Estimation of the risk of fipronil ingestion through the consumption of contaminated table eggs for the Italian consumer

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Summary
Fipronil is an insecticide which is not approved for use in any food-producing animal species in the European Union (EU). However, the inappropriate use of fipronil in mites' disinfestation products utilized in poultry farms in the Netherlands and other EU countries in 2017, led to the detection of residues of this pesticide in eggs across Europe. In Italy, a national monitoring plan was established to verify the possible misuse of fipronil in Italian laying hens. Out of 577 sampled farms, 23 eggs resulted contaminated (4.0%; 95% CI: 2.7%-5.9%). A higher prevalence of contamination was observed in flocks kept on cage (8.7%; 95% CI: 6.0% - 12.4%) than on ground (1.6%; 95% CI: 0.7% -3.7%); Chi-square = 16.1; P < 0.001). The results allowed developing a stochastic model for estimating the risk of fipronil ingestion through the consumption of contaminated table eggs for the Italian consumer. The probability that an individual ingests a dose of fipronil greater than the acute reference dose (ARfD, equal to 0.009 mg/kg body weight) was assessed as very low, ranging from values very close to 0 in people with more than 10 years of age and 0.0007 in infants less than 3 years.

Introduction

Fluocyanbenpyrazole, known as Fipronil, (±) -5-amino-1- (2,6-dichloro-α, α, α-trifluoro-p-tolyl) -4-trifluoromethylsulfinylpyrazole-3-carbonitrile (IUPAC), is a member of the class of pesticide chemicals known as phenylpyrazoles. Fipronil is a N-phenylpyrazole insecticide with a trifluoromethylsulfonyl moiety. It has a broad spectrum of activity, being used for controlling insect pests of crops (rice and cotton), locusts and grasshoppers, fleas and ticks on domestic animals, and cockroaches and ants (EFSA 2006).

Although fipronil is selectively toxic to insects, its toxicity has also been observed in mammals. In laying hens, the sulfone metabolite (MB43136) of fipronil has been detected in different tissues (peritoneal fat, eggs, skin and liver) after oral administration (Stewart 1994). The World Health Organization (WHO) classifies fipronil as a moderately hazardous substance "moderately toxic" to humans, and therefore a risk to public health is very unlikely for humans (Yadav *et al.* 2017). Fipronil and its metabolites persist for a long time in the environment and in the soil (EFSA 2006), being harmful not only to the environment, but also to fishes, crustaceans and bees (EFSA 2013). For these reasons, the administration of this pesticide in the production of food for human consumption is prohibited.

Fipronil is authorised as an insecticide in plant protection products. As acaricide, its use in veterinary medicinal products is not allowed on food-producing animals. Therefore, residues of fipronil are not expected in eggs and poultry muscle/fat, since the authorisations exist only in a limited number of crops, in particular the use of fipronil is permitted only where the seed coating is performed in professional seed treatment facilities, which must apply the best available techniques (European Commission 2011).

During the summer of 2017, the European Commission was informed through the Rapid Alert System for Food and Feed (RASFF) of the illegal use of fipronil in some European countries, as pesticide added to an insecticide (Dega-16) for the disinfestation of laying hens flocks against red mites (*Dermanyssus gallinae*) to increase its effectiveness (RASFF 2017a). Unauthorized use of fipronil in the farms led to the contamination of the concerned eggs produced. The countries initially affected by the problem were Belgium and the Netherlands, but due to egg exports, many other countries were soon involved, and in particular: Italy, Germany, Sweden, France, Great Britain, Austria, Ireland, Luxembourg, Poland, Romania, Slovenia, Slovakia, and Denmark (RASFF 2017 b-e). Eggs contaminated with fipronil were quickly identified in more than 16 countries of the European Union (EU) as well as Switzerland and China (Stafford *et al.* 2018).

