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Beware of button batteries! A potential hazard for young children

Small, flat, round button batteries are invading our homes and yet few people are really aware of the risk of accidents associated with their ingestion. They are found in numerous everyday objects: in addition to toys, they can be found in remote controls, car keys, thermometers, hearing aids, kitchen scales, light pens, musical greeting cards, bathroom scales, etc.

Young children are very attracted to these small, round, shiny objects and like to put them in their mouths. As well as being in the various objects already mentioned, children can also come across these batteries on their own (left within reach, just purchased and still in the packaging, in containers for used batteries, etc.)

Like any other foreign body, if a child puts one of these batteries in their mouth, it can be inhaled, entering the airways and causing coughing or even respiratory distress, which always requires urgent treatment. But these batteries can also be swallowed and become stuck in the oesophagus or even in the stomach.

However, unlike coins, to which they are often wrongly compared, these button batteries are not inert objects. When they come into contact with a moist mucous membrane, they can cause potentially deep chemical burns. This is because they deliver an electric current responsible for hydrolysis, which then produces highly alkaline hydroxide ions leading to internal damage. Thus, regardless of the route of penetration (children can also put them in their nose or ears), these batteries can lead to deep burns related, among other factors, to the battery's size, charge and voltage, and to its contact time with the mucous membrane.

If the battery gets stuck in the oesophagus, there is a very high risk of complications, mainly because the oesophagus is close to the airways and the large vessels (particularly the arteries and aorta). Oesophageal burns can therefore lead to perforation of adjacent structures and result in respiratory distress, or sudden massive haemorrhage leading to the child's death [1].

A young child can ingest a button battery without the parents' knowledge, and this is an alarming situation. Indeed, if the battery is lodged in the oesophagus, the child may initially remain asymptomatic and then present very unspecific symptoms that are often not of great concern, such as fever and anorexia, which are common to many other disorders (particularly infectious digestive diseases) and do not point to a diagnosis of button battery ingestion. It is usually only when a late complication has already become serious that the diagnosis is made.

This is why, even if ingestion is only suspected (there is no room for doubt), the child should be given an urgent X-ray to locate the battery and, if one is found to be trapped, it should be removed immediately by emergency oesophageal duodenoscopy. The French Society of Clinical Toxicology recently published an opinion on the initial management of calls about suspected button battery ingestion by young children [2].

International and French poison control centres (PCCs) have already addressed this issue, and numerous articles have appeared in the international literature. For example, in 2017, French PCCs published a retrospective observational study based on cases registered in the PCCs' information system (SICAP) between 1 January 1999 and 30 June 2015 [3]. In this study, 4,030 cases were found, including 21 severe cases, and two deaths were observed. In both fatal cases, the button battery had become lodged in the oesophagus. Both deaths occurred even though the battery had either been passed spontaneously in the stool (death 19 days after spontaneous expulsion of the battery) or removed by fibroscopy (death 10 days after battery removal).

Following this study, the PCCs suggested conducting a prospective study (Pilboutox® study[1]) to describe cases of exposure to button batteries more precisely.

1.Study design available at https://clinicaltrials.gov/ct2/show/NCT03708250?term=pilboutox&rank=1

This study was conducted between 1 June 2016 and 31 May 2018: it included any exposure to a button battery that had led to a call to a PCC. The parameters studied were age, route of exposure, symptoms, abnormalities observed on initial fibroscopy, severity according to the Poisoning Severity Score (PSS[2]) and characteristics of the battery involved. Five hundred and nine cases were reported, of which 465 (91%) were by ingestion

Subjects were aged between 3 months and 96 years; 375 children (74%) were under 6 years of age. Nine cases (2%) of high severity (PSS3) were observed and four deaths, all ages combined (including two in children under 3 years of age). The detailed results of this study are currently being analysed, but a preliminary review of the results confirmed the characteristics already described in other studies, in particular, severity related to the young age of the child and to a battery diameter greater than 15 mm.

Although the complications related to button battery ingestion by children are well documented, few studies have analysed the time that passes before treatment, the early clinical signs, with a view to the creation of a specific care system for these poisonings.

The expected results of the Pilboutox® study should shed new light on certain aspects of this medical management.

Lastly, in conjunction with the industrial federations concerned, ANSES, experts from the PCCs and the Necker Hospital (Paris), the Ministry of Health and the Ministry of the Economy have taken joint action to:

- alert the general population, healthcare professionals and early childhood professionals to the risk of ingesting button batteries through the distribution of an information sheet (https://solidarites-sante.gouv.fr/IMG/pdf/infographie_piles_bouton.pdf);
- work with industry federations to obtain voluntary commitments from them to improve the safety of their products or the information provided to consumers.

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2.https://www.who.int/ipcs/poisons/pss.pdf

Syndromic surveillance: applying big data to vigilance

What is it for?

The aim of a health vigilance scheme such as toxicovigilance is to detect signals which, if validated, will trigger immediate actions and measures to correct a situation where there is a risk of human poisoning and prevent similar new episodes (information, investigation, withdrawal of a consumer product, etc.).

