The Director General

Maisons-Alfort, 10 August 2017

NOTE
of the French Agency for Food, Environmental and Occupational Health & Safety

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

ANSES undertakes independent and pluralistic scientific expert assessments.
ANSES's public health mission involves ensuring environmental, occupational and food safety as well as assessing the potential health risks they may entail.
It also contributes to the protection of the health and welfare of animals, the protection of plant health and the evaluation of the nutritional characteristics of food.

It provides the competent authorities with the necessary information concerning these risks as well as the requisite expertise and technical support for drafting legislative and statutory provisions and implementing risk management strategies (Article L.1313-1 of the French Public Health Code).

Its opinions are made public.
This note is a translation of the original French version. In the event of any discrepancy or ambiguity the French language text dated 10 August 2017 shall prevail.

On 7 August 2017, ANSES received a formal request from the Ministries of Agriculture, Health and Consumer Affairs for scientific and technical support on the risks to human health associated with the presence of fipronil in eggs intended for consumption.

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1. BACKGROUND AND PURPOSE OF THE REQUEST

On 20 July, the Belgian authorities informed the European Commission *via* the European food and feed safety alert network (RASFF) that high levels of fipronil had been detected in eggs and poultry meat (conventional and organic).

Fipronil is an active substance authorised at European level as a plant protection substance for the following uses: treatment of seeds intended to be sown in greenhouses as well as for crops such as onions, shallots, leeks and some vegetables of the Brassicaceae family intended to be sown in open fields and harvested before flowering. The treatments that were previously authorised, in particular for oilseed rape, sunflower, maize and potato, have been prohibited since 2013, with a grace period until February 2014. As a result, there are no longer any uses intended for animal feed[1] or for crops attractive to bees. No plant protection preparation containing fipronil is currently authorised in France.

Fipronil is also an active substance authorised at European level as a biocidal substance. Biocidal products containing fipronil have been authorised in France, mainly products for use against ants or

[1] European Food Safety Authority, 2014. Reasoned opinion on the modification of maximum residue levels (MRLs) for fipronil following the withdrawal of the authorised uses on kale and head cabbage. EFSA Journal 2014;12(1):3543, 37 pp. doi:10.2903/j.efsa.2014.3543

cockroaches. The uses of these products do not lead to direct or indirect exposure of the consumer *via* food.
Fipronil is also authorised in France as an antiparasitic in veterinary medicinal products for pets. It is not authorised for the treatment of livestock intended for consumption. No consumer exposure *via* food is therefore expected for such uses.

The investigations carried out in Belgium demonstrated the presence of this substance in "natural" plant-based antiparasitic products that had been adulterated. These products were marketed under the names DEGA 16 and COOPER BOOST, and were used in poultry farms.

The recommended uses of DEGA 16, in its non-falsified version, are for spraying in the environment during fallowing or directly on animals for antiparasitic treatment of hens (control of red lice).

More than 60 farms in Belgium and 180 in the Netherlands have been blocked because of the suspected presence of fipronil in products of animal origin, due to the probable use of this antiparasitic in these farms. The number of farms affected is still provisional, as the analysis of thousands of samples taken in the Netherlands and in Belgium is still in progress.
In Belgium, a criminal investigation was launched for fraud by the supplier of the product used. The Dutch and Belgian authorities are simultaneously conducting investigations to trace the marketing channels for the contaminated batches. Several European countries are currently affected.

In this context, ANSES was asked to address the following three issues:

- Analyse the available toxicological data relating to fipronil in light of the risk to humans by ingestion of contaminated foods;
- Conduct an assessment of the risk to previously identified populations (young children, pregnant women, adults) associated with the consumption of contaminated poultry products (eggs, meat);
- Formulate risk management recommendations for processed products in which contaminated eggs may have been incorporated.

These issues were examined within the Regulated Products Assessment Department, the Risk Assessment Department, the Health Monitoring and Alerts Department and the French Agency for Veterinary Medicinal Products.

2. AVAILABLE TOXICOLOGICAL DATA RELATING TO FIPRONIL IN LIGHT OF THE RISK TO HUMANS BY INGESTION OF CONTAMINATED FOODS

TOXICOLOGICAL PROFILE OF FIPRONIL

The data below reflect the conclusions of the assessment in the framework of the European procedure for approving plant protection[2] and biocidal[3] active substances.
A harmonised classification is also available (Regulation (EC) No 1272/2008).

1. Absorption, distribution, metabolism, elimination (toxicokinetics)

Fipronil is rapidly and extensively absorbed by the oral route (nearly 100%). It is extensively metabolised and distributed in the body, with an affinity for adipose tissue. It is eliminated slowly by

[2] EFSA (2006). Conclusion regarding the peer review of the pesticide risk assessment of the active substance fipronil; finalised: 3 March 2006, revised 12 April 2006. EFSA Scientific Report (2006) 65, 1-110

[3] Assessment Report (2011). Inclusion of active substances in Annex I or IA to Directive 98/8/EC: Fipronil, Product type PT18 (insecticides, acaricides and products to control other arthropods); finalised: 6 May 2011.

the faeces, urine and bile. This slow elimination is mainly related to the extensive distribution in adipose tissue and the gastrointestinal reabsorption after elimination of bile.

