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Investigate, evaluate, protect

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Most everyone in France has heard of the crisis of **eggs contaminated with fipronil** that shook the European food safety system this summer. The fraudulent use of this biocidal agent – authorised as an insecticide outside the food chain or as a veterinary medicine – in a mixture intended to eradicate insects from laying-hen houses, led to the distribution throughout Europe and beyond of eggs and egg products containing quantifiable traces of this product. During this health and media emergency, the French health authorities asked ANSES for an assessment of the risk to the population of consuming products contaminated with fipronil. An article in this issue of Vigil'Anses explains how the expert appraisal and data from the poison control centres contributed to this assessment.

Six other articles on the topic of vigilance are also presented here.

The first one concerns an everyday consumer product: **pine nuts**. If you eat them in a cake or a salad, you do not expect to be left with a bitter taste in your mouth, especially one that lasts long after the meal. However, this is what happened to many consumers in France and other European countries between 2008 and 2010, leading to a European alert and preventive measures. Vigil'Anses Issue 4 reviews this alert and takes stock of the current situation.

Another article describes the **Phyt'attitude** scheme set up by the Agricultural Mutual Insurance Scheme (MSA) in 1991 and generalised in 1997 to the whole of metropolitan France, with the aim of protecting its beneficiaries. It collects data on the adverse effects associated with the use of plant protection products in the agricultural environment, and thus contributes to phytopharmacovigilance.

Hairdressers and beauticians handle many chemicals, including products containing **persulphates** for bleaching hair. Some people develop skin or respiratory allergies to these products that may force them to change profession, even though preventive measures exist. The data from the National Network for the Monitoring and Prevention of Occupational Diseases (RNV3P) presented here show chronological trends in these diseases in this occupational environment.

Electronic cigarettes appeared on the French market in 2010 as a substitute for tobacco consumption, for people wishing to reduce the risks of smoking. Regardless of the health effects of vaping, are these devices safe? An article presents the analysis of data from Poison Control Centres on cases of acute poisoning associated with these devices and with e-liquid refills.

Lastly, in the news section, you can read or re-read the news update published by ANSES in November 2017 on the risks associated with the consumption of food supplements containing **spirulina**, as well as extracts from the annual report of the French Agency for Veterinary Medicinal Products on **the adverse effects of veterinary medicinal products on animals.**

Juliette Bloch, Editor-in-Chief of Vigil'Anses

Food supplements containing spirulina: choose trustworthy supply channels

Under the national nutrivigilance scheme, reports of adverse effects potentially associated with the consumption of food supplements containing spirulina have been brought to the attention of ANSES. These reports led ANSES to assess the risks associated with the consumption of this type of food supplement. On 30 November, ANSES issued an opinion on the risks associated with the consumption of food supplements containing spirulina.

Spirulina (a cyanobacterium that is generally offered for sale in powder form) has long been a traditional food consumed in several countries. In France, it is found on the market as a conventional food (alone or as an ingredient) or as a food supplement, with claims for beneficial effects on health.

Several cases of adverse effects occurring following the intake of food supplements containing spirulina have been brought to the attention of the ANSES nutrivigilance scheme or published in scientific journals. The doses consumed in these cases are not precisely known, and the reported effects vary considerably: digestive disorders, allergies, muscle or liver damage.

According to the available studies, spirulina does not seem to present a health risk at low doses (up to several grams per day in adults). Nevertheless, the available epidemiological studies concern too few subjects to be able to demonstrate rare effects such as individual hypersensitivity.

Products containing spirulina can be contaminated by cyanotoxins (especially microcystins), bacteria or trace metal elements (lead, mercury and arsenic).

The Agency's recommendations for consumers

In view of the risk of spirulina becoming contaminated by cyanotoxins, bacteria or trace metal elements, the Agency recommends that consumers of food supplements containing spirulina choose trustworthy supply channels controlled by the public authorities (compliance with French regulations, traceability and identification of the manufacturer).

Furthermore, in light of the characteristics of spirulina and the adverse effects reported, ANSES advises against the consumption of these food supplements by individuals suffering from phenylketonuria (a rare genetic disease related to accumulation in the body of the amino acid phenylalanine) or with an allergic predisposition.

Lastly, the Agency emphasises that spirulina is not a reliable source of vitamin B12 for vegans, as it is mostly in the form of an inactive analogue. Furthermore, the consumption of 5 g/d of spirulina (maximum quantity recommended by certain food supplements) provides from 7 to 8.5 mg of beta-carotene, whereas the maximum daily intake of beta-carotene from food supplements has been estimated at 7 mg/d, which is in addition to spontaneous intake.

Other recommendations

In view of the risk of spirulina becoming contaminated by cyanotoxins (especially microcystins), bacteria or trace metal elements, the Agency insists on the importance of the quality of the water used in spirulina cultivation and of the producers' full control over the different stages of production.

ANSES considers it necessary to conduct an expert appraisal to establish a threshold for microcystins in food supplements containing spirulina that takes into account other dietary intakes of microcystins, and the tolerable daily intake (TDI) of 0.04 µg/kg/d set by the WHO for chronic exposure. In addition, in the light of this TDI, ANSES deems it necessary to reassess the limit for microcystins set at 1 µg/g for food supplements containing Klamath algae.

The Agency reminds healthcare professionals of the need to report to its nutrivigilance scheme any adverse effects liable to be associated with the consumption of food supplements about which they become aware.

Lastly, ANSES emphasises the value of setting up a joint international project on the monitoring of adverse effects associated with the consumption of food supplements.

Gwenn VO VAN REGNAULT (Anses)

TO FIND OUT MORE, VISIT:

Opinion of the French Agency for Food, Environmental and Occupational Health & Safety on the risks associated with the consumption of food supplements containing spirulina

Veterinary pharmacovigilance: 2016 review of adverse effects in animals

In November 2017, ANSES published its 2016 report on post-marketing authorisation (MA) surveillance of veterinary medicinal products. This report, prepared by the French Agency for Veterinary Medicinal Products (ANMV), presents the main results and actions concerning market surveillance of French veterinary medicinal products and veterinary pharmacovigilance.

Since 2011, the number of pharmacovigilance reports has increased by 46%. In 2016, the ANMV recorded 4,113 cases of adverse effects in animals in its national database, 51% of which were considered serious.

This increase in the total number of reports has been accompanied by a change in the reporting channels, with in particular the continuing growth of direct transmissions (by mail or electronic submission) to the ANMV. Compared with 2015, the number of reports via this transmission channel increased by 24%, and reporters are increasingly turning to electronic submission (81% of reports sent directly to the ANMV in 2016).

More than 90% of these reports were sent by veterinary practitioners (90.8%). Animal owners and breeders submitted 7.8% of all reports. The remaining reports were sent by veterinary schools (1.1%) and pharmacists (0.3%).

As in previous years, the vast majority of adverse effects reported in 2016 involved domestic carnivores, with around 80% of reports concerning dogs or cats. Cattle represented 9% of all reports and other species accounted for less than 3% per species.