These signals can come from different complementary sources that are either qualitative ("spontaneous" reporting, scientific monitoring) or quantitative (statistical analysis). First of all, healthcare professionals can notify the competent authorities of situations they consider abnormal. As part of their toxicovigilance mission, the eight poison control centres (PCCs), each covering a part of the country, report to ANSES any unusual, serious and/or avoidable cases of poisoning of which they become aware. However, for any given PCC, identification of these cases, although exhaustive and objective, is based on an assessment of "only" those cases of which it has been informed, and does not by definition allow for any comparison with cases of which the PCC is unaware. A single PCC does not necessarily have the means to detect a possible link between poisoning cases with shared characteristics (exposure agent, circumstances, severity, symptoms, etc.) in different parts of the country. On the other hand, this "diffuse" signal can be more easily detected by statistically analysing the Poison control centres' national database (SICAP), where the data from all the PCCs are gathered, , especially since these data are numerous and go back such a long way in time, enabling statistical comparisons.

This is why the challenge for vigilance in recent years has been to develop automated signal detection methods based on statistical algorithms, which analyse large health databases in search of an "unusual event" that could pose a risk to the population [1,2]. In early 2018, in conjunction with Inserm[1] and the PCC network, ANSES set up an automated toxicovigilance signal detection programme based on SICAP data, one of whose components concerns "syndromic surveillance".

How does it work?

In toxicovigilance, syndromic surveillance is based on the systematic analysis in "real time" (or quasi-real time) of poisoning cases recorded by the PCCs in SICAP, with the aim of detecting unusual peaks of cases, compared to what has been observed in the past, which then correspond to a "statistical" signal.

In particular, the analysis focuses on "medical entities" (or syndromes), which are defined as a group of clinical signs or symptoms, each of which can be used independently for coding SICAP poisoning cases. These entities correspond to an affected organ, function or system of the human body (cardiac rhythm disorders, skin rash, irritation of the upper airways, consciousness disorders, "anticholinergic eye", etc.), without any prior knowledge of the agents that may be responsible for their occurrence. Initially designed to detect the health consequences of acts of bioterrorism, syndromic surveillance should help identify cases of poisoning with similar clinical evidence, spread unevenly across the country, without prior knowledge of whether the subjects were exposed to the same agent or the same family of agents. Syndromic surveillance aims to identify both accidental exposure and malicious acts.

A total of 66 medical entities were predefined with the help of PCC expert toxicologists, and then tested. In practice, monitoring a syndrome means monitoring poisoning cases in SICAP that include at least one of this entity's clinical signs.

For each of the medical entities, a statistical query performs a daily comparison (on day D) of the number of cases observed over the last seven days (from D-1 to D-7) with the "average number" of cases observed successively during previous weeks (from D-14 to D-21, from D-22 to D-29, etc.), including the entire history of SICAP data going back almost 20 years. The algorithm detects a statistical signal when the number of cases observed is higher than expected. Any possible seasonality of the poisoning cases of the monitored medical entity and the overall activity of the PCCs, which may change over time, are all taken into account by the statistical model.

1. Inserm: National Institute of Health and Medical Research

Statistical analysis does not, and is not intended to, establish an actual link between poisoning cases of the same signal. In the event of a signal, the toxicologists from ANSES and the PCCs review the medical records of the poisoning cases making up the signal, using the forms available in the SICAP, and validate or rule out the signal. If the poisoning cases are linked (= seem to be caused by the same agent, even if unidentified), the signal is validated, which enables a possible risk for the population to be confirmed and characterised. If the poisonings are not related to each other (e.g. different agents), the signal is ruled out.

What are some specific examples?

This scheme was introduced in April 2018. An initial analysis of syndromic surveillance showed that out of 20 statistical signals detected between April and December 2018, the majority (16 signals) corresponded to a chance association of cases, without any link between them (situations having no common points, notably regarding the agent). These signals were not validated ("false positives"). This initial assessment led to certain medical entity definitions being modified, by refining their detection criteria. For example, for analysis of the "visual acuity disorders" entity, cases exposed by the ocular route were ruled out in order to exclude vision disorders due to eye splashes, which are usually of very diverse origin.

However, four signals were validated and led to health alerts being issued.

On 26 April 2018, analysis of the 255 cases in the "rash" medical entity signal[2] identified 28 cases due to snake bites, showing an earlier occurrence of viper poisonings for the season. The alert was given in the context of stock shortages of viper anti-venom, which had been recurring since 2016.

On 31 July 2018, surveillance of the "anticholinergic eye[3]" entity detected a signal consisting of 31 cases, including six clustered cases, of people who had consumed jimsonweed leaves (*Datura stramonium*) [3] sold in a market in place of spinach leaves. The seller was not identified.

On 30 October 2018, a signal consisting of 25 cases, also of the "anticholinergic eye" entity (Figure 1), revealed collective food poisoning on Reunion Island of six people who thought they had collected edible leaves, which were in fact jimsonweed leaves.

Lastly, on 20 November 2018, a signal concerning two cases of the "anticholinergic syndrome" entity (Figure 1) was the starting point for an alert due to organic buckwheat flour contaminated with jimsonweed and sold in supermarkets. These cases concerned two people poisoned during a meal on 17 November, after having eaten home-made pancakes prepared with a bag of flour purchased in a supermarket.