2. Acute toxicity – irritation – sensitisation

Fipronil has moderate toxicity after single oral, dermal and inhalation exposure. It has been classified at European level (ATP 10 of Regulation (EC) 1272/2008) for acute toxicity in Category 3 for the oral route (H301), for the dermal route (H311) and by inhalation (H331).

3. Subchronic toxicity

The short- and medium-term effects of fipronil were studied by the oral route in 28-day and 90-day studies in rats and dogs, as well as in 1-year studies in dogs. Toxicity by the dermal route was also studied in rabbits after exposure for 21 days.

The target organs identified were essentially the central nervous system in all species, the liver in rats and dogs, and the thyroid gland in rats only.
The observed effects were clinical signs such as neurological disorders including convulsions, tremor, abnormal posture etc., an increase in liver weight associated with hepatocyte hypertrophy, and follicular hypertrophy/hyperplasia of the thyroid. Few neurological effects have been reported in rats.
A no observed adverse effect level (NOAEL) of 0.35 mg/kg/d was established for the oral route at European level on the basis of these effects in dogs (90-day and 1-year studies) and in rats (90-day study). This dose was used to establish the acceptable level of operator exposure in the framework of the plant protection regulations and the medium-term acceptable exposure level (medium-term AEL) in the framework of the biocide regulations.

For the dermal route, a higher no observed adverse effect level (NOAEL) of 5 mg/kg/d was established at European level on the basis of the neurotoxic effects observed in rabbits.

4. Genotoxicity

Five *in vitro* studies (Ames, chromosomal aberration tests and genetic mutation tests) as well as three *in vivo* studies (micronucleus tests and UDS test) were carried out to investigate the genotoxic potential of fipronil.

The *in vitro* tests were interpreted as negative, with the exception of the chromosomal aberration test on Chinese hamster lung cells, which was positive at cytotoxic doses with and without metabolic activation. However, as the *in vivo* tests were interpreted as negative, fipronil was not considered genotoxic in the European assessments.

5. Chronic toxicity and carcinogenicity

The long-term effects of fipronil were studied by the oral route in rats in a 2-year study and in mice in an 18-month study.

In rats, effects on the liver, thyroid and kidney were observed at the highest dose (12 mg/kg/d).
A dose-dependent incidence of convulsive episodes was also observed at all doses, except for the lowest one (0.019 mg/kg/d). Mild effects on circulating T4 hormones and cholesterol levels were noted at a low dose, but were not regarded as relevant from a toxicological point of view.
Therefore, **a no observed adverse effect level (NOAEL) of 0.019 mg/kg/d was established at European level. This dose was used to establish the acceptable daily intake (ADI) in the framework of the plant protection regulations and the long-term acceptable exposure level (long-term AEL) in the framework of the biocide regulations.**

At the highest dose (12 mg/kg/d), an increase in the incidence of thyroid tumours was observed. However, all the available mechanistic data in the dossiers led the European experts to conclude that these tumours were not relevant for humans.
Taking into account the results of these mechanistic studies, it was established that these tumours were specific to rats and were induced by a disruption of the hypothalamic-pituitary-thyroid axis, rather than a direct effect of fipronil.

In mice, a decrease in weight gain and an increase in liver weight associated with an increase in the incidence of hepatocyte vacuolation were observed. A no observed adverse effect level of 0.05 mg/kg/day was proposed. No carcinogenic effect was observed.

Fipronil was not regarded as a carcinogen in the framework of the European assessment.

6. Reprotoxicity

The effects of fipronil on the reproductive parameters were studied in a two-generation reproductive study in rats and in two teratogenicity studies in rats and rabbits.

Fertility
In the two-generation reproductive study, effects on the liver and thyroid were observed at doses greater than or equal to 2.5 mg/kg/d, and a decrease in weight gain associated with a decrease in food consumption and neurotoxicity was observed at 25 mg/kg/d.
A slight decrease in mating and in the fertility index was observed at the toxic dose of 25 mg/kg/d. Reduced viability, neurotoxicity and delayed development were observed in the offspring at this same dose. Consequently, a no observed adverse effect level (NOAEL) for general toxicity was set at 0.25 mg/kg/d and a NOAEL for reproduction at 2.5 mg/kg/d.

Teratogenicity
In the teratogenicity studies in rabbits and rats, no effect on litter parameters or on embryo-foetal development was observed. The only effect observed was that of a decrease in maternal weight. The rabbit is the most sensitive species, with a maternal NOAEL of 0.2 mg/kg/day and a NOAEL for development greater than 1 mg/kg/d. In rats, these doses were respectively 4 mg/kg/d and greater than 20 mg/kg/d.
Thus, in the European assessments, fipronil was not regarded as toxic to reproduction.