The relative share of the different therapeutic categories involved varied by species. In cats, the primary therapeutic category mentioned was antiparasitics. In dogs and cattle, vaccines were the most frequently mentioned category.

In veterinary pharmacovigilance, reports are classified into four different types: strict adverse effects, suspicions of lack of efficacy, issues of residues in foodstuffs, and environmental problems. Cases of strict adverse effects in animals made up a clear majority (89%). Suspicions of lack of efficacy accounted for just under 11% of all reports, and other cases accounted for less than 0.4%.

The total number of reports of lack of efficacy increased compared with previous years (406 in 2016 compared with 363 in 2015). This increase applied to all the main species. This change could indicate greater awareness among veterinarians and breeders of this component of pharmacovigilance, as a result of the communication and training measures implemented in recent years.

The reports are used to supplement the information available in the summaries of product characteristics (SPCs) of veterinary medicinal products. For example, in 2016, the SPCs of 39 medicinal products were amended following pharmacovigilance reports and due to data from the scientific literature: these amendments mainly concerned the "Adverse events" section (addition of new adverse effects and/or revision of the frequency of occurrence of effects that are already known) but also other sections such as "Special warnings", "Special precautions for use in animals" or "Contraindications".

In addition, following reports of serious adverse effects in certain countries (mainly Denmark), sometimes resulting in the death of dairy cows, the authorisation for the medicinal product VELACTIS® was suspended in Europe in August 2016. This medication containing cabergoline was authorised for inducing a reduction in milk production in cows during dry-off.

As part of the promotion of pharmacovigilance among veterinarians, the ANMV continued its different training and communication initiatives for veterinarians in 2016, in particular with the publication of a note on the "Definition of a serious pharmacovigilance case in an organised production sector", and a complete dossier on nonsteroidal anti-inflammatory drugs for dogs.

To ensure that knowledge on veterinary medicinal products is continually updated, the ANMV reminds you that any adverse effect observed following the use of veterinary medicinal products can be reported via the dedicated website https://pharmacovigilance-anmv.anses.fr/

Sylviane LAURENTIE (Anses-ANMV)

TO FIND OUT MORE, VISIT:

Post-MA surveillance of veterinary medicinal products. Annual Report

Anses publishes its first phytopharmacovigilance fact sheets

On 2 February, ANSES published the first in a series of fact sheets summarising the data it collects for each active substance under the phytopharmacovigilance scheme it coordinates. The aim of phytopharmacovigilance is to be able to take swift action on a product's marketing authorisation if a harmful effect is observed, in order to prevent its occurrence – for example by amending the product's conditions of use, limiting its uses, or even withdrawing the marketing authorisation. These summarised fact sheets, which contain all the information from the surveillance and vigilance schemes working in partnership with phytopharmacovigilance, are therefore particularly useful to ANSES in the context of the decisions associated with the process of examining marketing authorisation applications for plant protection products, as well as to risk managers, for defining the measures to be put in place if needed.

To find out more, visit:

Phytopharmacovigilance fact sheets

Phytopharmacovigilance: the only vigilance scheme of its kind in Europe. Vigil'Anses no. 3.

Consumption of pine nuts: report any lingering bitterness!

Although pine nuts are highly nutritious oil seeds rich in fatty acids, vitamins and minerals and are commonly used in cooking, certain species are not edible.

Some pine nuts can cause a taste disturbance called "dysgeusia", which occurs 24 to 48 hours after consumption and can last for several days. While the reported symptoms are mild and without known sequelae, they are particularly unpleasant, with poisoned individuals describing a metallic and/or bitter taste exacerbated by the consumption of food.

In France, the first case was reported to the poison control centre (PCC) in Strasbourg in 2008. A retrospective study conducted from March 2008 to January 2010 then found more than 3,000 similar cases reported to the PCC network [1], with an epidemic peak of around 700 cases in August 2009.

This outbreak, widely reported on internet forums, was global, being observed at the same time in Europe, the United States and Australia.

Investigations have shown that it was due to the consumption of newly marketed species of pine nuts from China: *Pinus armandii* and to a lesser extent *Pinus massoniana*.

These species, not listed as edible by the Food and Agriculture Organization of the United Nations (FAO), were exported in 2009 by traders wishing to take advantage of the large increase in the price of edible pine nuts (*Pinus pinea*, *Pinus koraiensis*, etc.). This led the Chinese authorities to put in place strict measures for the export of their pine nuts (approval of exporters by the authorities, mandatory listing of the botanical and common names – in English – of the pine nut species on the bags, etc.), and European import controls on pine nuts were reinforced.

In order to distinguish edible from inedible pine nuts, ANSES published an opinion in 2010 [2] recommending the use of morphological (1) and chemical (2) criteria: (1) visual sorting and sieving of pine nuts, as the inedible ones are smaller, less angular and duller than the edible ones (see photograph); (2) analysis of the fatty acid composition, as the profiles for certain types of unsaturated fatty acids vary according to the pine nut species (Destaillats index). However, no genetic criterion for differentiating pine nut species is currently available.

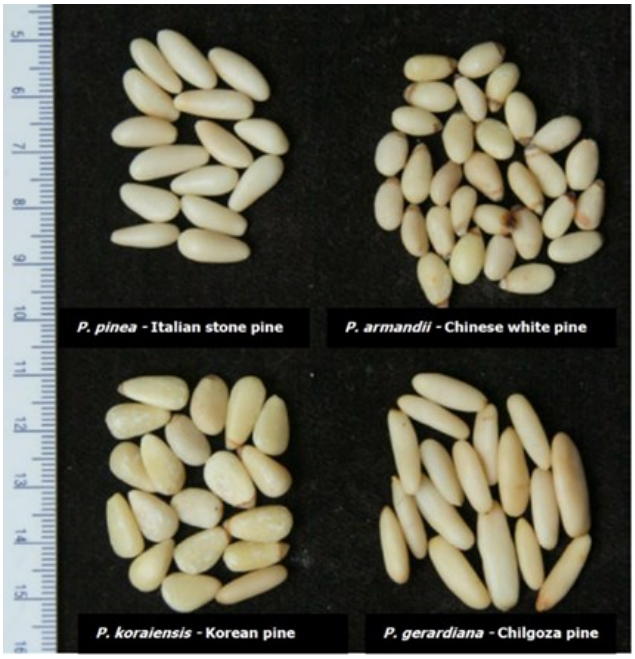

Photo: Examples of pine nut varieties (samples from France, Switzerland and the Netherlands) [4]. According to the FAO, the species *Pinus pinea*, *Pinus koraiensis* and *Pinus gerardiana* are edible, while the species *Pinus armandii* is not.

Then in late July 2017, following a new case reported by a doctor, the Directorate General for Competition, Consumer Affairs and Fraud Control (DGCCRF) asked ANSES to find out whether cases of dysgeusia were persisting. ANSES and the PCC network therefore produced a new list of cases of exposure to pine nuts reported to the PCCs between 1 January 2010 and 31 September 2017.