As a consequence of the identified misuse of fipronil in chicken farms, an *ad hoc* monitoring programme was set up in the EU. The major purpose of the *ad hoc* monitoring programme was to get a comprehensive view on the contamination of eggs and poultry products related to illegal uses of acaricides. Member States were requested to take samples of chicken eggs, chicken fat and muscle for the period 1 September to 30 November 2017, to analyse them for fipronil and additional acaricides and to report the results to EFSA (EFSA *et al.* 2018).

The legal residue definitions (LRD) and maximum levels of pesticide residues (MRL) of fipronil are laid down in EU Regulation (European Union 2014). LRD comprises not only the active substance, but also its metabolite sulfone: therefore, the LRD is the sum of fipronil and sulfone metabolite (MB46136) expressed as fipronil. This value has been set to 0.005 mg/kg as analytical determination limit for poultry eggs (i.e., whole eggs, yolks, or whites) and muscle/fat (EFSA 2014). As regards humans, in a scientific opinion published in 2014, EFSA defined the maximum acceptable daily intake (ADI) of fipronil for humans as 0.0002 mg/kg of body weight, and the acute reference dose (ARfD) as 0.009 mg/kg of body weight (EFSA 2014).

As a consequence of the identified misuses of fipronil in foreign chicken farms by RASFF, the Italian alert resulted in identifying, blocking and tracing of the contaminated consignments by Regional health authorities and by the Carabiners Unit, responsible for preventing the adulteration of foodstuffs and beverages. Additionally, on August 11 2017 an *ad hoc* sampling plan was set up on the national territory to get a comprehensive view on the contamination of eggs and poultry products related to the illegal use of acaricides containing fipronil. Subsequently, on August 28, an *ad hoc* monitoring plan was established to verify the possible use of unauthorized fipronil on Italian laying hens.

This paper presents the results of the sampling activities carried out in Italian farms in the context of the "Sampling plan for the control of the level of fipronil in Italian laying hens". Moreover, the risk of fipronil ingestion through the consumption of contaminated table eggs for the Italian consumer was estimated by developing a stochastic model.

Materials and methods

Sampling plan

On August 28 2017, a national survey on laying hen farms was launched by the General Direction of Animal Health and Veterinary Medicines (AHVM) of the Italian Ministry of Health. The survey aimed at quantifying the prevalence of fipronil contamination in Italian flocks of laying hens and the levels of contaminations, through the laboratory examination of a sample of table eggs collected on farm. According to the statistics of the National Poultry Association almost the entire amount of table eggs consumed in Italy are produced within the country (Unaitalia) and importations concern only eggs-derived products or ingredients. The quantification of the level of fipronil contamination in table eggs produced in Italy allowed estimating the level of exposure for the Italian consumers. Therefore, ingestion of fipronil through egg-derived products (pasta, mayonnaise or other sauces, ice-creams, desserts, etc.) is not considered in this study.

The sampling schema considered in the survey assumed that the most probable exposure way for laying hens was related to a repeated spray of acaricide products within the animal stables, in the environment or over the litter. Hence, it was assumed that all the animals belonging to the same flock had the same probability to be exposed to fipronil contamination, and therefore, the single laying hen flock was considered as reference sampling unit. Flock is defined as "all poultry of the same health status kept on the same premises or in the same enclosure and constituting a single epidemiological unit; in the case of housed poultry, this includes all birds sharing the same airspace" (European Commission 2003).

A sample of 842 randomly selected laying hen flocks was included in the survey. This sample size was calculated to estimate the prevalence of contaminated flocks with an accuracy of ± 3%, with a 95% of confidence, and an expected prevalence of 50% (Cannon and Roe 1982). Then, the number of flocks to be tested was stratified according to the consistency of the laying hen population in each Italian region and on the basis of the types of rearing systems: on cages or on ground. The latter stratification was considered to evaluate any difference in prevalence of contamination between these two rearing systems. Four aliquots of 12 whole eggs each were sampled in each selected flock (European Commission 2002), paying attention to collect the eggs randomly among those produced during the entire day by the selected flock. Three aliquots were dispatched to the laboratory, whereas the fourth was stored by the flock's owner for possible further examinations. The laboratories tested one aliquot, while the other two were stored for possible repeated examinations. The final resulting egg sample size was able to estimate the mean level of fipronil concentration in eggs, with an accuracy of ± 0.0025 mg/kg, taken into account that a first explorative set of 32 egg samples resulted in 6 positive samples with a mean level of contamination equal to 0.037 mg/kg, with a standard deviation of 0.036 mg/kg.