7. Neurotoxicity

This toxicity was examined through different studies provided in the framework of the European dossiers.

In two acute neurotoxicity studies in rats, neurotoxic effects (decrease in motor activity, mobility) were observed without any neuropathological changes. A NOAEL of 2.5 mg/kg/d was established at European level.
This dose was used to establish the short-term acceptable exposure level (short-term AEL) in the framework of the biocide regulations.

In a study in dogs exposed for 14 days, functional observations (without histopathological changes) and a loss of body weight were observed at the single tested dose of 20 mg/kg/d.

In a 90-day neurotoxicity study in rats, no neurological effect was reported up to the maximum tested dose of 8.9 mg/kg/d. A NOAEL for general toxicity was established at 0.3 mg/kg/d on the basis of a decrease in body weight and food consumption.

In a developmental neurotoxicity study in rats, neurobehavioural effects without neuropathological effects were observed in the offspring at the dose of 15 mg/kg/d. At this same dose, a decrease in body weight and food consumption were observed in the dams.
NOAELs for developmental neurotoxicity and maternal toxicity were therefore established at 0.91 mg/kg/d. **This dose was used to establish the acute reference dose (ARfD) in the framework of the plant protection regulations.**

A decrease in weight gain of the offspring was also observed during lactation, and a no observed adverse effect level of 0.05 mg/kg/d was established.
It should be noted that this study was not available in the European dossier regarding approval of fipronil as a biocidal active substance at the time of its assessment.
In conclusion, fipronil is neurotoxic for all species tested for single toxicity and/or repeated doses.

The clinical symptoms observed are consistent with a mode of action of fipronil on the GABA-chloride channels of the central and peripheral nervous systems. The neurotoxicity studies show that fipronil's neurotoxicity is pharmacological, and repeated exposure does not lead to histopathological changes in the brain or in other parts of the nervous system.

Thus, fipronil was classified at European level (ATP 10 of Regulation (EC) 1272/2008) for repeated toxicity (STOT RE 1, H372).

8. Toxicity reference values established at European level

bw: body weight

	Value	Type of study/Species	Safety factor	Value	Type of study/Species	Safety factor
	Plant protection			**Biocide**		
Oral absorption	Rapid and nearly 100%					
ADI	0.0002 mg/kg bw/d	Combined chronic/carcinogenicity study in rats (effect of neurotoxicity and on the thyroid)	100	Not established		
Long-term AEL	Not applicable			0.0002 mg/kg bw/d	Combined chronic/carcinogenicity study in rats *(effect of neurotoxicity and on the thyroid)*	100
AOEL (equivalent to medium-term AEL in biocides)	0.0035 mg/kg bw/d	90 days by oral route in rats and 90 days/1 year in dogs *(effects of neurotoxicity, effect on the liver and thyroid)*	100	0.0035 mg/kg bw/d	90 days by oral route in rats and 90 days/1 year in dogs *(effects of neurotoxicity, effect on the liver and thyroid)*	100
Short-term AEL	Not applicable			0.025 mg/kg bw/d	Acute oral neurotoxicity study in rats	100
ARfD	0.009 mg/kg bw	Developmental neurotoxicity study in rats	100	Not established		

The TRVs laid down in the framework of the plant protection product regulation are (respectively for each type of exposure taken into account) equal to or lower than those established in the framework of the approval of the biocidal active substance.

It should be noted that the toxicity of the metabolite MB 46136 (sulfone, included in the definition of the residue in foods, see below) is comparable to that of the parent fipronil. The same reference values are therefore applicable.

REFERENCE VALUES IN LIGHT OF THE RISK TO HUMANS BY INGESTION OF FOOD CONTAMINATED BY FIPRONIL

Consumer risk assessments have been carried out at European level in the framework of the plant protection uses, coordinated by EFSA. The most recent assessment was conducted in 2014[1] in the framework of Article 43 of Regulation (EC) No 396/2005 and led to the establishment of the MRLs currently in force for the substance's use in plant protection products. It also led to the lowering of the MRLs in foodstuffs of animal origin, in particular eggs and poultry tissue.

The fipronil residues found in eggs and poultry meat in July 2017 are the result of fraudulent use of this substance to treat red lice in hens. Fipronil is not authorised for this type of use. The residues found in the eggs exceed the applicable MRLs (0.005 mg/kg, which corresponds to the analytical limit of quantification).

In the plant health context, the applicable MRLs for eggs and poultry meat are related to consumption by the animals of feed produced from treated crops. The information on fipronil presented below comes from the assessment conducted in this context.