This new study [3] showed that while the number of pine nut exposure cases reported to the PCC network had fallen sharply between 2010 and 2012, from about 200 to five cases per month, cases were still being regularly observed several years after the alert: about 10 to 15 per month in 2014, and 5 to 10 cases per month since then.

A total of 1,960 cases of symptomatic exposure to pine nuts were registered in the French PCC national database (SICAP) from 2010 to September 2017, of which 1,949 involved dysgeusia, alone or associated with minor digestive symptoms; the remaining 11 cases presented only a few digestive signs (nausea, vomiting, etc.).

The individuals concerned by the cases were predominantly female (sex ratio 0.60) and 39 years of age on average. While only 0.6% were under 5 years of age, the minimum age was 2 years, which in practice corresponded to reports by parents who had themselves presented with dysgeusia following a family meal. They had also observed a loss of appetite in their children and so assumed that they had experienced the same unpleasant taste.

All the symptomatic cases were mild. An 8-year-old child suffered an anaphylactic shock (allergic reaction that is life-threatening if untreated) due to an allergy to pine nuts. The symptoms regressed after the child was immediately taken to a hospital emergency department. It should be noted that allergy to pine nuts can occur with both edible and inedible species.

The dossiers on the most recent cases were reviewed to search specifically for information on the purchase of pine nuts. Among the 156 cases reported from January 2015 to September 2017, this information was mostly only partial: trade names were identified for only 29 cases (19%), and the origin of the pine nuts for only 26 cases (17%). It should be noted that the place of purchase, the brand name and the batch number were all known in only five cases (3%). Most of the time, the people questioned could not remember exactly where they had bought the products, had not kept the packaging, and could not give details, even for cases where the people were contacted afterwards by telephone or post (some PCCs conducted follow-up).

Considering the cases where the necessary information for an investigation was available, the PCCs issued five alerts to the regional health agencies (ARS) during this period (2015-2017). An investigation was carried out in April 2015, but no inedible pine nuts were found in samples taken from an unopened bag of the same brand from the same shop, but with a different batch number from the one that caused the poisoning.

At present, although the occurrence of dysgeusia seems to be related to the consumption of certain Asian varieties of pine nuts, the precise cause and mechanism of the taste disturbance have still not been determined. Genetic variations ("genetic polymorphisms") are thought to lie behind the "sensation" of bitterness, which varies among individuals. This could explain why only some consumers experienced dysgeusia. Research into the neurotoxic mechanisms that may be responsible for the protracted nature of these taste disorders should be encouraged.

Some time after the initial alert, it therefore remains important to collect any information useful for investigating each case of dysgeusia reported following pine nut consumption (source, trade name and batch number, place and date of purchase, expiry date, etc.).

This is why ANSES and the PCC network are continuing their surveillance and developed a specific questionnaire to collect all relevant data when disorders related to pine nut consumption are reported to a PCC [3].

So, if you notice a bitterness that lingers after consuming pine nuts, do the right thing... report it to a poison control centre, making sure to keep and specify any useful information on the purchase of these pine nuts!

Sandra SINNO-TELLIER (Anses)

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[1] Flesch F, Daoudi J. Pignons de pin et dysgueusie retardée [Pine nuts and delayed dysgeusia]. Internal request by the Toxicovigilance Coordination Committee, October 2010, 19 p.

http://www.centres-antipoison.net/cctv/Rapport_CCTV_Pignons_de_pin_2010.pdf

[2] ANSES Opinion of 26 July 2010 concerning the implementation of an experimental protocol for the analysis of pine nuts https://www.anses.fr/fr/system/files/RCCP2009sa0289EN.pdf

[3] Sinno-Tellier S, Tournoud C. Dysgueusie associée à la consommation de pignons de pin : note d'actualisation des cas rapportés au réseau des Centres antipoison entre le 1er janvier 2010 et le 30 septembre 2017 [Dysgeusia associated with pine nut consumption: update note on cases reported to the network of poison control centres between 1 January 2010 and 30 September 2017]. Internal request by the Toxicovigilance Coordination Committee, December 2017, 19 p.

http://www.centres-antipoison.net/CCTV/Pignons_de_pin_Rapport_CCTV_Vf.pdf

[4] Zonneveld, B.J.M. Pine nut syndrome: a simple test for genome size of 12 pine nut-producing trees links the bitter aftertaste to nuts of *P. armandii* Zucc. ex Endl. Plant Syst Evol (2011) 297: 201-206.

Crisis of eggs contaminated with fipronil : contribution of the Poison Control Centres

On 20 July 2017, the Belgian authorities informed the EU Member States and the European Commission via the Rapid Alert System for Food and Feed (RASFF) of the presence of fipronil in eggs and poultry meat, detected during checks in various production facilities. These products had been exported to many countries in Europe and beyond. The first alert concerning the export of contaminated products to France was issued by the Netherlands on 5 August.

Fipronil is an insecticide active substance that is no longer approved for plant protection use in Europe; it has approval as a biocidal active substance (product type 18: insecticide and acaricide) and as a veterinary antiparasitic for the treatment of pets. However, it is not authorised as a medicine for treating livestock intended for human consumption. So-called "natural" plant-based pest control products containing fipronil, marketed under the names DEGA 16 and COOPER BOOST, had been used in poultry farms in the Netherlands and Belgium, both as an environmental spray during fallowing and directly on the animals for antiparasitic treatment, resulting in contamination of eggs and meat from these animals and consequently, consumer exposure.

Fipronil is a neurotoxic substance that interferes with the normal inhibitory action of gamma-aminobutyric acid (GABA) receptors, resulting in excessive neuronal excitation. It is classified as toxic by ingestion, dermal contact and inhalation, as well as by repeated exposure due to its neurotoxicity. Toxicovigilance data collected from humans in the workplace[1] show that the effects resulting from acute exposure to preparations containing fipronil are usually mild. In the case of eye splashes, skin contamination or exposure to aerosols, the only disorders observed are generally mild signs of local irritation. In view of fipronil's mechanism of action and experimental data, the effects expected in the event of acute systemic poisoning are neurotoxic, mainly with convulsions.

On 7 August, ANSES was asked by the Ministries of Agriculture, Health and Consumer Affairs to assess the risk to consumers exposed to fipronil in light of the concentrations observed in contaminated eggs. Alongside the conventional risk assessment, which was based on estimating the ingested dose of fipronil according to the type of food then comparing this to the ARfD[2] of fipronil, ANSES asked the network of French Poison Control Centres (PCCs) to conduct a study of cases of human exposure to fipronil reported to them.

A search for commercial mixtures containing fipronil was conducted in the National Database on Products and Compositions (BNPC) of the PCCs' information system (SICAP)[3]: 88 agents containing fipronil were identified.

Cases of exposure to these agents between 1 January 2011 and 30 June 2017 were extracted from SICAP. This found 356 cases of accidental symptomatic poisoning with non-null causality[4]. The analysis focused on the 107 cases of oral poisoning, because cases of exposure via the dermal and/or ocular route alone were not relevant for a risk assessment of fipronil in foodstuffs.