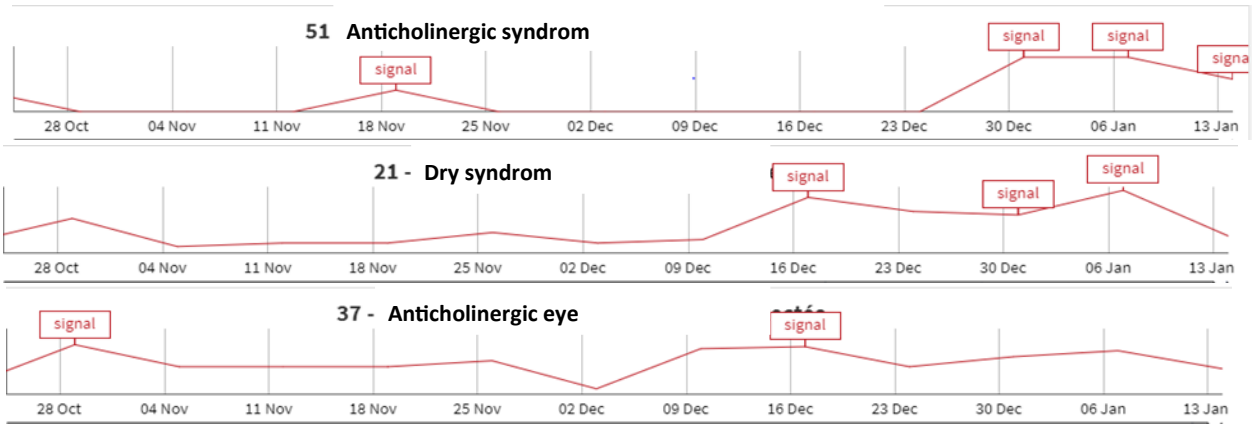

Figure 1: Change over time in the "anticholinergic syndrome", "dry syndrome" and "anticholinergic eye" medical entities monitored in syndromic surveillance. Source: R Connect®, ANSES.

2.This entity includes signs of skin irritation, redness, oedema, burning, etc.
3.This entity consists of signs of pupil dilation, decreased visual acuity, dry eyes, etc.

In addition to the syndromic surveillance, the search for similar cases in SICAP then identified a second episode of collective poisoning of four people who, also on 17 November, had presented with anticholinergic signs after consuming homemade pancakes made with a bag of flour of the same brand and from the same supplier, but purchased in a supermarket in a different region.

Following this alert and the traceability investigation with the producer that marketed the flour, on 23 November the DGCCRF[4] asked the interdepartmental directorates located near the hypermarkets and supermarkets concerned to take steps, without delay, to withdraw and recall the contaminated batch of flour, in order to prevent the risk of new poisoning cases [4].

However, on 14 December 2018, a signal consisting of 11 cases of the "dry syndrome[5]" entity (Figure 1) identified four further cases of poisoning with the buckwheat flour responsible for the alert (same brand and batch number), but in which the bags had been purchased on 8 December, after the first management measures had been introduced. Four days later (18 December), a new signal for this entity identified six further cases of poisoning by the same flour, this time bought on 15 December in another shop. ANSES alerted the DGCCRF to the developments in the situation and new measures to withdraw/recall contaminated products were taken [3]. Three new cases, involving flour purchased on 5 January 2019, were detected on 12 January ("anticholinergic syndrome", Figure 1). In total, as of 15 January 2019, 73 cases of poisoning in 23 different medical files[6] had been identified (Figure 2).

What is the outlook?

Syndromic surveillance is a useful tool for the early detection of weak health signals. Developed for toxicovigilance less than a year ago, it has helped with the prompt identification of several signals.

Other methods of automated signal detection are being developed using PCC data.

Studying chronological trends in exposure cases associated with certain families of agents makes it possible to detect progressive increases in these poisonings, not through "epidemic" peaks in cases, which are more easily detected in the short term, but through medium-term increases.

Lastly, the automated search for new, unknown and/or abnormally frequent associations between certain characteristics of poisoning cases and agents (symptoms, substances in the products, exposure circumstances, etc.), known as non-targeted data mining, is another automatic detection method that can reveal weak signals.

Together with the continuation of active reporting schemes, this work represents one of the tools for future toxicovigilance.

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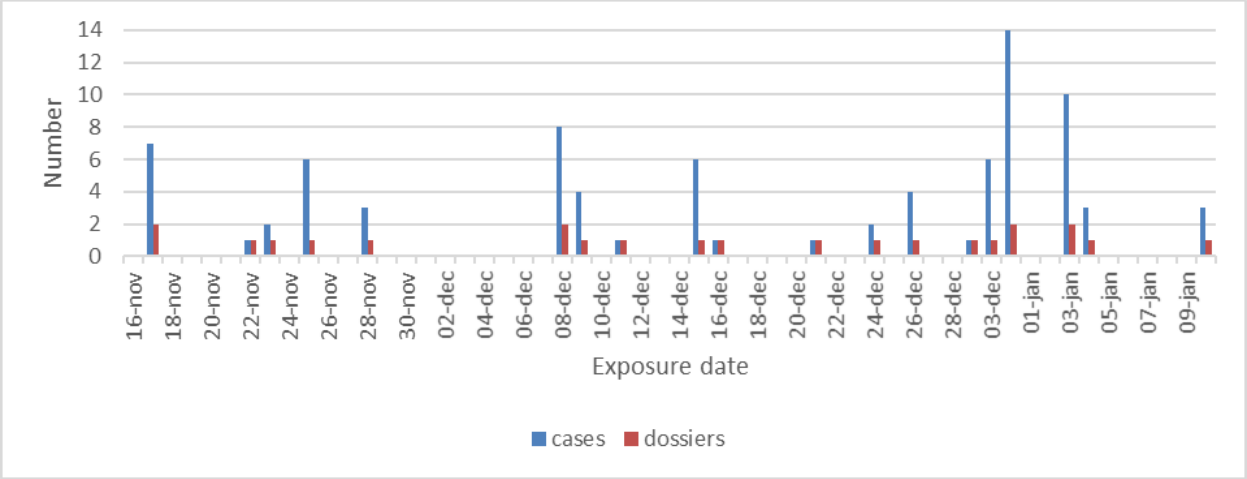