1. Reminder of the principles relating to the establishment of MRLs for plant protection products

Maximum residue limits (MRLs) for plant protection products:

- For each plant protection product intended for human consumption, and for each food of plant or animal origin, the nature of the residue is defined at **EU level** (active substance and/or any relevant metabolite(s)).
- Then the residue levels determined from tests carried out according to the proposed farming practice are taken into account. Depending on the distribution of the results, a proposed MRL is established that ensures the compliance of agricultural productions. The MRL thus obtained should ensure that the theoretical consumption of all foods that may contain these residues remains below the toxicity reference values, by applying large safety margins, taking into account the dietary habits of all the **consumer groups in each Member State**.

The principles of establishing an MRL:

- The **MRL for a given food of plant or animal origin** is defined from:
  - The definition of the residues (active substance and/or potential relevant metabolites);
  - The residue levels determined experimentally in the matrix in question following use(s) of the product in the recommended good practice conditions, taking into account all the authorised uses.
- The toxicity reference doses for the active substance in question are defined at **EU level** on the basis of the results of experimental studies conducted in animals.

- The acute reference dose (**ARfD**) is the maximum amount of active substance, expressed in mg/kg body weight/day, that can be ingested by the consumer for a short period, i.e. during a meal or a day, in food or drinking water, without an adverse effect on health;
- The acceptable daily intake (**ADI**) is the amount of substance, expressed in mg/kg body weight/day, that can be absorbed on a daily basis throughout a person's lifetime without any side effects being manifested.

Only MRLs guaranteeing that consumer exposure remains below the values considered to be without risk to health in the short and long term are established.

To this end, the **consumer risk assessment** carried out *a priori* in the regulatory framework for establishing MRLs takes into account:

- The toxicity reference doses for the active substance in question;
- The definition of MRLs in all the raw foodstuffs liable to contain the plant protection active substance; for processed products (wine, beer, etc.), transfer factors are calculated from specific studies.
- The consumption, estimated from acute and chronic models.
  - For each requested use, consumer exposure is calculated taking into account all the other foods of plant or animal origin that may contain this residue. Use on a crop or group of crops intended for human food or animal feed is thus only authorised if the risk to the consumer is considered acceptable.
  - **The risks specific to certain populations that are more vulnerable or that have a special diet (infants, pregnant women, young children) are taken into account.**
  - The consumption data used are those found in EFSA's PRIMo Rev.2 model. This model takes into account the different diets of the consumer groups available within the Member States. The consumption data therefore take into account the different forms in which a food can be found (for example, the "eggs" data includes the amount of "shell egg" as well as the amount of eggs consumed via processed products).

2. Establishment of MRLs for fipronil – from the European dossier for the substance

EFSA's reasoned opinion (2014)[4] summarises the data used to establish the MRLs currently in force.

a/ Toxicity reference values taken into account

The toxicity reference values were assessed at European level in the framework of Directive 91/414/EEC and the data led to the establishment of an ADI of 0.0002 mg/kg bw/d and an ARfD of 0.009 mg/kg bw (see previous section).

b/ Residue definition and establishment of MRLs in plant foodstuffs

The nature and concentration of residues in plants resulting from authorised uses of fipronil led to a residue definition for enforcement and risk assessment: sum of fipronil and its sulfone metabolite MB43136 expressed as fipronil. Validated analytical methods for enforcement were available with a LOQ of 0.005 mg/kg in high oil content, high water content and dry matrices. The number of residue trials was sufficient to estimate the expected level of residues in the treated crops considered in this assessment. On the basis of this information, EFSA was able to propose robust MRL levels guaranteeing that consumer exposure remains below the values considered to be without risk to health in the short and long term.

c/ Residue definition and establishment of MRLs in animal foodstuffs

Concerning livestock animals, in the context of use in plant protection products, the presence of residues in foodstuffs of animal origin comes from the consumption of treated plants.
In foodstuffs of animal origin, the nature of the residue retained was identical to that defined for plants, with analytical methods available for this definition with a LOQ of 0.002 mg/kg in milk and 0.005 mg/kg for other foods.

Indeed, metabolism studies on animals, including a study on layer hens, were assessed in the European dossier and in particular enabled the residue to be defined in poultry as well as in eggs. The high levels observed in adipose tissue are consistent with the fat-soluble characteristics of the substance. The residues in foodstuffs of animal origin have therefore been classified as fat soluble.

Animal feed studies, including one on laying hens, were also provided and assessed, enabling the level of transfer of the active substance to tissues and eggs to be estimated. In particular for hens, samples of muscle, fat, liver, kidney and eggs were analysed from animals exposed to different doses of substance. Fipronil residues as well as the metabolites MB43136 (fipronil sulfone) and MB45950 (fipronil sulphide) were screened for. As the metabolite MB45950 has never been detected, it was therefore not taken into account by EFSA.
The residue levels obtained from the animal feed studies according to the residue definition retained enabled EFSA to propose robust MRLs guaranteeing that consumer exposure remains below the values considered to be without risk to health in the short and long term. Indeed, the *a priori* consumer risk assessment conducted in this context with EFSA's PRIMo Rev.2 model showed that the above-mentioned toxicity reference values were not exceeded.

