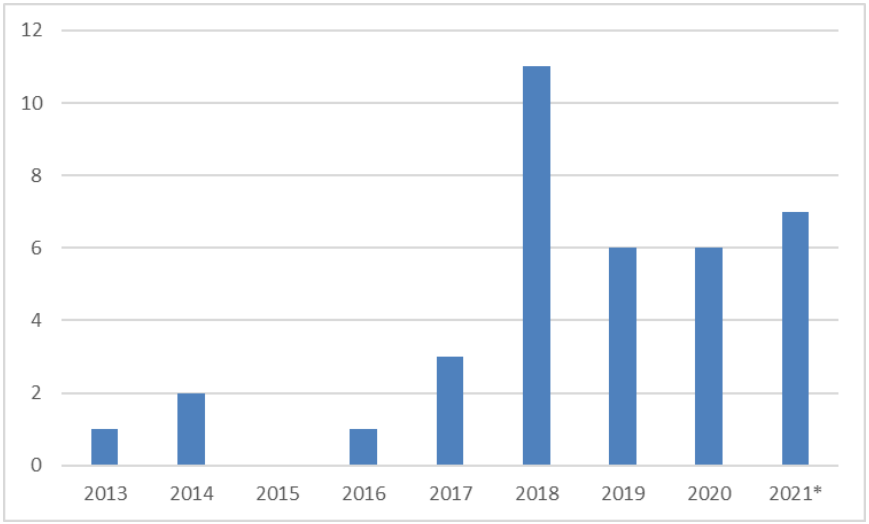


Figure 1: Change over time in the number of cases of adverse effects in humans after accidental ingestion of PRASCEND® (source: ANMV).
* For 2021: period from 1 January to 30 June only

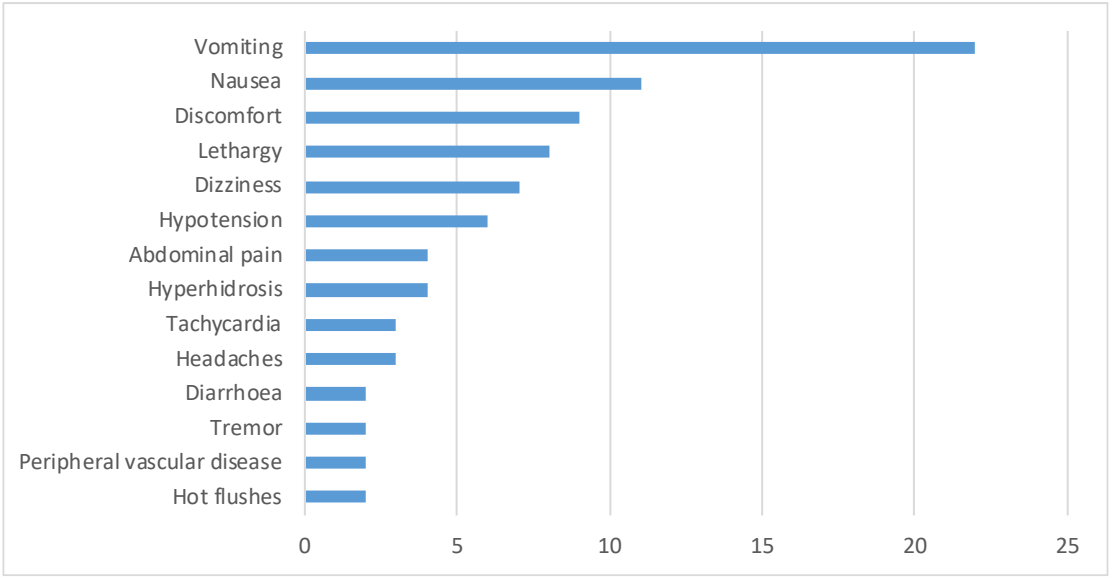


Figure 2: Distribution of clinical signs reported after human ingestion of PRASCEND, for 2018 (source: ANMV).

Precautions to be taken to avoid these accidents

Given the methods conventionally used for administering this drug to horses, it is important that owners be informed of the risks of accidental ingestion whenever PRASCEND® is prescribed.

The treatment should be prepared at the stable where the horse is kept and at the very last moment, just before administration. However, if advance preparation cannot be avoided:

- prepare only one dose at a time, to limit the severity of poisoning in case of accidental ingestion;
- minimise the time between preparation and administration to the horse;

In the period before administration:

- place the treatment in a sealed box, correctly labelled (with the horse's name, for example);
- place this box somewhere where people will not be passing through (in an isolated room), out of immediate reach (at the top of a cupboard for example), the best place being in a locked room.