Figure 2: Distribution of exposures to buckwheat flour contaminated with jimsonweed (*Datura stramonium*), recorded by the PCCs since the beginning of the alert (number of cases and medical files – a medical file includes all cases of people having consumed the same meal).

4.DGCCRF: Directorate General for Competition, Consumer Affairs and Fraud Control.
5.An entity consisting of signs of dryness of the mucous membranes, including dry eye syndrome (or anticholinergic eye).
6.Each medical file contains either a single case or collective cases for people who shared the same meal.

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When unauthorised plant protection products remain in circulation

The European Union and France have been working over the last 20 years to improve the safety of plant protection products (PPPs)[1] and reduce their use. Implementation of the active substance review programme has resulted in the elimination of many substances that are hazardous to humans and/or the environment. As a result, while around a thousand active substances were available on the market at the end of the 1980s **[1]**, only 489 substances now have approval[2] in Europe. Not all of them are marketed in France, where 440 substances are found in products with marketing authorisations[3] (MAs).

In France, governmental actions to halve the volumes of PPPs used by 2025 were introduced in 2008: the Ecophyto II plan continues to pursue the objectives set and the actions implemented by the Ecophyto 2008 plan, which resulted from the Grenelle Environment Round Table. One of the measures taken in 2008 concerned the withdrawal from the market of PPPs containing non-approved active substances, as well as PPPs whose re-examination had shown an unacceptable risk for consumers or the environment, or those whose expected benefits were now outweighed by the risks. Lastly, certain PPPs containing active substances that were still approved but were not supported by any industrial company at the national level were also withdrawn **[2]**. Almost all of these substances were subsequently banned across Europe. Any of these PPPs still in the possession of distributors after the marketing deadline or of users after the use-by date were henceforth regarded as waste, with their holders being responsible for their disposal (Article L. 541-2 of the French Environmental Code). Campaigns to raise awareness among agricultural stakeholders were then launched by the Ministry of Agriculture to alert farmers and distributors to the risks and penalties of using prohibited substances.

However, the ban on the marketing and use of PPPs has not eliminated their fraudulent use. This may result from stockpiling of these products or illegal imports from border countries where they may still be on the market. In addition, some products may be used for malicious acts, especially on domestic or wild animals.

The possession and use of unauthorised PPPs is also an issue in the French overseas territories (DROM and COM), which have land and/or sea borders with other countries: in South America (French Guiana), the Caribbean (Guadeloupe and Martinique), Africa (Reunion Island) and French Polynesia. The French poison control and toxicovigilance centres (CAPTVs) had in particular pointed out the persistent use of paraquat, particularly in French Guiana, where the ban since 2007 has had little impact on the number of poisonings **[3]**. Similarly, several cases of poisoning by aldicarb, which was banned in 2007, have been reported in Guadeloupe **[4]**. A veterinary study carried out on the circumstances of deaths of necrophagous birds (raptors) in the French Pyrenees between 2005 and 2012 found that in 24% of cases the animals were poisoned, mainly by carbofuran (which was banned in Europe in 2008) and aldicarb (which was permanently banned in Europe in 2007) **[5]**. The question of the impact of bans and the origin of PPPs that have been banned in France (whether or not they are authorised in neighbouring countries) can be addressed through the poisonings recorded by the CAPTVs and veterinary PCCs (CAPVs) as part of their emergency telephone hotline service.

A study was therefore carried out based on calls recorded by the French CAPTVs and CAPVs over the period from 01/01/2012 to 31/12/2016. This study period was chosen in order to be able to verify whether these products were still present and/or in use a sufficient period after when the ban came into effect. This study set out to describe the spatial and temporal distribution of cases of exposure to certain unauthorised PPPs in France and the circumstances of their occurrence. The PPPs and substances targeted were those listed in the opinion of the Ministry of Agriculture and Fisheries published in the Official Journal on 28 March 2008 **[2]**.

1.Plant protection products are designed to protect plants and plant products against pests.
2.In the European Union, active substances used in plant protection products must undergo periodic re-assessments of the risks to human health, the environment and non-target organisms. At the end of this process, the substance is either "re-approved" for a certain period of time or banned.
3. https://ephy.anses.fr/

It should be noted, however, that some banned active substances may have benefited from exemptions for use when no alternatives were available, for short (maximum 120 days) renewable periods, thus making them available; it was not feasible to trace these exemptions and these substances were therefore included in the study. Furthermore, French Polynesia has a special status, as the local government has jurisdiction over regulation of pesticides[4] and European regulations do not apply there. The 14 Polynesian cases, including 11 cases of poisoning by PPPs containing paraquat (banned in 2015), were however included in this study.