Fipronil laboratory detection method

Egg samples were analysed by chemical accredited laboratories of the Public Health Institutes (Istituti Zooprofilattici Sperimentali - IIZZSS), applying Gas and Liquid Chromatography coupled to tandem mass spectrometry (GC-MS/MS and LC-MS/MS), and Ultra-High-Performance Liquid Chromatography coupled to High Resolution Mass Spectrometry (U-HPLC-HRMS). The analytical method was based on QuEChERS approach according to what prescribed by the European Commission (European Union Reference Laboratories for pesticides 2015). The twelve eggs of the same aliquot were pooled together and tested. The results were expressed as mg/kg of fipronil (as sum of fipronil and its sulfone metabolite) in compliance with EU Regulation 1127/2014 (European Union 2014). The limit of quantification (LOQ) differs from the analytical method used, with values from 0.0015 to 0.0025 mg/kg for the single residue (fipronil and its sulfone) and from 0.003 to 0.005 mg/kg for the legal sum. All samples with fipronil residues greater than 0.005 mg/kg (including the measurement uncertainty) were considered not compliant (European Union 2014).

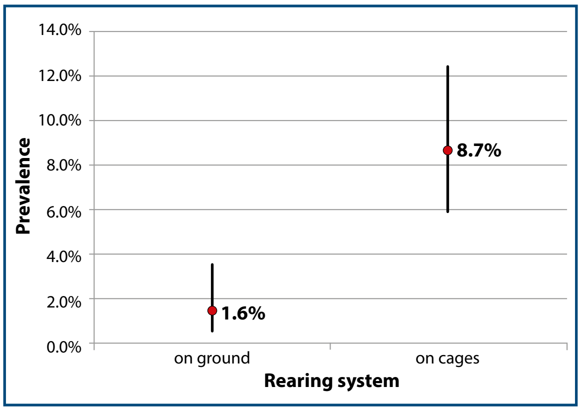

Figure 1. *Prevalence and 95% CI in positive flocks with fipronil residue levels (sum of fipronil and sulfone expressed as fipronil) higher than 0.005 mg/kg.*

Data analysis

Data descriptive analyses were performed using Microsoft Excel©. The significance of differences of contamination prevalence between flocks with different rearing systems (on cages or on ground) was checked using chi-square test (Siegel and Castellan 1988). The distributions best fitting the observed data on contamination levels were evaluated using a Maximum Likelihood Estimate (MLE) approach and considering the values of Akaike information criterion (AIC) and Bayesian information criterion (BIC).

A stochastic model was developed for estimating the levels of fipronil ingested by the Italian consumer through the consumption of contaminated table eggs. For the model, the prevalence of not compliant

Table I. *Description of the input variables used in the risk model.*

Input variable	Definition	Source
P	Prevalence of contaminated eggs	Results of national survey. Modelled as Beta(x+1, n-x+1), where: x = number of positive samples n = total number of tested samples
F	Concentration (mg/kg) of fipronil in eggs	Results of national survey. For not compliant eggs: best fitting distribution For eggs with < than 0.005 mg/kg: Uniform (0, 0.005)
μBwi	Average body weight (kg) for each *i* category of consumer (by gender and age)	Leclercq *et al.* 2009
σBwi	Standard deviation of body weight (kg) for each *i* category of consumer (by gender and age)	Leclercq *et al.* 2009
μEci	Average individual daily consumption of table eggs (g) for each *i* category of consumer (by gender and age)	Leclercq *et al.* 2009
σEci	Standard deviation of individual daily consumption of table eggs (g) for each *i* category of consumer (by gender and age)	Leclercq *et al.* 2009

samples was assumed equal to the prevalence of not compliant table eggs (with detectable residues of fipronil, expressed as mg/kg of fipronil as sum of fipronil and its sulfone metabolite) of national origin. The consumption of table eggs imported from abroad was considered negligible. The input variables are listed in Table I. Data on table egg consumption have been derived from the results of a national dietary survey performed by the Italian National Research Institute for Food and Nutrition (INRAN) in 2005-2006 (Leclercq *et al.* 2009). The model was performed in @Risk (Palisade©), with 10.000 iterations, Latin Hypercube sampling. In Figure 1, the structure of the model is reported.