The ANMV also wishes to reiterate that in the event of accidental ingestion, medical advice must be sought rapidly from a poison control centre, emergency services (dial 15 in France) or a general practitioner, for example.

Conclusion

Due to the number of regularly reported cases of poisoning, the summary of product characteristics for PRASCEND® was amended in October 2020 to update the precautions to be taken by the person administering the drug (Section 4.5). The risk of accidental ingestion is not unique to PRASCEND®, as it is inherent in any veterinary medicine prepared in advance of administration, such as antiparasitic solutions for dilution. However, the very nature of this treatment and its serious risks to humans call for major preventive measures. Veterinarians should be aware of this risk from the moment that administration of PRASCEND® is delegated to a third party. It is therefore their responsibility to remind people of the good practices to be followed here.

Sandrine ROUGIER (Anses-ANMV) and Sylviane LAURENTIE (Anses-ANMV)

References

[1]. DOLIGEZ P. & DELERUE P (2019): Le syndrome de Cushing, fréquent chez les chevaux âgés [Equine Cushing's disease: comon in elderly horses]. Cheval Santé, **125**: 48-51

[2]. SCHOTT HC (2002): Pituitary *pars intermedia* dysfunction: equine Cushing's disease. Vet Clin North Am Equine Pract, **18**: 237-270

[3]. ADRAC (2004): Cardiac valvulopathy with pergolide. Aust Adv Drug React Bull, **23** (4): 12-15

[4]. ANSES (2019): Cases of human exposure to veterinary medicinal products – Retrospective study of cases recorded in the veterinary pharmacovigilance database in 2018 – Study report

Where should reports be made?

To report an adverse effect in an animal following the use of a veterinary drug:

https://pharmacovigilance-anmv.anses.fr

To report an adverse effect in a human following the use of a veterinary drug:

https://signalement.social-sante.gouv.fr/psig_ihm_utilisateurs/index.html#/accueil

FOR MORE INFORMATION ABOUT THIS MEDICINAL PRODUCT:

http://www.ircp.anmv.anses.fr/rcp.aspx?NomMedicament=PRASCEND+1+MG+COMPRIMES+POUR+CHEVAUX

Beware of the risk of liver toxicity from overconsumption of foodstuffs or food supplements containing cinnamon

Cinnamon bark, especially from Chinese cinnamon, contains high levels of coumarin, which is toxic to the liver in large doses. There is no maximum regulatory level for coumarin in food supplements, despite the fact that consumption of food supplements containing cinnamon can lead to the Tolerable Daily Intake (TDI) for coumarin being greatly exceeded. ANSES therefore recommends a maximum daily intake of coumarin in food supplements of 6 mg for a 60-kg adult, and advises against their consumption by people with a history of liver disease. Lastly, ANSES also recommends taking special care with regard to the oral intake of cinnamon essential oils for dietary purposes.

Coumarin, a compound found in varying levels in certain plants

Coumarin is a compound occurring naturally in certain plants such as **cinnamon**, tonka bean and sweet clover. The coumarin content in these plants or their essential oils is highly variable. In food, maximum levels [1] of coumarin have been set for food ingredients where it occurs naturally. However, these plants and essential oils are sometimes used in food supplements without any coumarin content being specified. Coumarin is also used in some cosmetic and household products (perfumes, air fresheners, etc.), where human exposure is not negligible [2].

Cinnamon is considered to be the main dietary source of coumarin. The cinnamon used in foodstuffs and food supplements is usually the bark of Chinese cinnamon (*Cinnamomum cassia* (L.) J.Presl) or Indonesian cinnamon (*Cinnamomum burmanni* (Nees & Nees)). These cinnamons have a far higher coumarin content than Ceylon cinnamon.

Plants containing coumarin, in particular cinnamon, are most often found in food supplements claiming to "maintain blood sugar levels".

Toxicity of coumarin

When taken in high doses, coumarin poses a **risk of liver toxicity**. This is manifested by abnormal liver biology (increase in circulating concentrations of liver enzymes), which is reversible after cessation of exposure. At very high doses, it causes more serious liver damage (hepatic cytolysis, liver failure) [4].

To limit dietary exposure, the European Food Safety Authority (EFSA) has set a TDI of 0.1 mg/kg of body weight per day for coumarin [3].

Adverse effects identified by the vigilance schemes for food supplements

Between January 2006 (date of the first case reported to poison control centres) and February 2020, 66 cases of adverse effects associated with the consumption of food supplements containing coumarin were recorded in the poison control centres' information system. Of these, 52 (79%) involved essential oils. Around 40% of these reported adverse effects were digestive disorders (abdominal pain, vomiting, diarrhoea, etc.).