Four hundred and eight cases of human exposure (symptomatic or not) were reported to the CAPTV network during the study period. The substances most often incriminated were dichlorvos, paraquat and aldicarb. There was a sharp decrease in the number of poisonings, from 119 cases in 2012 to 47 cases in 2016, except in the French overseas territories where the numbers have remained stable (Figures 1 and 2). Most of the 72 serious cases in this series (death or severe life-threatening symptoms) were associated with exposure to paraquat, aldicarb or carbofuran. The temporal distribution of these serious cases over the study period was fairly constant from year to year.

The cases of occupational exposure were due to the use of fungicides (anthraquinone, dinocap and carbendazim). The origin of the products was provided for 14.7% of the cases: half of these resulted from the storage of old products and the other half from illegal imports, mainly from Surinam for paraquat or from North Africa for dichlorvos.

Over the same period, 149 cases of animal exposure were reported to the CAPVs, mainly involving insecticides (87.9%) and, less frequently, herbicides (10.1%). The two substances most often incriminated were carbofuran and aldicarb, particularly in malicious acts. These misuses of carbamate insecticides seemed to persist until 2015. A downward trend can then be seen in 2016, which remains to be confirmed.

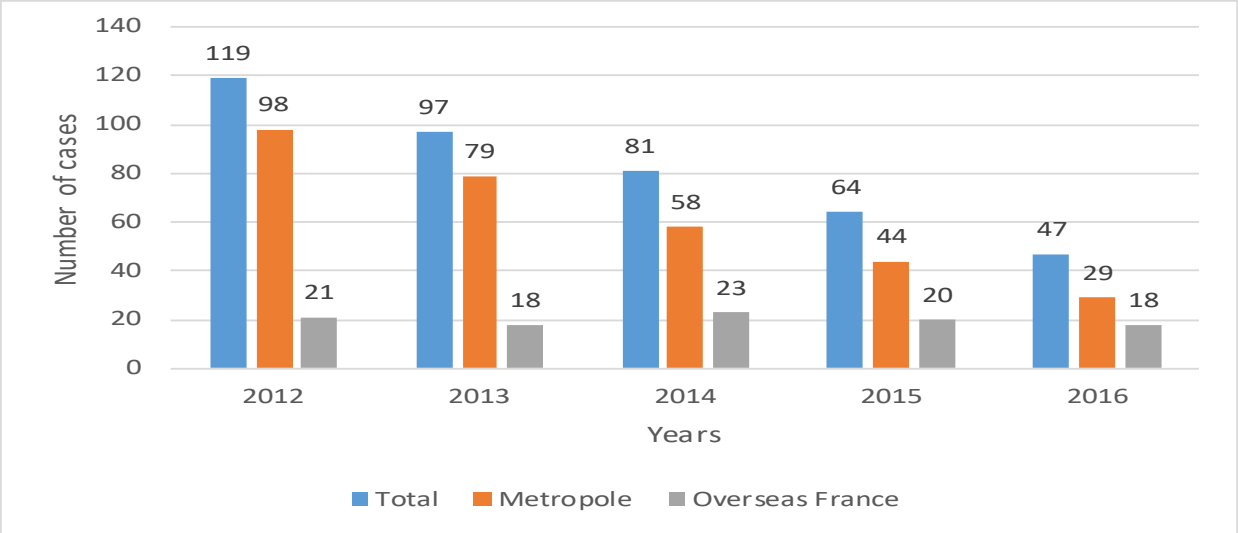

Figure 1: Annual change in the total number of cases associated with unauthorised PPPs in metropolitan France and in the overseas territories

The results of this study on the use or possession of certain PPPs prohibited since 2008 in France, through data collected by the PCCs over the period 2012-2016, suggest that their ban has had the logical consequence of reducing poisoning cases in metropolitan France; however, in the overseas territories, this collateral effect is less pronounced.

Among the unauthorised PPPs, the study highlighted the preponderance of insecticides from the carbamate class and the existence of illegal imports of substances such as dichlorvos or paraquat in French Guiana, which were responsible for fatal poisonings, as well as the use of certain fungicides in the professional agricultural sector.

4.The list of authorised compounds is governed by a local law of 2011 and is laid down by Ministerial Order. It was last updated on 24/04/2018.