Results

Out of 577 laying hen sampled farms, 23 resulted positive (4.0%; 95% Confidence Interval (CI): 2.7%-5.9%), with at least one sample tested positive for the detection of fipronil (expressed as mg/kg of fipronil as sum of fipronil and its sulfone metabolite). As regards the regions, positive farms were reported throughout the Italian regions: Puglia (the "heel" of Italy) reported the highest number of positive farms, followed by Veneto, Lombardia, and Emilia Romagna; Piemonte, Campania, Abruzzo, Calabria, Friuli Venezia Giulia, and Lazio also reported positive farms. The prevalence was significantly higher in southern farms than in northern farms (Chi-square = 9.0831; $P < 0.05$).

About the flocks, out of 682 sampled flocks (81%), 31 were positive (4.5%, 95% CI: 3.2% -6.4%), with fipronil residue levels (sum of fipronil and sulfone expressed as fipronil) higher than 0.005 mg/kg. Figure 1 shows the prevalence of positive flocks according to the rearing system (on ground and on cages). The difference of prevalence between the two rearing systems was statistically significant (Chi-square = 16.1; $P < 0.001$; OR = 5.89 (C.L. 95% OR = 2.23-15.54), with a higher prevalence of contamination in flocks keeping the animals in cages (8.7%; 95% CI: 6.0% - 12.4%) than those on ground (1.6%; 95% CI: 0.7% - 3.7%).

The distribution of contamination values of positive eggs followed a log-normal distribution with mean of 0.42 mg/kg and a standard deviation of 3.81 mg/kg (Figure 2).

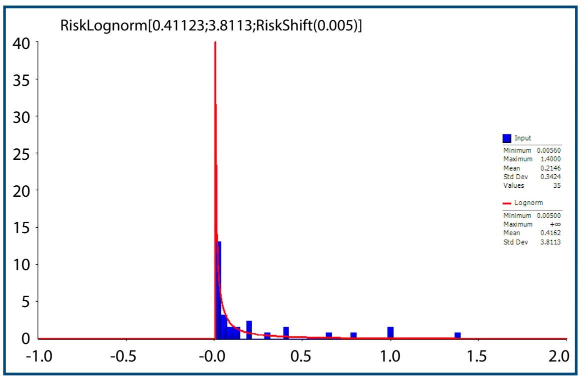

Figure 2. *Log-normal distribution of contamination values of positive eggs.*

The structure of the stochastic model developed for estimating the risk of fipronil ingestion through the consumption of contaminated table eggs for the Italian consumer is shown in Figure 3. As regards the dietary intake, table 2 summarizes the estimated quantities of ingested fipronil (mg/day/kg of body weight) for each individual and for each category of people: infants (0-2.9 years), children (3-9.9 years), adolescents (10-17.8 years), adults (18-64.9 years), and elderly (≥ 65 years). The estimated probability that an individual ingests a dose of fipronil greater than that expressed by ARfD (0.009 mg/kg body weight) is always very low, ranging from values very close to 0 in people with more than 10 years of age and 0.0007 in infants less than 3 years (Table III).