These MRLs are published in Regulation (EU) No 1127/2014. With regard to eggs and poultry meat/tissue, they were established at the following values:

[4] European Food Safety Authority, 2014. Reasoned opinion on the modification of maximum residue levels (MRLs) for fipronil following the withdrawal of the authorised uses on kale and head cabbage. EFSA Journal 2014;12(1):3543, 37 pp. doi:10.2903/j.efsa.2014.3543

Food	MRL (in mg/kg)
Birds' eggs	0.005*
. Hen	0.005*
. Duck	0.005*
. Goose	0.005*
. Quail	0.005*
. Other	0.005*
Tissue (basic)	
. Poultry	
. Muscle	0.005*
. Adipose tissue	0.006
. Liver	0.005*
. Kidneys	0.005*
. Edible offal (other than liver and kidneys)	0.005*
. Other	0.005*

*MRL at the analytical limit of quantification

d/ Data available in processed foods

Studies concerning the effects of industrial processing on the nature of the fipronil residue are present in the European dossier for the substance. These studies can be used to simulate the effects of pasteurisation, baking/brewing/boiling as well as sterilisation. In the case of fipronil, their results led EFSA to conclude that no significant impact on the nature of the residue is expected as a result of the application of such processes. It was therefore concluded that the residue definition for processed foods is identical to that for non-processed foods, namely the sum of fipronil and its sulfone metabolite MB43136 expressed as fipronil.

OBSERVED EFFECTS OF FIPRONIL IN HUMANS

The AFSSA-AFSSET report "Assessment of the risks to human health associated with exposure to fipronil" published in 2005 reviewed the available data on the effects of fipronil in humans. This report helped establish for the first time a summary of all the available data. This was rapidly updated in the framework of preparing this STS.

The international literature remains relatively scarce: on publication of the report, three articles reporting a total of 10 cases had been published and were included in the summary. Two articles published subsequently were identified:

- Clin Toxicol (Phila). 2010 Aug;48(7):737-44.

Acute illnesses associated with exposure to fipronil--surveillance data from 11 states in the United States, 2001-2007.

Lee SJ, Mulay P, Diebolt-Brown B, Lackovic MJ, Mehler LN, Beckman J, Waltz J, Prado JB, Mitchell YA, Higgins SA, Schwartz A, Calvert GM.

- Toxicol Int. 2015 Jan-Apr;22(1):165-6.

Fipronil Compound Consumption Presenting as Status Epilepticus.

Bharathraj MY, Venugopal K, Jaligidad K, Karibasappa H, Kumar H.

The human toxicity data analysed in the AFSSA-AFSSET report (2005) mainly came from observations collected by the poison control centres (CAPs) and the French Agency for Veterinary Medicinal Products (ANMV), as well as by the different vigilance networks working more specifically in occupational environments; some additional data from *ad hoc* studies implemented by manufacturers are also available. Since the report was published:

- A study conducted in the framework of toxicovigilance and targeting exposure to veterinary drugs in children (Symptomatic human exposure to veterinary drugs in children: retrospective study of exposure cases compiled by the CAPTVs in 2011 – August 2012) included eight cases of exposure to fipronil among the symptomatic exposures to antiparasitics;

- A rapid and preliminary analysis was performed of cases recorded since 2011 in the poison control centres' information system (SICAP).

A total of 1152 cases of exposure to fipronil were identified, including 37 deliberate exposures (with a suicidal purpose), 1104 accidental, and 11 whose circumstances were not determined. Among the 1104 accidental poisoning cases, 398 were symptomatic, including 356 where causality was non-null.