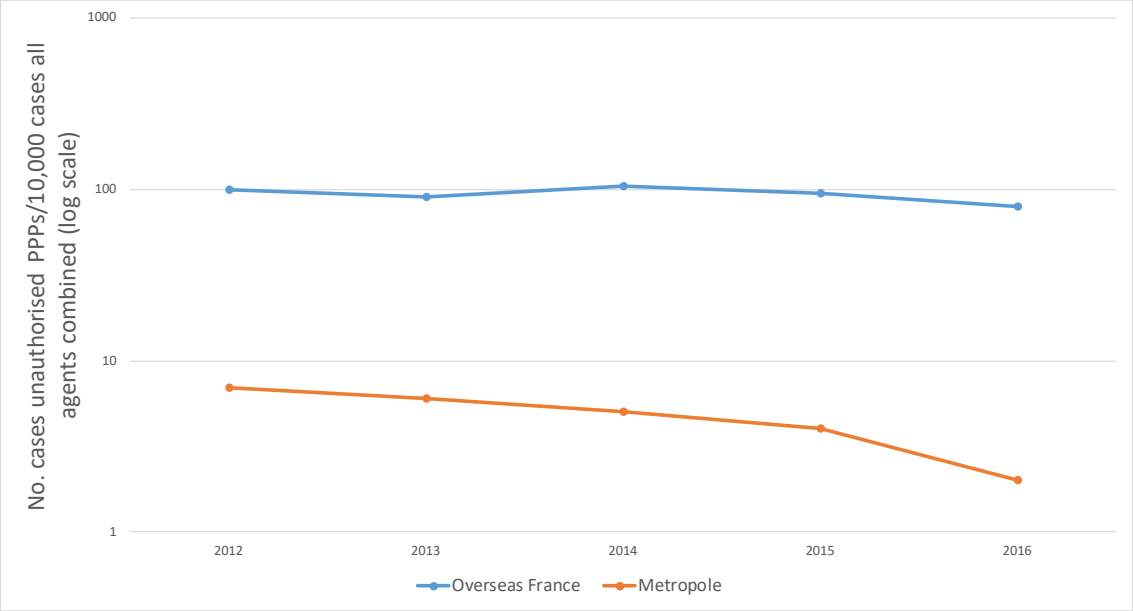

Figure 2: Annual change in the number of cases associated with PPPs in relation to the number of cases from all agents combined, recorded by the PCCs, for the overseas territories and for metropolitan France.

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In France, anyone using or possessing unauthorised products is liable to severe penalties of up to seven years' imprisonment and a fine of up to €750,000. The use of unauthorised PPPs poses risks to humans, animals and the environment, and action must be taken to prevent the use of these products.

Distributing information on the withdrawal of authorisations and, more generally, on the rules applicable to the use of PPPs (e.g. the principle behind the MA, compliance with the conditions of use) is probably a first step towards prevention. This information is widely available at present **[6]**, but active communication campaigns could be considered, in particular through field players in contact with potential users (mainly agricultural professionals and healthcare professionals). However, the populations to be targeted should be clarified because the present study, mainly due to the method of data collection based solely on cases recorded by the PCCs, offers only a partial view of the circumstances in which exposures occur.

Eliminating stocks of PPPs following their withdrawal from the market, particularly in the overseas territories, is also one way of preventing the use of unauthorised products. Information campaigns should be conducted regularly and collection points for these non-usable PPPs should be established in the overseas *départements* and regions, following the example of what has been set up by ADIVALOR[5] in metropolitan France.

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http://www.adivalor.fr/collectes/produits_phytosanitaires.html

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TO FIND OUT MORE, VISIT:

ANSES report on exposure to plant protection products containing unauthorised active substances in mainland France and the overseas territories – Retrospective study of observations recorded by French poison control and toxicovigilance centres and veterinary poison control centres (2012-2016)

Series of poisonings by metam-sodium fumes in Maine-et-Loire

The facts

In September and October 2018, three consecutive episodes of multiple poisoning affected a total of around a hundred people in Maine-et-Loire. The first one, in late September, concerned a vocational high school, while the second, in early October, affected agricultural workers in a plant nursery and walkers in Brain-sur-l'Authion, a municipality located near the vocational high school. The third episode affected walkers in the municipality of Mazé-Milon. Each time, the victims suffered similar symptoms such as respiratory tract or eye irritation, or vomiting, and some of them had to be admitted to Angers university hospital.

These poisoning cases were quickly attributed to plant protection products containing metam-sodium used for disinfecting soil in greenhouses and market garden plots between crops. When in contact with water, metam-sodium releases methyl isothiocyanate (MITC), which has fungicidal, nematicidal and insecticidal properties. Immediately after the product has been applied, it must be watered to ensure it migrates deep into the soil, then the treated ground must be covered with a tarpaulin to limit dispersion of the MITC and optimise the effectiveness of the disinfection. In addition, a "re-entry interval" must be observed before anyone can return to the treated plot.

The particularly hot and dry weather conditions of early autumn 2018 favoured the evaporation of metam-sodium and its dispersion in the surrounding area. This then exposed people nearby, in areas where market garden crops were grown adjacent to housing. It was also found that some users had not complied with the conditions of use for this type of product, failing to water the ground or cover the soil, or applying at temperatures above 25°C.

Local emergency management measures

Following this series of poisonings and to prevent their re-occurrence, on 12 October 2018 the Prefect of Maine-et-Loire decided to ban the use of products containing metam-sodium for 15 days as a precautionary measure, pending the results of investigations. This ban was then extended until 31 December 2018, after it was found that the techniques for using metam-sodium were not being properly applied.

Regulatory re-assessment of products containing metam-sodium

At the same time, in autumn 2018, following the re-approval[1] of metam-sodium at European level, ANSES was re-examining all products containing this active substance with a view to renewing their marketing authorisations. At the end of this re-assessment, it was found that the uses claimed by the manufacturers did not comply with the regulatory requirements, due to the existence of various risks: for farm workers entering an area after treatment, for people in the vicinity of treatments and for groundwater.

Outcome

In view of the unfavourable conclusions of the regulatory assessment of metam-sodium products, ANSES decided to withdraw the marketing authorisations for all products containing this substance. The series of poisonings that occurred in Maine-et-Loire simply reinforced this decision, which would have been taken anyway.