Around half of cases concerned children under 10 years of age (52.3%). The vast majority of poisonings were of low severity (95.3%). Only four cases were of moderate severity (4.7%), three of which concerned children. No cases of high severity were found.

For these 107 cases, various symptoms were reported such as vomiting (36%), oropharyngeal irritation (33%), abdominal pain (20%) and diarrhoea (11%).

1. https://www.anses.fr/fr/system/files/RCCP-Ra-Fipronil.pdf

2. The acute reference dose (ARfD) is the maximum amount of active substance, expressed in mg/kg body weight, that can be ingested by the consumer in food or drinking water over a short period, i.e. during a meal or a day, without any adverse effect on health.

3. When a call is received by the toxicology emergency telephone hotline (RTU) of a poison control centre, a medical record is created. This contains information on the person(s) exposed, the agents involved, the routes of exposure and the symptoms, among other things. It is coded with an agent from the BNPC and then recorded in the National Database of Poisoning Cases (BNCI). These two databases form the PCCs' Information System (SICAP).

4. Causality established according to the method for determining causality in toxicovigilance (Version 7.6 - June 2015), which determines, using five levels (causality excluded I0, unlikely I1, possible I2, likely I3 and very likely I4), the strength of the causal link between exposure to an agent and the occurrence of a symptom, syndrome or disease https://tv.toxalert.fr/v7.6/Calcul_imputabilite_v7.6.html

In 51 cases, the products concerned were biocides for the eradication of insects, while 52 cases concerned commercial veterinary products. For four cases, the category was unknown.

Analysis of these data showed that accidental acute oral poisonings with doses more than 10 times the ARfD, set at 0.009 mg/kg body weight, did not result in systemic and neurological effects. However, PCC dossiers only concerned cases of acute exposure, and there were no cases of chronic exposure.

This example demonstrates the importance of the data collected continuously by poison control centres as part of their emergency telephone hotline activities, and their ability to rapidly provide observed evidence of the human toxicity of a product or substance by querying their information system.

These human toxicity data are an invaluable complement to the opinion that ANSES issued on 10 August 2017 on the acute risk to human health from fipronil in eggs intended for consumption.

Chloé GREILLET (Anses)

TO FIND OUT MORE, VISIT:

ANSES Note on a request for scientific and technical support (STS) regarding the health risk assessment concerning the presence of fipronil in eggs intended for consumption

STS note on the maximum concentration of fipronil not to be exceeded in egg products and other processed products containing eggs, to ensure that consumer exposure remains below the acute toxicological reference value

Do electronic cigarettes cause serious accidents?

Use of electronic cigarette or e-cigarette, almost unknown in 2010, has very quickly become widespread in Europe, where it is seen as a new product that could gradually replace tobacco use, mainly with the aim of stopping smoking altogether. In 2014, INPES[1] (now *Santé Publique France*) stated that 26% of the French population had reported smoking an e-cigarette and more than one and a half million people may use them daily [1].

These electronic cigarettes come with e-liquid refill cartridges or containers containing a solvent (mainly propylene glycol), possibly with nicotine and flavourings (used in food or not). The liquid content of these cartridges or containers could accidentally come into contact with the skin or mucous membranes in the event of a leak, when the cartridge is filled, or if the battery were to explode. These cases of accidental exposure can be hazardous and cause adverse health effects, especially in children.

Do electronic cigarettes cause serious accidental exposure?

To answer this question, a group of expert toxicologists coordinated by the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) retrospectively analysed the cases recorded by French poison control centres (PCCs) between 1 January 2013 and 30 June 2014.

The cases selected for this study corresponded to all accidents, with or without symptoms, related to electronic cigarettes, refills, disposable e-liquid containers or cartridges, with or without nicotine. Cases of deliberate exposure and those where causality[2] was zero were excluded.

In the end, 1,178 cases were identified for the given study period. The age of the exposed subjects ranged from two months to 95 years, with a median at 25 years. Almost half of the subjects in the cases (47%) were aged from 18 to 39 years, which also corresponds to the age group with the highest proportion of e-cigarette users according to INPES (9.6% for men, 6.6% for women) [1].

Children under four years of age accounted for 27% of exposure cases.

Of these 1,178 people, 683 were symptomatic (58%): 32% suffered eye exposure, 57% oral and 5% respiratory exposure.

In the cases of eye exposure, symptoms were almost always observed (88% of cases), with eye redness (64%) and pain (48%) reflecting the irritating nature of the e-liquid.

With oral contact or accidental ingestion of e-liquid, 49% of cases were symptomatic, including mouth and throat irritation (9.3%), vomiting (9.2%) and local pain (8.7%).

No very serious cases were reported among the 683 symptomatic cases. Almost half of the cases of oral contact or ingestion of e-liquid were of low severity, in children under four years of age and adults (there were fewer than 10 cases in children over five years of age and adolescents). For eye exposure, cases mainly concerned people over 18 years of age and were of low severity.

Fewer than 5% of the cases were of moderate severity. As an example, regarding the oral route, two children four to six years of age ingested an e-liquid containing nicotine. The accident occurred because an adult had poured the e-liquid into a glass. Vomiting following ingestion, abdominal pain and pallor were reported. The one case in which progression was known had a favourable outcome. In any event, the quantities ingested seemed to be small, probably due to the unpleasant taste of the e-liquid. Regarding eye exposure, four accidents in adults involving splashes of e-liquid when filling the electronic cigarette caused burning sensations, eye pain, swelling of the eyelids and conjunctival redness. In principle, the splashed quantities were very small and all came from e-liquids containing nicotine. After treatment, progression was favourable for three of them (and was unknown in one case). Lastly, a 12-year-old child mistakenly received an e-liquid instillation in the eye due to confusion with a bottle of eye drops, causing a burning sensation that progressed favourably after treatment. This situation of confusion with a medicine accounted for 4% of eye exposure cases, underlining the need for greater vigilance on the part of users during therapeutic treatment involving eye drops.

1.National Institute of Prevention and Health Education

2.Causality is the link between exposure to the e-cigarette and the patient's symptom. This causality was calculated according to version 7.6 of the method for determining causality in toxicovigilance (the method and a calculator are available at tv.antipoison.fr). When this causality was zero, it meant that the symptoms presented by the exposed individual were not related to the e-liquids, which explains why these individuals were excluded from the study.

The study of exposure circumstances by route showed that for the ocular route, most exposure was due to splashes when filling the electronic cigarette. This high proportion raises issues about the safety of the devices sold. The symptoms observed seemed to relate to an irritative syndrome explained by the irritant or sensitising nature of the e-liquid compounds, particularly nicotine. However, the experts were unable to unequivocally correlate an irritant syndrome with the nicotine concentrations in e-liquids, due to a lack of knowledge or doubts about the nature of the products allegedly involved according to the calls to the PCCs.