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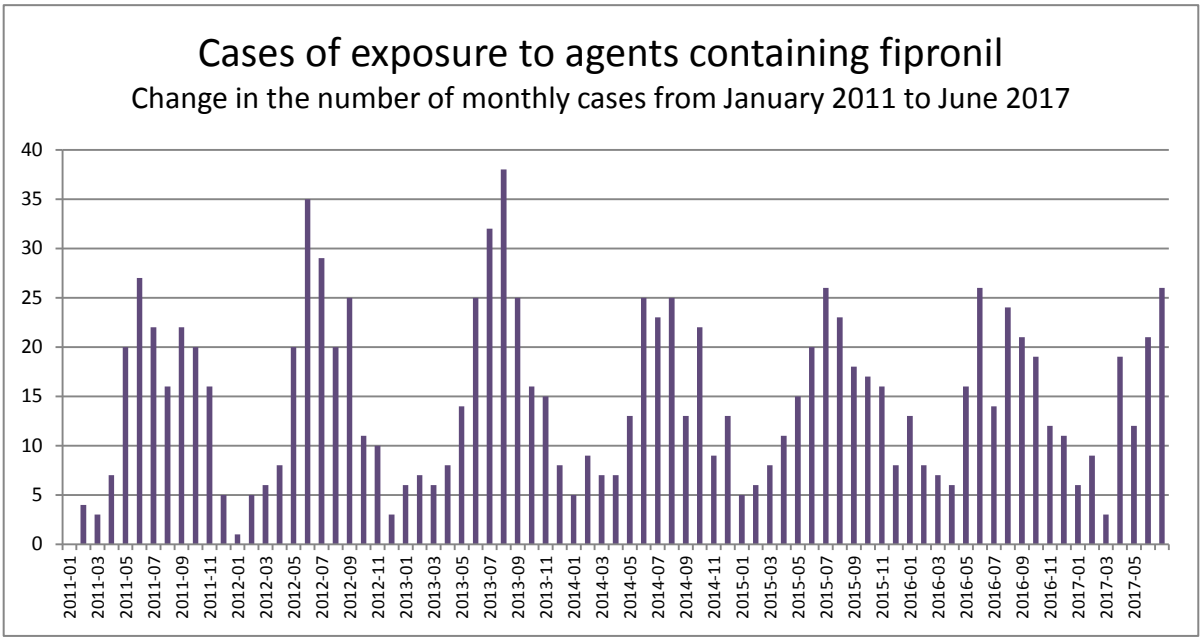
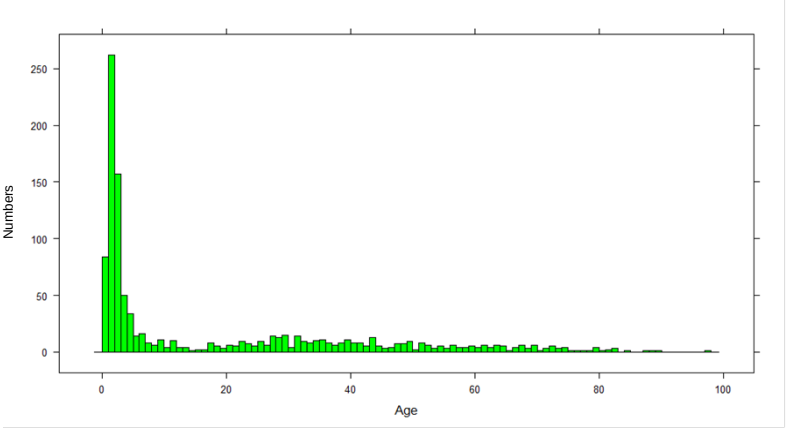


The following analysis focused on the poisoning cases (exposure with symptoms) for which the symptoms may be related to the exposure.

Breakdown of poisoning cases by age:

Age group	Total	%
Newborn	1	0.3
Infant	5	1.4
Child (1-4 years)	90	25.3
Child (5-9 years)	16	4.5
Adolescent (10-14 years)	18	5.0
Adolescent (15-19 years)	9	2.5
Young adult	36	10.1
Adult	136	38.2
Older adult	23	6.5
N/D	22	6.2
Total	356	100



Poisonings in children under the age of 10 accounted for 31.5% of the cases.

The poisonings were of low severity: only 35 cases were of moderate severity and there were no cases of high severity.

Severity	N	%
Nil	18	5.1
Low	303	85.1
Moderate	35	9.8
High	0	0
Total	356	100

Among the symptomatic accidental poisoning cases where causality was non-null, for 220 cases the route of exposure was exclusively ocular, dermal, respiratory or nasal, by injection or auricular. These exposure routes are not relevant to the issue of the effects of fipronil present in food products.

For 107 poisonings, the route of exposure was at least oral (sometimes associated with dermal and/or ocular exposure). The following symptoms were reported: vomiting (36%), oropharyngeal irritation (33%), abdominal pain (20%), diarrhoea (12%), hypersalivation (5%).

In 51 cases (out of 107), the products concerned were pesticides intended for insect eradication (ants, flying insects, etc.) and in 52 cases they were antiparasitic veterinary products intended for domestic animals. In four cases, the precision of the mixture was unknown: they directly referenced the substance fipronil.
For the pesticide products, four cases of poisoning were of moderate severity: they involved three children and one adult, with vomiting, dysphagia and hypersalivation for the adult case.
For the veterinary products (n=52), the severity was still low (vomiting, oropharyngeal irritation), with the exception of one case where the vomiting and its consequences were more marked (moderate severity).
Many of the symptoms observed were mainly attributable to the co-formulants of the commercial products (solvents, etc.).

In conclusion, at this stage of the analysis, it can be said that with accidental acute oral exposure, dose levels in excess of 10 times the acute reference dose (ARfD) have not led to general (systemic) effects being observed, including in children; only digestive disorders have been reported.

- No reports relating to fipronil have been notified by other vigilance networks.