Moreover, a search for similar cases in the poison control centres' national database showed that there had already been numerous earlier poisonings attributed to metam-sodium, to the point that the prefect of Maine-et-Loire had previously been required to issue a prefectural order on 20 January 2017. These cases had not specifically been reported to ANSES and its phytopharmacovigilance scheme [1].

Improving feedback for phytopharmacovigilance

This episode illustrates the importance of reporting to ANSES any adverse event associated with the use of plant protection products, whether serious, benign, localised or generalised. Moreover, the reporting of adverse effects is a regulatory requirement for professionals, pursuant to Article L. 253-8-1 of the French Rural and Maritime Fishing Code. But any individual or healthcare professional can also report adverse events via the reporting portal. These phytopharmacovigilance reports enable the Agency to act promptly to prevent and control risks.

Ohri YAMADA (Anses)

References

[1]https://vigilanses.anses.fr/sites/default/files/VigilansesN3_Pr%C3%A9sentationPPV.pdf

1.In the European Union, active substances used in plant protection products must undergo periodic re-assessments of the risks to human health, the environment and non-target organisms. At the end of this process, the active substance is either "re-approved" for a certain period of time or banned.

Vaccination in dogs: an essential preventive measure, but one that should be used with care

Vaccines are widely used in dogs and are a pillar of preventive veterinary medicine.

Although commonly used and sometimes trivialised, they are still medicinal products and can cause adverse effects, as stated in their summary of product characteristics (SPC). These effects are rare and mostly mild: local reactions at the injection site, a transient mild fever and occasional digestive disorders can all be observed. However, far more serious adverse effects can sometimes occur, such as anaphylactic reactions[1], which are well known and potentially fatal post-vaccination phenomena.

In order to analyse these serious adverse effects (SAEs) observed in dogs following vaccination, a five-year retrospective study was carried out by the French Agency for Veterinary Medicinal Products (ANMV) between 1 January 2012 and 31 December 2016[2].

Reports corresponding to cases considered non-serious, cases considered serious but for which a cause other than the vaccine was identified (causality N: unlikely) or for which the data were insufficient to conclude (causality O/O1: unclassifiable/inconclusive) were excluded from the study[3].

During the study period, 62 different vaccines marketed in France were mentioned in at least one report. The number of valences[4] contained in each vaccine varied from one to nine. Sales figures for the different vaccines studied were provided by the marketing authorisation holders. Based on these data, it was estimated that 21,303,160 dogs were vaccinated during the five years of the study, i.e. an average of 4,260,632 dogs per year, which corresponds to 58% of the French dog population (7,340,000 individuals according to FACCO-KANTAR TNS[5]).

Results

Over the period from 1 January 2012 to 31 December 2016, 2,083 reports concerning dogs were registered with the ANMV. Almost all of these adverse effects were reported by veterinarians (98%), with owners accounting for only 2% of reports in this study.

Among these 2,083 reports, 1,313 were regarded as serious. Of these, 723 reports (789 dogs) where the causality was declared A (likely) or B (possible) were selected for analysis.

All vaccines combined, the SAEs occurred only very rarely: one SAE per 32,875 vaccinated dogs, or 0.37 cases per 10,000 vaccinated dogs.

The vast majority of reported SAEs were life-threatening anaphylactic reactions. They resulted in states of shock, which were regularly associated with other signs such as localised oedema (face, throat, limbs), urticaria, digestive disorders (vomiting, diarrhoea +/- haemorrhagic) and/or respiratory disorders (dyspnoea, cough, nasal congestion). In 70% of cases, these reactions were diagnosed within one hour of the injection.

In this study, the population's characteristics were taken into account when they were mentioned in the reports. Thus, of the 789 dogs concerned, age was recorded in 724 cases (92%), breed in 660 cases (84%) and weight in 521 cases (66%).

In 55% of the cases in this study, reports of SAEs concerned dogs under 1 year of age. This age group represents only 5% of the dog population in France (FACCO 2012-2016) but it is also the most widely vaccinated, as it is estimated that about 40% of the vaccine doses of the most common valences are used in dogs under 1 year of age.

Similarly, small dogs weighing 5 kg or less were also over-represented in our study compared to the weight distribution estimated by FACCO in its surveys between 2012 and 2016. This imbalance is partly explained by the over-representation of young dogs in serious cases (see below), but it was also found after puppies were excluded, as shown in the graph below.

1.Anaphylaxis can be defined as a severe, rapid-onset, life-threatening allergic reaction.

2.https://pharmacovigilance-anmv.anses.fr/

3.https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-9/vol_9b_2011-10.pdf

4.The part of a vaccine that provides protection against a single germ.

5.French Federation of Food Manufacturers for Dogs, Cats, Birds and other Pets

Lastly, certain dog breeds weighing less than 5 kg were mentioned most often, such as the Chihuahua, Yorkshire Terrier, Bichon or Shih Tzu (6%, 6%, 4% and 3.5% of reports respectively).

Discussion and conclusion

This study had a number of biases and limitations that need to be borne in mind when interpreting the results.