Electronic cigarettes were also responsible for symptomatic **respiratory** exposure in vapers at the time of vaping. In some cases, symptoms were reported immediately after vaping, presumably under normal conditions of use of the electronic cigarette, raising the question of nicotine's role in the occurrence of these symptoms. More often, they were individuals who had recently started vaping, in whom a nicotine overdose was suspected. Despite uncertainties during calls to the poison control centres about the exact nature of the products to which individuals were exposed, the observation of these cases raises questions about the information and relevance of the advice received or not by vapers when purchasing electronic cigarettes. Even though the outcome was favourable, the nicotine contained in e-liquids is still a pharmacologically active substance which, even at very low concentrations, can cause toxic effects.

During the study period, two cases of explosion were reported, both symptomatic, with eye pain and conjunctivitis that rapidly improved. An electronic cigarette caught fire and emitted smoke exposing twenty-four people very briefly, showing no symptoms. This is the only recorded case of combustion. Since the study ended, several other cases of explosion have been recorded by the PCCs, some of which have resulted in severe burns.

Since its introduction, the electronic cigarette has stimulated and continues to stimulate scientific and societal discussions on the risks associated with its use, and on its potential benefits in helping people stop or reduce smoking. The acquisition of additional data, through epidemiological or experimental studies, should provide answers to these questions.

According to this review between January 2013 and June 2014, although the severity of the poisoning cases was low or moderate, caution should still be exercised when using e-cigarettes, as well as regarding possible confusion with drug treatments, and accessibility of the devices to children. On this point, regulations now require manufacturers to provide their e-liquid refills with safety caps, which should reduce the exposure of children.

The regulations applicable to e-cigarettes will make it possible to acquire more precise information on the composition of e-liquids. Indeed, the European Directive 2014/40/EU (the Tobacco Products Directive) has been transposed into French law by Ordinance 2016-623, incorporating new provisions in the French Public Health Code (Article L. 3513-1 *et seq.*). By the Decree of 22 August 2017, ANSES has been given responsibility for receiving and analysing the information provided by manufacturers and importers of e-cigarettes and e-liquids containing nicotine. Before they can place their products on the market, these companies will have to submit data on the composition, toxicity and emissions generated by their e-liquids, to a European portal. These data will be analysed to more precisely characterise the risks – particularly the chronic risks to human health – of these new devices.

Cécilia SOLAL (Anses)

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[1] National Institute of Prevention and Health Education (INPES). 2015. Premiers résultats tabac et e-cigarette – Caractéristiques et évolutions récentes. [Initial results for tobacco and e-cigarettes – Characteristics and recent developments.] Results of the INPES 2014 Health Barometer

TO FIND OUT MORE, VISIT:

http://www.centres-antipoison.net/CCTV/CCTV_Rapport_Cigarettes_electroniques_VFINALE.PDF

Hairdressers still at risk of allergy to persulfates found in hair bleach

Persulfates are powerful oxidising agents used in hair bleach and some swimming-pool products (for individual pools or Jacuzzis/hot tubs). These substances are irritating and sensitising for the skin and respiratory tract, and have already been described in numerous scientific publications on occupational asthma and eczema in hairdressers. Sometimes reaching a concentration of 60% in hair bleach, they were found by the French National Network for the Monitoring and Prevention of Occupational Diseases (RNV3P)to be involved in numerous occupational health problems between 2001 and 2009. In 2011, under the European REACh[1] and CLP[2] regulations, the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) identified ammonium, sodium and potassium persulfate salts as priority chemicals involved in work-related allergies. In a scientific opinion published in February 2014 on the best risk management option analysis for these persulfates [1], ANSES confirmed the risk from occupational use of hair bleaching products. The Agency then recommended assessing persulfate salts under the European Cosmetics Regulation[3], which falls within the remit of the ANSM[4] and the SCCS[5].

The RNV3P data were analysed again for the period 2001-2015 to assess recent trends in diseases related to persulfate exposure, as part of a doctoral thesis in medicine [2]. The study selected patients for whom the conclusion of their consultation in an occupational pathology consultation centre (CCPP) was "occupational disease possibly related (causality not excluded) to exposure coded as 'persulfate', 'oxidants' and 'bleach (cosmetics)' or 'bleach, hair lightening'". Patients for whom one of the following keywords appeared in the free-text part of the RNV3P dossier were also included: persulfate, peroxymonosulfate, swimming pool, commercial products containing peroxymonosulfates, if and only if a possible link between the disease and this exposure was specified.

The observed diseases were grouped into three main categories – asthma, rhinitis and allergic contact dermatitis (ACD) – and studied separately.

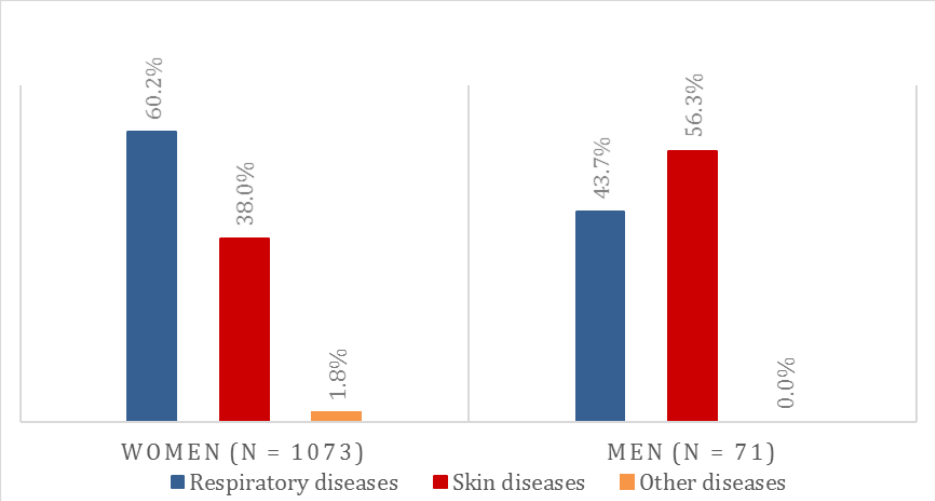

Figure 1: Distribution of diagnosed diseases related to persulfate exposure, and by gender.

1. 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)
2. Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures
3. Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products
4. French Health Products Safety Agency
5. European Commission's Scientific Committee on Consumer Safety

During the study period, 1,144 patients were registered as having a disease possibly related to persulfate. The vast majority of these were women (94%), with an average age of 29 (versus 34 years for men). One in four patients was an apprentice, despite them accounting for only 1.5% of all patients seen in the CCPPs. Not surprisingly, the most widely represented industry sector was hair and beauty (98% of cases).

Women were more likely to have a respiratory disease (asthma or rhinitis), while men were more prone to skin diseases (Figure 1). Of the other diseases observed in women, conjunctivitis was the main one.

The time trend analysis showed that the role of persulfates in cases of asthma related to occupational exposure fell by 74% between 2001 and 2015 (Figure 2), and by 68% for rhinitis (Figure 3). In contrast, persulfate-related allergic contact dermatitis (ACD) remained stable over this period (Figure 4).

The impact on these trends of improved protective measures (for asthma and rhinitis) on these trends, or their persistent inadequacy (for ACD), has yet to be demonstrated by appropriate studies in the workplace.