Ultimately, in light of these points, the conclusions contained in the 2005 report "Assessment of the risks to human health associated with exposure to fipronil" are not called into question, in particular:

- The available data show that the effects observed in humans following acute exposure to preparations containing fipronil are usually mild: In the case of eye splashes, dermal contamination or exposure to aerosols, the only observed disorders are generally mild signs of local irritation.

- The effects expected in the event of acute systemic poisoning, in view of fipronil's mechanism of action and experimental data, are neurotoxic effects, mainly convulsions. However, this type of effect has not been observed in the framework of the toxicovigilance scheme. The few observations noted were the result of massive poisoning following the ingestion of fipronil products.

- The available data also do not show any alarming effects from repeated exposure to fipronil. Most of the available reports concern a few local mild symptoms.

3. HEALTH RISK ASSESSMENT CONCERNING THE CONSUMPTION OF CONTAMINATED EGGS

3.1 Data on egg consumption by the populations concerned

The consumption data used for this risk assessment come from several individual and national studies on food consumption.

The INCA2 study (AFSSA, 2009[5]) was conducted in three phases between late 2005 and April 2007 in order to take account of seasonal variations. Two distinct populations were included in the study: children aged 3 to 17 years and adults aged 18 to 79 years. Data on food consumption were collected over 7 consecutive days using a consumption diary. This methodology was necessary for carrying out risk assessments: chronic over a long period and acute over a short period. Each day was broken down into three meals and three snacks between meals. For each snack or meal, the participant had to give details of all the foods and beverages consumed, estimate the quantity consumed with the help of a photograph manual of servings, or household measures, or unit weights or volumes, and provide information on the type of product (industrial/home-made, fresh/canned/frozen, fortified/low-fat or not).

The information collected in the consumption diary on the foods and supplements was verified and harmonised by dieticians. Codification of foods was based on the INCA2 nomenclature of 43 groups created specifically for the study and enhanced relative to the previous version used in the INCA1 study. This nomenclature is compatible with that of the nutritional composition of foods from the French Information Centre on Food Quality (CIQUAL) set up by AFSSA.
For children under three years of age, the calculations performed were based on consumption data from the Nutri-bébé-SFAE survey. This study was conducted in the field from 12 January to 10 March 2005 by TNS-SOFRES for the French Association for Children's Food, a member of Alliance 7. Consumption data were collected in the homes of 713 children (between the ages of 15 days and 36 months and 15 days), using the food diary technique, on three consecutive days, meal by meal. They were noted by the children's caregivers (usually the mother and/or nanny, with the father's participation).

This study included infants and young children who were not breastfed (exclusively or partially) and who did not attend a day nursery or a school in the three days following recruitment. Indeed, because it is difficult to assess the amount of milk consumed by a breastfed baby, this would have required a specific protocol and an analysis of the breast milk for each nurse, or even for each feed, given the variations in the content of mother's milk. Breastfed children were therefore excluded by TNS-SOFRES.

Thus, data could be analysed for a total of 705 children; eight food diaries were excluded from the analysis because they were found to be incomplete.

This consumption study's classification included 32 main food categories. Some of these categories contained sub-categories (e.g. the cereals category included infant cereals and breakfast cereals).

Table 1 presents the data for egg consumption (in the form of eggs and omelette) from these studies, expressing the daily serving (in g) per unit of body weight (kg bw), for adults and children.

[5] AFSSA (2009). INCA2. Individual and National Study on Food Consumption.

Table 1: Egg consumption (in the form of eggs and omelette), expressing the daily serving (g) per unit of body weight (kg bw), for adults and children

Eggs + omelette	**Average serving** **g/kg bw/d**	**Serving 97.5th percentile**[6] **g/kg bw/d**	**Maximum serving** **g/kg bw/d**
Adults (18 years and over)	1.45	3.85	7.66
Children (3-17 years)	2.66	7.69	20.83
Children (1-3 years)	2.07	7.87	10.00

3.2 Health risk assessment concerning the consumption of eggs containing fipronil

In a theoretical scenario, it is possible to estimate from French consumption data **the concentration of fipronil in eggs not to be exceeded** to ensure that exposure remains below the acute toxicity reference value (ARfD of 0.009 mg/kg bw). On the basis of the maximum consumption for children aged 3-17 years (20.83 g/kg bw/d), this concentration **would be 0.43 mg/kg of egg for the sum of fipronil and its sulfone metabolite MB46136**[7]**.**

It is also possible **to estimate the number of eggs that can be consumed** without reaching the acute toxicity reference value (ARfD). In the absence of data collected in France on contamination of eggs by fipronil, this calculation can be performed with the maximum concentration of fipronil found so far in the contaminated eggs in Europe, which is 1.2 mg/kg of egg (for the sum of fipronil and its sulfone metabolite MB46136).

[6] The level of consumption that is not exceeded by 97.5% of the study population

[7] On the basis of a less maximalist scenario, an approach based on consumption data relating to the 97.5th percentile would lead to a maximum concentration of 1.17 mg/kg of egg for the sum of fipronil and its sulfone metabolite MB46136.