Discussion

The intentional or accidental exposure of food-producing animals to compounds, such a fipronil, that have a lipophilic or sustained-release nature is concerning because these compounds tend to have extremely long half-lives. Serious consideration should be given to whether exposed animals should enter the food chain because the residues are likely to persist for prolonged periods of time (Stafford *et al.* 2018). Ingestion of large amounts of fipronil can lead to kidney, liver, and thyroid damage. However, the results of the *ad hoc* monitoring programme set up in the EU

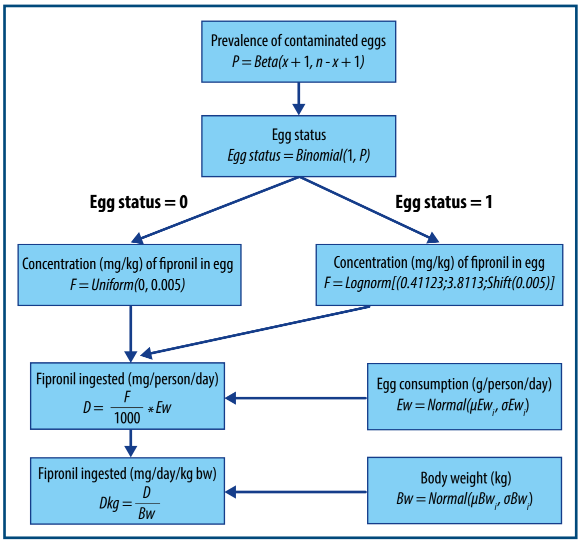

Figure 3. *Structure of the risk model.*

Table II. *Estimation of the quantities of ingested fipronil (mg/day/kg of body weight) for each individual and category of people in Italy.*

	Infants (0-2.9 years)	Children (3-9.9 years)	Adolescents (10-17.8 years)		Adults (18-64.9 years)		Elderly (≥ 65 years)	
			Male	Female	Male	Female	Male	Female
95% UCL	6.14949E-05	5.42062E-05	2.01143E-05	2.20631E-05	1.83429E-05	1.88198E-05	1.86654E-05	1.76480E-05
95% LCL	7.75238E-08	6.03476E-08	2.67048E-08	3.27278E-08	2.85489E-08	2.52002E-08	2.14380E-08	2.71639E-08
Mean	2.96274E-05	2.79461E-05	1.02281E-05	1.42178E-05	8.99724E-06	8.81838E-06	1.04883E-05	9.80357E-06
Maximum	3.60980E-02	3.21126E-02	7.66465E-03	1.25922E-02	1.03682E-02	4.06690E-03	6.49202E-03	1.10017E-02
Minimum	4.67089E-10	3.86286E-11	2.57203E-11	9.53634E-11	4.76530E-11	5.09103E-13	6.27070E-11	9.74953E-11

Table III. *Estimation of the probability that an individual of each category ingests a dose of fipronil greater than the ARfD (0.009 mg/kg body weight) in Italy.*

	Infants (0-2.9 years)	Children (3-9.9 years)	Adolescents (10-17.8 years)		Adults (18-64.9 years)		Elderly (≥ 65 years)	
			Male	Female	Male	Female	Male	Female
Probability of having > ARfD (0.009 mg/kg)	0.0007	0.0004	0	0.0002	0.0001	0	0	0.0002

(EFSA 2018) suggest that the amounts of fipronil present in the contaminated eggs are much lower than the limit set up by the EU regulation, and at that levels it is unlikely to represent a tangible risk to public health. Anyway, the contamination of chicken products leading to exceedance of the legal limits was almost exclusively related to fipronil. The food products affected were mainly chicken eggs (including products of egg yolk and egg white) and fat of laying hens. Samples with MRL exceedance originated from eight Member States, including Italy. In any European country, to date, there are no cases of human acute intoxication related to the use of contaminated eggs; this occurrence is however unlikely, given the level of contamination detected and the normal average consumption of eggs in the population.

The results of the Italian sampling plan have clearly demonstrated the use of fipronil also in Italian flocks of laying hens. Taking into account a significant percentage of poultry farms that appeared having used this substance (around 4%), the levels of contamination found in the eggs were minimal. Of the 35 non-compliant egg samples, 32 (91.4% of positive samples) showed contamination values below 1 mg/kg and 16 of these (45.7% of positive samples) had doses lower than 0.5 mg/kg.