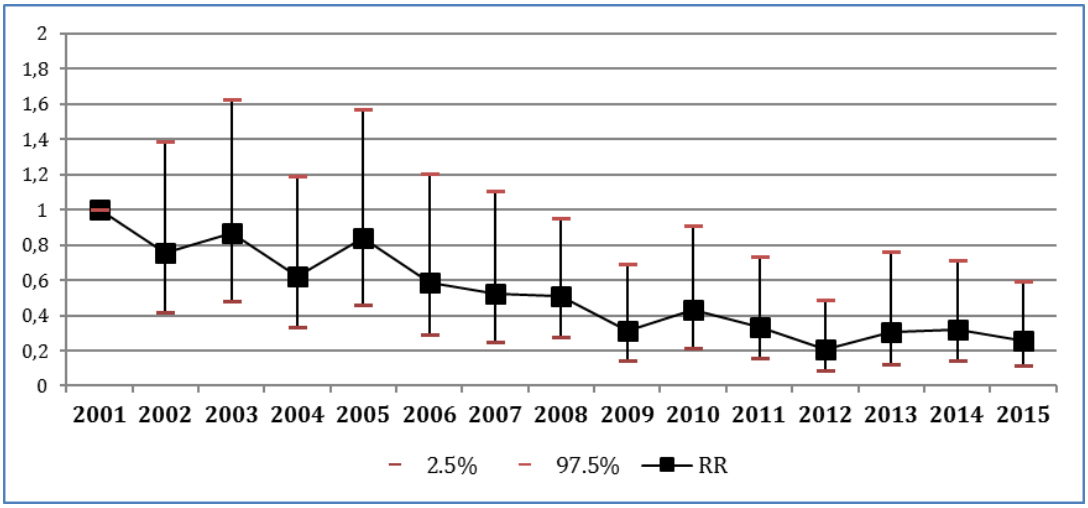

Figure 2: Relative risk (RR) of persulfate-related asthma compared to 2001, adjusted for age, reporting year, number of non-persulfate-related asthma cases, and 95% confidence interval.

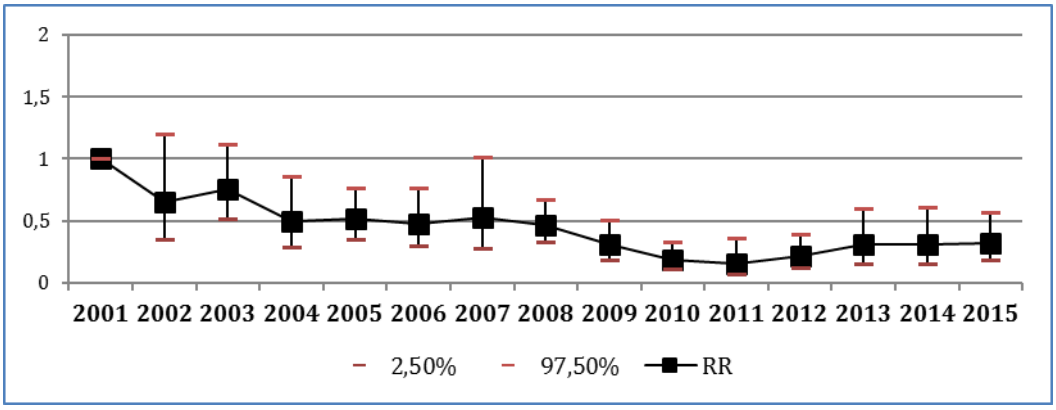

Figure 3: Relative risk of persulfate-related rhinitis compared to 2001, adjusted for age, reporting year, number of non-persulfate-related rhinitis cases, and 95% confidence interval.

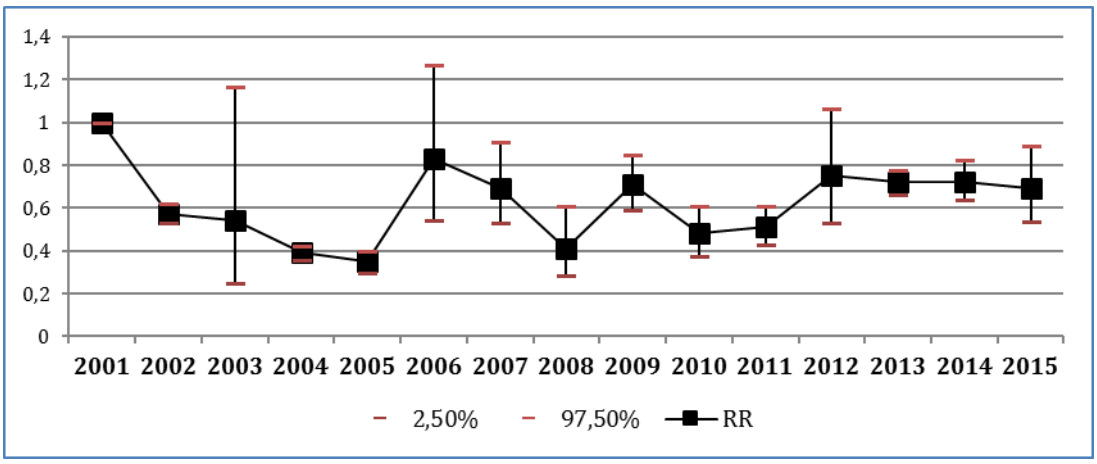

Figure 4: Relative risk of persulfate-related ACD compared to 2001, adjusted for age, reporting year, number of non-persulfate-related ACD cases, and 95% confidence interval.

The early onset of these diseases in professional life in the hair and beauty sector, and their finality once the allergy has become established, underline **the need to further strengthen personal and collective preventive measures** to address the risks associated with persulfate exposure. Apprentices, who are particularly exposed, should be trained in these risks as soon as possible.

Measures could include opting to use hair bleach in granular or cream form rather than powder, as well as "closed-loop" packaging that enables products to be mixed without opening the packets. General ventilation of the room where the hair treatment is applied is essential, along with cleaning of all surfaces with a damp cloth. Lastly, the use of work gloves during bleach preparation, application and rinsing, as well as when cleaning equipment, is key to prevention of contact dermatitis.

Juliette BLOCH (Anses)

To find out more, visit

[1] Opinion of the French Agency for Food, Environmental and Occupational Health & Safety on the best risk management option analysis for cosmetic uses of potassium, ammonium and sodium persulphates (6 February 2014)

[2] Tomas-Bouil Aurélie. Étude des cas d'exposition professionnelles et non professionnelles aux persulfates dans les dispositifs de vigilance [Case study of occupational and non-occupational exposure to persulphates in vigilance schemes]. Thesis for the State diploma of Doctor of Medicine. University of Versailles-Saint-Quentin en Yvelines. December 2017. https://www.anses.fr/fr/content/réseau-national-de-vigilance-et-de-prévention-des-pathologies-professionnelles-rnv3p

Toxicovigilance in agriculture: the Phyt'attitude network

Phyt'attitude is a vigilance network created in 1991 by the Agricultural Mutual Insurance Scheme (MSA) and generalised to all départements of metropolitan France in 1997. It works to record and analyse all information on accidents, incidents and health effects occurring during the use of chemical products (plant protection products, biocides, veterinary medicinal products, others) by employees and operators in the agricultural sector and certain related sectors, such as plant nurseries, maintenance of green spaces, etc., in order to improve prevention by reporting information to manufacturers and public authorities. Reports are then analysed to identify the acute and subacute adverse effects of these products, in order to develop collective and individual preventive measures through recommendations to users, while taking the real working conditions into account.