Table 2: Number of eggs that can be consumed without reaching the acute toxicity reference value (ARfD)

	Mean body weight (kg)	Maximum concentration** (mg/kg of egg)	Number of eggs
Adults	70	1.2	≤ 10
Children aged 11 to 17 years	54	1.2	≤ 8
Children aged 3 to 10 years	25	1.2	≤ 3
Children aged 3 years	14.5	1.2	≤ 2
Children aged 1 to 3 years	12.4	1.2	≤ 1

* mean weight of an egg = 50 g
** for the sum of fipronil and its sulfone metabolite MB46136

In the absence of consolidated data on the concentrations of fipronil in the eggs potentially placed on the market in France, it was not possible to conduct a quantitative risk assessment over the long term. It should be remembered, however, that compliance with the MRLs also aims to prevent the risks induced by chronic consumption of a substance.

The present assessment focuses on contaminated egg consumption scenarios. So far, no consumption of meat from broiler chickens contaminated with fipronil has been reported. However, if the analyses available at European level, which also examined hen muscle, are taken into account, the maximum observed concentration amounts to 0.175 mg/kg of muscle. In these conditions, the acute toxicity reference value could only be exceeded by consuming several kilograms of contaminated poultry meat on a single occasion for adults (and around one kilo for children).

4. CONCLUSIONS

Fipronil has moderate toxicity after single oral, dermal or inhalation exposure. It has been classified at European level (ATP 10 of Regulation (EC) 1272/2008) for acute toxicity in Category 3 for the oral route (H301), for the dermal route (H311) and by inhalation (H331).
Fipronil is not considered to be genotoxic, carcinogenic or toxic to reproduction.

Fipronil is neurotoxic for all species tested in experimental studies, for single toxicity and/or repeated doses. Thus, fipronil was classified at European level (ATP 10 of Regulation (EC) 1272/2008) for repeated toxicity (STOT RE 1, H372).

A **residue definition** is available for enforcement and risk assessment in animal products: the sum of fipronil and its sulfone metabolite MB43136 expressed as fipronil. The residue definition for processed foods is identical to that for non-processed foods.

MRLs, published in Regulation (EU) No 1127/2014, are available for eggs and poultry meat/tissue. As a reminder, only MRLs guaranteeing that consumer exposure remains below the values considered to be without risk to health in the short and long term are established, taking into

account total consumption of all foods that may contain these residues. They have been established at the following values:

Food	**MRL (in mg/kg)**
Birds' eggs	0.005*
. Hen	0.005*
. Duck	0.005*
. Goose	0.005*
. Quail	0.005*
. Other	0.005*
Tissue (basic)	
. Poultry	
. Muscle	0.005*
. Adipose tissue	0.006
. Liver	0.005*
. Kidneys	0.005*
. Edible offal (other than liver and kidneys)	0.005*
. Other	0.005*

*MRL at the analytical limit of quantification

The available data show that the **effects observed in humans** as a result of acute oral exposure to preparations containing fipronil are usually mild. Dose levels in excess of 10 times the acute reference dose (ARfD) have not led to systemic effects being observed, including in children.

The available data also do not show any alarming effects from repeated exposure to fipronil.

On the basis of the observed national consumption practices, the work to assess the risk to the consumer based on characterisation of the hazard firstly identified the maximum concentration of fipronil in eggs that ensures that the acute toxicity reference value is not exceeded. In the context of the most conservative scenario, for children, this value is set at 0.43 mg/kg of egg.

In addition, this same work identified for different populations the maximum quantity of eggs that can be consumed on a single occasion without exposing the consumer to an acute risk, on the basis of the maximum concentration of fipronil reported so far in the contaminated eggs in Europe (1.2 mg/kg of egg). This consumption for which the risk can be ruled out varies from 1 egg per day for children aged 1 to 3 years, to 10 eggs per day for adults, including pregnant women.

A quantitative assessment of the chronic risks could not be carried out. It should nevertheless be remembered that by nature, compliance with the value of the MRL is also intended to prevent the occurrence of such a risk.

In the event of the consumption levels identified by the Agency being exceeded, the risk cannot be ruled out. However, for the fipronil concentrations observed so far and considering the characterisation of the hazards of this substance, the risk of occurrence of health effects appears very low.

5. RECOMMENDATIONS

In the first place, ANSES reiterates that, under the regulations, products in which the fipronil concentration exceeds the MRL should not be marketed or should be withdrawn from sale.

If measurements are taken of the level of fipronil contamination in prepared food products likely to contain contaminated eggs or egg products, it will be necessary to take account of the dilution factor of the eggs or egg products in these food products to compare these results to the MRL.

If poultry, eggs or egg products that are contaminated or likely to be contaminated need to be eliminated, it will be necessary to ensure that the elimination process used guarantees that there is no subsequent contamination of the food chain.

Dr Roger GENET