An interesting result of the sampling plan was the higher prevalence of contamination observed in on caged in comparison to on ground flocks. The reason for this difference could be explained in more frequent or serious infestation problems (i.e., insects, parasites) in this type of farming, and therefore, a greater frequency of treatments in on cage farms due to the high density of the animals, or to a higher persistence of residues in the environment due to a greater difficulty to perform efficient cleaning and disinfection actions where cages are used for rearing animals. In any case, it would be useful to carry out further investigations to determine whether or not different levels of infestation exist in the different types of farming or to identify other possible risk factors potentially associated with higher residues of fipronil in the environment.

The simulation model developed to estimate the risk of fipronil intake by Italian egg consumers and based on the results of the national monitoring plan, has shown that, with the levels of contamination observed and the quantity of eggs consumed with the diet, values near or higher than the ARfD value have a very low probability to be reached. It must be noted that the developed model, if on one hand tends to overestimate the final risk by assuming as non-compliant (> 0.005 mg/kg) all the eggs produced by the positive groups, on the other hand does not consider the contamination values below the detection limit of 0.005 mg/kg, which, although minimally, could still influence the human health. However, the probability for an individual to ingest a dose of fipronil greater than the ARfD value (0.009 mg/kg of body weight) is very low, even considering other sources of eggs and egg products in the diet (pasta egg, ice cream, cream, etc.). A higher probability can be identified in children less than 10 years of age who, in proportion to their body weight, could ingest larger amounts of eggs and derived products.

Authorities of other European countries carried out risk assessment on the acute toxicity for the consumer of eggs and poultry. The Food Safety Agency of Belgium, based on the value of the ARfD determined by EFSA, calculated the maximum concentration of fipronil beyond which consumers of eggs and poultry suffer of acute toxic effects (FASFC 2017a), to decide whether to proceed with the recall of non-compliant products: i.e. food with concentrations of fipronil exceeding the regulatory standard (0.005 mg/kg), even if they did not present a risk for public health (FASFC 2017b). The German Federal Institute for Risk Assessment (BfR) came to similar results: in one study, taking into account different patterns of egg and egg-based consumption, it was considered the 0.72 mg/kg MRL calculated by the Belgian Food Safety Agency as appropriate (BfR 2017). The French Agency for Food, Environmental and Occupational Health & Safety (ANSES) carried out an analogous study, considering three different categories of consumers (children 1-3 years; children 3-17 years; and adults) and data on the consumption of eggs. The results of the study showed that to avoid acute toxicity in children aged 3 to 17 years, the maximum concentration of fipronil in eggs should be 0.43 mg/kg (ANSES 2017a). Subsequently, ANSES published a further assessment of the risk related to the maximum value of fipronil in egg products, calculating for these foods an even more restrictive limit equal to 0.23 mg/kg (ANSES 2017b).

It is important to underline that if a contaminated egg was consumed, nothing would have happened because the values found in the contaminated eggs were nevertheless very low compared to the acceptable daily intake that was estimated in humans. As always, young people, as well as the elderly and patients with kidney problems may be the most sensitive (VesA Marche 2017).

Conclusions

It is noteworthy that tools for rapid communication among countries in course of emerging public health threats like the RASFF play an important role in consumer protection along the world food trade. The RASFF was put in place to provide food and feed control authorities with an effective tool to exchange information about measures taken responding to serious risks detected in relation to food or feed. During the fipronil crisis, this exchange of information helped the involved EU countries to act more rapidly and in a coordinated manner in response to the health threat caused by the inappropriate use of this insecticide in cleaning products used on poultry farms. Subsequently, an *ad hoc* monitoring plan was established in Italy by the Veterinary Authority to verify the possible use of unauthorized fipronil on Italian laying hens. Out of 577 laying hen sampled farms, 23 resulted positive (4.0%; 95% CI: 2.7%-5.9%), with at least one sample tested positive for the detection of fipronil. These results, together with the data of table eggs consumption, allowed to estimate through a stochastically model a very low risk of fipronil intake by Italian egg consumers.

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