The Phyt'attitude network operates on the principle of voluntary reporting of adverse events immediately after their occurrence via a freephone number, which has been in operation since 2004[1]; these health events can also be reported during periodic medical check-ups or company visits.

A dense network covering the entire country

The network is based on the 35 MSA funds and particularly the occupational health and safety departments and their multidisciplinary teams (occupational physicians, nurses specialised in occupational health, prevention advisors). Symptoms suspected to be related to the handling or contact with these products are reported by occupational physicians. These reports may concern situations of acute exposure or the delayed occurrence of diseases following chronic exposure, which are dealt separately. The information collected includes anonymised medical data, the names of the suspect products and details of the exposure (industry sector, crop, task, temperature and wind conditions, equipment, etc.), including collective and individual preventive measures used (type of tractor cab, personal protective equipment, etc.). Report collection is often accompanied by a technical investigation conducted by a prevention advisor at the place of exposure.

Dossiers relating to "acute" diseases are then sent to a toxicology expert, who assigns causality[2] to each "symptom/product" pair. The findings of each investigation are sent by the toxicology expert to the reporting physician and the MSA Central Fund (CCMSA). Product causality is not assigned for chronic or delayed diseases.

All reports relating to plant protection products, biocides or veterinary medicinal products are entered into the Phyt'attitude database, which is managed by the CCMSA.

A few figures

From when the Phyt'attitude network was rolled out across the country up to 30 December 2016, a period of almost 20 years, a total of 3,506 dossiers were transmitted. Nearly 85% of them concerned "acute" cases, while 15% were related to chronic or delayed diseases. It should be noted, however, that over the last 10 years, transmission of dossiers on chronic or delayed diseases has continued to grow, with them now accounting for 23% of all dossiers transmitted on average.

Over the period 2011-2014, 409 dossiers concerning acute diseases related to plant protection products were registered; the causality in 226 of these was higher than I1.

Men accounted for 79% of the reports, reflecting their predominance in the agricultural population of plant protection product users.

The occupational categories "Farmer" (31%) and "Agricultural employee" (66%) together accounted for 97% of attributable reports. Of these 97%, women accounted for 22% of reports and were most often agricultural employees (90%), with just 10% of them being farmers. Half of the women were indirectly exposed when working on recently treated plots, in the vicinity of ongoing treatment or when handling treated seeds. Nearly 35% of reports concerned a specialised crop sector such as cereals, floriculture, market gardening, endives, nurseries, arboriculture or mushroom farming. Viticulture alone accounted for 22% of reports (Figure 1).

1. 0 800 887 887

2. This method is derived from the official French method used in pharmacovigilance for determining causality, which was developed in 1978 by J. Dangoumou, J.C. Evreux and J. Jouglard and updated in 1985 by B. Bégaud, J.C. Evreux, J. Jouglard and G. Lagier. Causality is rated from I0 to I4: excluded, unlikely, plausible, likely, very likely.

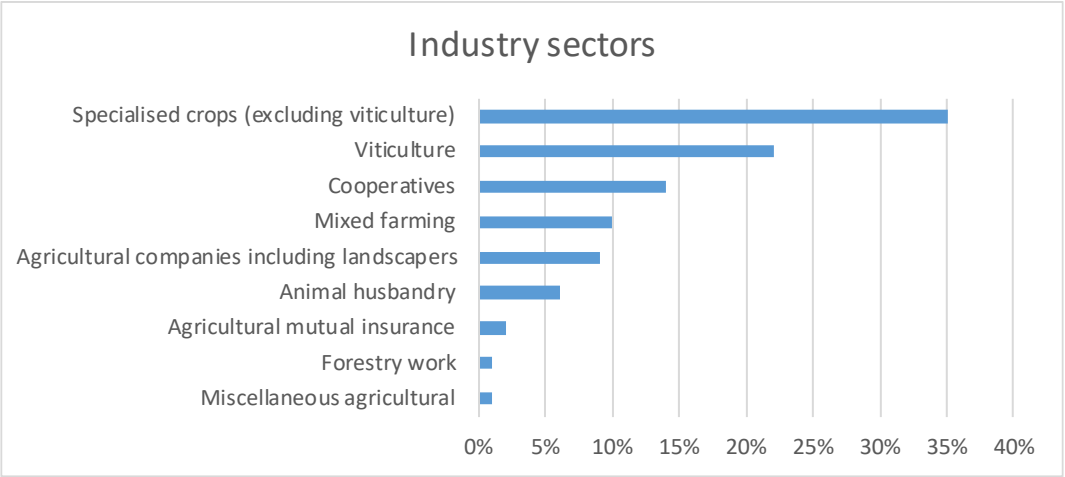

Figure 1: Industry sectors concerned by reports

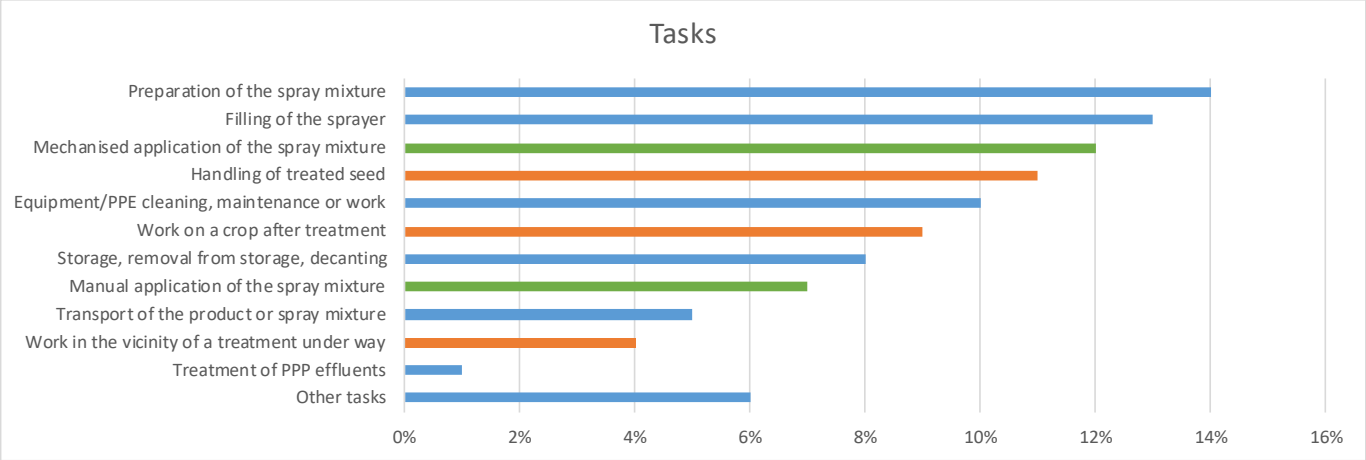

Figure 2 : Tasks being performed at the time of the incident

Among the tasks being carried out at the time of the incident, the phases of preparing the mixture and filling equipment were the most commonly reported, along with mechanised and manual application tasks. Despite a significant decrease in this use, manual application of the mixture is still common in the flower, ornamental tree, green spaces and viticulture sectors (56%) (Figure 2).