As the cases studied were spontaneous reports from the field, the first bias is the under-reporting of cases, which is difficult to assess, even though, according to a prospective study carried out by the ANMV **[1]**, the percentage of cases reported compared to cases observed by veterinarians was around 10% in 2014. Regarding the use of vaccines, since all the reference figures remain estimates and current vaccination practices cannot be taken into account due to a lack of data (use of several doses combined in the same syringe or use of multivalents, several injections at different points, etc.), it remains very difficult to draw conclusions as to the vaccination practices posing the greatest risks.

Nowadays, vaccine injections tend to be trivialised due to their routine use, but they are medicinal products in their own right and can cause adverse effects. These effects are all the more difficult for owners to accept, as vaccination is a prophylactic administered to healthy animals. Serious adverse effects, although very rare, make vaccination a controversial subject.

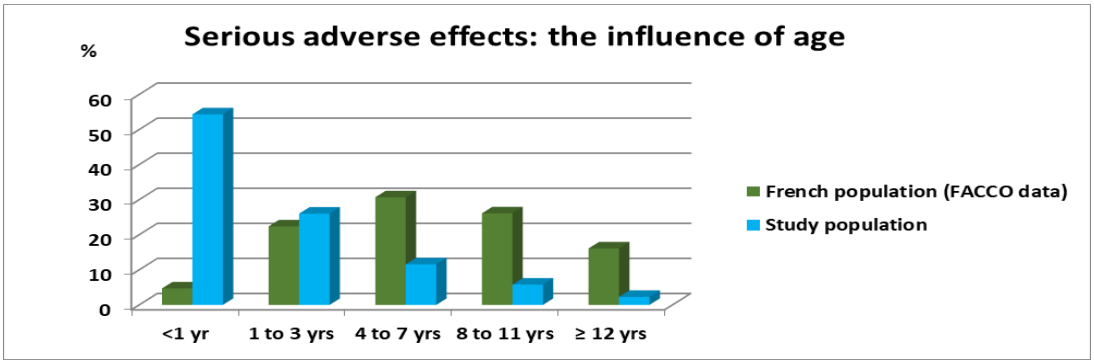
It is therefore important for the veterinarian to know how to adapt the vaccination protocols and the valences used to each animal, in order to provide the necessary protection with the least possible risk by avoiding unnecessary injections. Studies and recommendations on the subject are regularly published and can guide veterinarians in their choice of vaccine protocols **[2, 3]**.

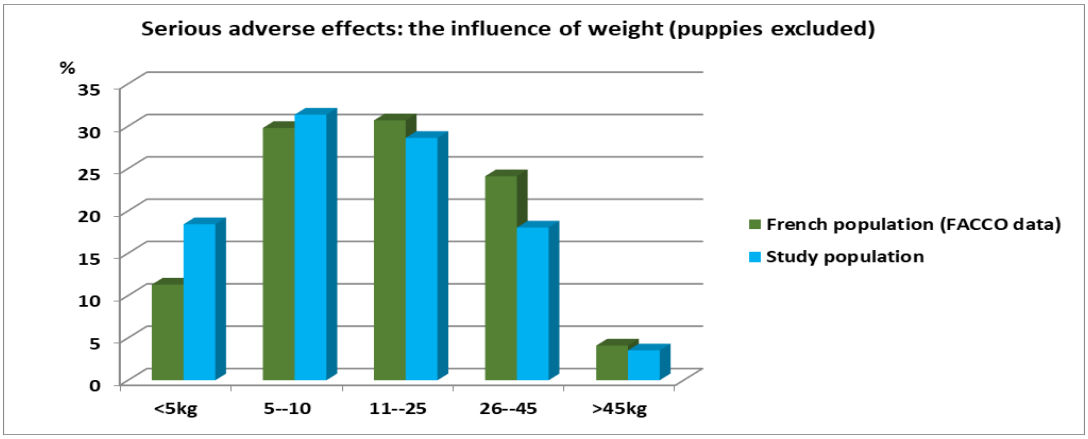
In dogs identified as being at risk of adverse effects (young dogs, small breeds, with an allergic predisposition, or having had a reaction to a previous vaccination), preventive measures can be implemented to limit the risk.

In addition, it is advisable to make all owners aware of the risks and the type of reactions that may occur following vaccination, as early action can improve the prognosis.

However, it should never be forgotten that the diseases against which dogs are vaccinated are often fatal and still frequently encountered, so the benefits of using vaccines in dogs are still generally greater than the risks, although these should always be weighed up for each individual.

Sylviane LAURENTIE (Anses-ANMV)





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[3] Day MJ, Horzinek MC, Schult RD, Squires RA. Guidelines for the vaccination of dogs and cats, compiled by the Vaccination Guidelines Group (VGG) of the World Small Animal Veterinary Association (WSAVA) 2016;57(1):E1-E47.

TO FIND OUT MORE, VISIT:

Lohezic J, Fresnay E, Bégon E, Rougier S, Boullier S, Laurentie S. Effets indésirables graves des vaccins chez le chien : réalité chiffrée [Serious adverse effects of vaccines in dogs: a quantified reality]. Point vetérinaire, Nov 2018, N°390

Definition of a serious adverse effect in animals
When occurring in animals, a serious adverse effect is one that:
- causes permanent or prolonged symptoms,
- results in a congenital anomaly or malformation or causes major disability or incapacity in the treated animal,
- may be life-threatening or results in the death of the animal.

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.

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