Eighteen percent of the cases involved otorhinolaryngologic disorders (oropharyngeal pain or irritation), 13% had general symptoms (headache, dizziness, etc.) and 11% concerned neurological disorders (drowsiness, loss of consciousness, etc.).

In addition, ANSES's nutrivigilance scheme received 48 reports of adverse effects liable to be associated with the consumption of herbal supplements containing coumarin, between the scheme's establishment in 2009 and the month of April 2019.

ANSES was able to analyse the causality in 28 of these 48 reports (the others were not sufficiently documented to be appraised). It should be noted that more than half of the cases (57%) involved products containing essential oils. The adverse effects reported mainly concerned liver (hepatic cytolysis) and digestive (nausea, vomiting, abdominal pain, etc.) symptoms.

What is the maximum daily intake of coumarin that can be safely consumed?

According to data from the Third Individual and National Study on Food Consumption (INCA3), exposure of the French population to coumarin through food can account for as much as 20% of the TDI [6], without including additional consumption from food supplements. There is therefore a high risk of this TDI being exceeded in heavy consumers of food supplements containing plants rich in coumarin, such as Chinese cinnamon.

Manufacturers and distributors of food supplements recommend daily cinnamon intakes of between 1000 mg and 8000 mg/d.

Assuming an average coumarin content of 3000 mg/kg of Chinese cinnamon, the consumption of food supplements could correspond to intakes of 3 to 24 mg of coumarin per day (without taking into account other sources of exposure, via food or otherwise). With these intakes, the TDI of 0.1 mg/kg body weight per day, i.e. 6 mg/day for a 60-kg adult, could therefore be largely exceeded. In addition, consumption may be subchronic, as the duration of use recommended by manufacturers can be as much as three months.

In view of the data on dietary exposure (excluding food supplements) and in order to comply with the TDI, ANSES recommends keeping coumarin intake through the consumption of food supplements below 4.8 mg of coumarin per day for a 60-kg person. This intake can be reached through consumption of food supplements containing around 1600 mg/d of cinnamon, which is quite common as shown above.

Important note

ANSES recommends taking special care with the use of cinnamon essential oils in products intended for food and food supplements, because these essential oils have been responsible for most of the adverse effects associated with coumarin recorded by nutrivigilance schemes. It recommends that coumarin consumption should not exceed the TDI.

The Agency also advises people with liver disease not to consume foods rich in cinnamon or food supplements containing coumarin.

Youssef EL-OUADRHIRI and
Gwenn VO VAN REGNAULT (ANSES)

TO FIND OUT MORE :

Opinion on the "assessment of the risk of hepatotoxicity associated with the coumarin content of certain plants that can be consumed in food supplements or in other foodstuffs"

References

[1] Regulation (EC) No 1334/2008 of the European Parliament and of the Council of 16 December 2008 on flavourings and certain food ingredients with flavouring properties for use in and on foods and amending Council Regulation (EEC) No 1601/91, Regulations (EC) No 2232/96 and (EC) No 110/2008 and Directive 2000/13/EC.

[2] Lake, B.G. 1999. "Coumarin metabolism, toxicity and carcinogenicity: relevance for human risk assessment." Food Chem Toxicol 37 (4):423-453.

[3] EFSA. 2004. "Opinion of the Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) related to Coumarin." EFSA Journal 2 (12):104.

[4] Abraham, K., M. Pfister, F. Wohrlin, and A. Lampen. 2011. "Relative bioavailability of coumarin from cinnamon and cinnamon-containing foods compared to isolated coumarin: a four-way crossover study in human volunteers." Mol Nutr Food Res 55 (4):644-53. doi: 10.1002/mnfr.201000394.

ANSES is in charge of several health vigilance systems: pharmacovigilance for veterinary medicinal products, nutrivigilance, phytopharmacovigilance, toxicovigilance and vigilance for occupational diseases. Our vigilance activities make little noise and are therefore poorly known to public health actors, health professionals, marketers and users in general. And so, in order to make our work more visible we have decided to create a dedicated newsletter entitled Vigil'Anses.

As news on each of our vigilance topics crops up, this quarterly newsletter presents the main results of the work carried out by ANSES within the framework of its vigilance missions, in conjunction with its partners, professional networks and expert groups, as well as the actions we have undertaken.
The articles are deliberately short, and are intended for all those involved in the occupational and environmental health and safety field: public authorities, health agencies, institutes and expert bodies that are partners of ANSES, prevention policy managers, the scientific community, professionals, associations and users. Vigil'Anses also invites the interested reader to delve deeper and discover publications, opinions and reports available online that will further their knowledge.

anses

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

www.anses.fr / @Anses_fr

ISSN : 2556-1790 – Legal deposit : November 2021 © Anses Edition : November 2021 – Achievment : ANSES – Photo credit : Getty Image, E. Fresnay