Twenty-six per cent of the dossiers reported an incident (mechanical, meteorological or related to personal protection), with 20% of them involving rupture of the equipment (cans, clamps, hoses, etc.) and 14% a fault with the personal protective equipment (tearing, soiling). Furthermore, in half of the reports, the subjects wore gloves for all tasks; if these are broken down, 77% wore gloves when preparing the mixture, 69% when applying it and 59% when filling and cleaning the equipment. Lastly, 64% said they showered at the end of the day and only 13% immediately after exposure.

There was a total of 392 products included in all dossiers in the period 2011-2014, the most common being fungicides followed by insecticide-acaricides, with 35% and 33% of all products respectively. More than 40% of the attributable reports mentioned the use of two or more plant protection products (Figure 3).

In the reported cases, the liquid form[4] of plant protection products was mentioned most often. For all disorders/symptoms and regardless of the formulation, skin symptoms were most commonly reported, followed by neurological/neuromuscular and hepato-digestive symptoms (Figure 4).

Fungicides and herbicides mainly induced skin symptoms, whereas insecticide-acaricides mainly generated neurological/neuromuscular disorders/symptoms. Medical intervention was required in 35% of reports, and hospitalisation in 3% of cases (6 out of 226).

4. As opposed to "wettable powder", "water-dispersible granules" and miscellaneous forms.

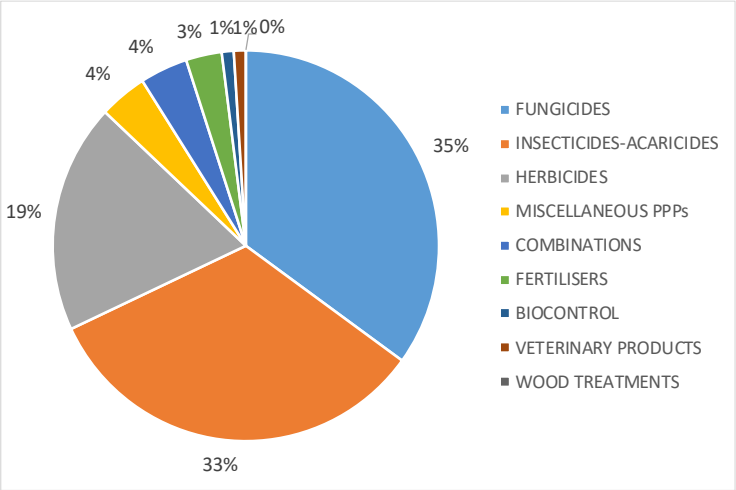

Figure 3: Categories of products used

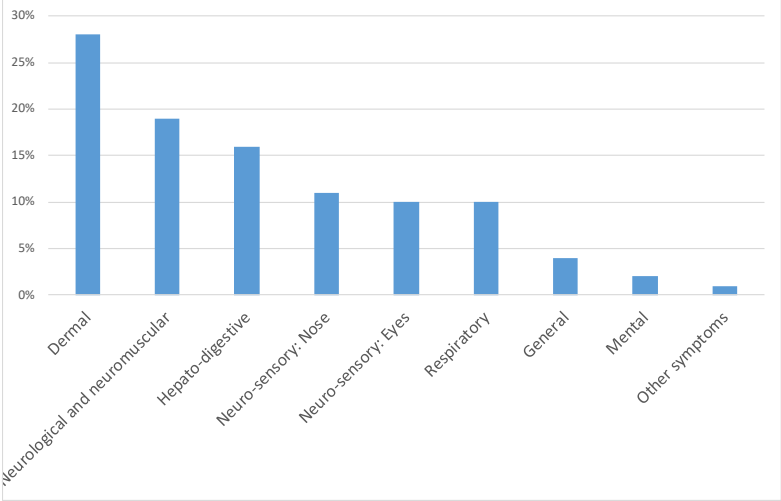

Figure 4: Types of symptoms

Phyt'attitude and ANSES

Cooperation on the use of data from the Phyt'attitude database was established between AFSSA[5] and the CCMSA in 2007, when the Agency was first entrusted with the assessment of plant protection products; this then continued with ANSES. Phyt'attitude data are analysed and systematically integrated into the conclusions of the plant protection product assessments conducted by ANSES.

For each active substance, the CCMSA thus extracts data from the Phyt'attitude database to identify all the reports available since 1997 involving at least one plant protection product containing the substance.

The purpose of the analysis is to identify symptoms that can be objectively attributed to the active substance and the product under assessment; another objective is to identify tasks or other potentially exposing factors that could call into question the conditions of use of a plant protection product containing this active substance in an occupational setting. In addition, data on active substances are included as far as possible in European RARs[6] and in the "substance" data sheets published by ANSES as part of the phytopharmacovigilance scheme. Lastly, these data provide invaluable information for ANSES's opinions in response to formal requests, such as the one on the health effects of neonicotinoids.

5. AFSSA: the French Food Safety Agency, which later became ANSES after merging with AFSSET (the French Agency for Environmental and Occupational Health Safety).
6. Renewal Assessment Report: monographs on active substances.

Aiming for a European toxicovigilance scheme for plant protection products

As with any vigilance scheme, the reports are neither exhaustive nor representative of every health effect, since the scheme is based on the principle of voluntary reporting. To raise awareness about this network among the farming community and encourage reporting, the CCMSA, in conjunction with the National Institute of Agricultural Medicine (INMA), has undertaken a number of initiatives, particularly with training for the Certiphyto certificate (mandatory for all users, advisors and sellers of plant protection products), during which specific information on Phyt'attitude is provided.
In spite of these limitations, the Phyt'attitude network has proved its value in the post-marketing authorisation (MA) monitoring of the effects of plant protection products in the field of occupational health, through its ability to provide accurate information based on feedback from the field that combines medical, technical and contextual data. This toxicovigilance scheme developed by the CCMSA is currently the only one in Europe to operate in the area of plant protection products, and it could be useful to replicate this example on a European scale in order to increase its effectiveness, following the example of the European pharmacovigilance scheme for human and veterinary medicinal products. This is one of the recommendations contained in the recently published EFSA Opinion[7] on taking epidemiological studies and vigilance data into account in risk assessments of plant protection products.

Marie-Odile RAMBOURG

TO FIND OUT MORE, VISIT:

http://www.msa.fr/lfy/sst/phyt-attitude/

7. Scientific Opinion of the PPR Panel on the follow-up of the findings of the External Scientific Report. "Literature review of epidemiological studies linking exposure to pesticides and health effects" EFSA Journal 2017;15(10):5007 [101 pp.].

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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