Consequences of fipronil exposure in egg-laying hens

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Inadvertent or intentional administration of pesticides to food animals such as egg-laying hens (layers) and broilers often leads veterinarians to contact FARAD to inquire about withdrawal intervals. Unfortunately, US law permitting ELDU does not include products registered by the EPA; thus, ELDU use of pesticides puts FARAD in a precarious situation. Fipronil, a broad-spectrum phenylpyrazole pesticide, is used to prevent insects such as fleas and ticks from plaguing cats and dogs as well as repelling a variety of insects from crops and homes. Fipronil is not approved for use in any food animal species in the United States or any other country. However, poultry in the Netherlands and other EU countries were inadvertently exposed to fipronil in 2017, and violative residues of the pesticide were detected in eggs across Europe and in China.[1] Because fipronil is highly lipophilic, it can become sequestered in tissues with a high lipid content for an extended period of time. Although no eggs from the Netherlands have been imported to the United States since July 2017, the purpose of this digest is to explain concerns with fipronil use or exposure in poultry and the difficulties associated with developing data-driven meat or egg withdrawal intervals.[2]

Background and Overview of the 2017 Fipronil Contamination of Poultry in the Netherlands and EU

As previously mentioned, fipronil is not approved for use in food-producing animals by either the European Medicines Agency in Europe or the US EPA. However, in 2017, an anonymous report to authorities in the Netherlands described the inappropriate use of fipronil in cleaning products used on chicken farms, which resulted in poultry being repeatedly exposed to the pesticide. A Belgian company was accused of combining a proprietary natural cleaning product, DEGA-16, with fipronil and selling that product to a Dutch pesticide supply company, which in turn knowingly sold it to numerous chicken producers.[3–5] Eggs contaminated with fipronil were quickly identified in > 16 countries of the EU as well as Switzerland and China. Although Belgium issued an EU-wide rapid alert in June 2017, Dutch officials alleged that Belgian officials knew about the contamination as early as November 2016.[1] As of August 2017, the financial damage to international egg-selling companies was estimated to be > $39 million, with 258 companies unable to sell any chickens or eggs during the recall period.[6] The Netherlands was historically the largest egg exporter to other countries in the EU, but following the discovery of the fipronil contamination issue and subsequent recall period, the United States became the largest egg exporter to those countries. Egg market prices are high in the EU; however, a USDA report issued in December 2017 described the EU market as "adequately supplied" and that, although the surge in prices was initially caused by fipronil contamination, prices at that time were in line with increased demand during the end-of-year holiday season as well as international price increases for breaking eggs.[7]

ABBREVIATIONS

ELDU	Extralabel drug use
EPA	Environmental Protection Agency
EU	European Union
FARAD	Food Animal Residue Avoidance and Depletion Program
FSIS	Food Safety Inspection Service
GABA	γ-Aminobutyric acid
ppb	Parts per billion
WHO	World Health Organization

US Regulatory Information

In the United States, ELDU of FDA-approved products is permissible pursuant to stipulations set forth by the AMDUCA of 1994, and is described in detail in Title 21, part 530 of the US Code of Federal Regulations.[8] The AMDUCA allows for the extralabel use of FDA-approved products by or on the lawful order

of a veterinarian in the context of a valid veterinarian-client-patient relationship.[8] In the United States, pesticide products for flea and tick prevention that are formulated for oral administration are regulated by the FDA, whereas topical pesticide formulations are regulated by the EPA. Because there are no FDA-approved fipronil products, the pesticide is regulated solely by the EPA in the United States. Products regulated by the EPA are not included in AMDUCA regulations; therefore, they can only be used in accordance with the information provided on the product label. Extralabel use of EPA-regulated products is expressly prohibited in the United States, and that prohibition applies to all poultry flocks regardless of whether they are large commercial flocks or small backyard flocks. To reiterate, extralabel use of fipronil, including inadvertent administration, to poultry is unlawful in the United States.

Fipronil Tolerances and Detection Limits

The European Food Safety Authority has defined the maximum acceptable daily intake of fipronil for humans as 0.0002 mg/kg of body weight, and the EU maximum residue limit of fipronil and its sulfone metabolite in eggs (ie, whole eggs, yolks, or whites) is 0.005 mg/kg/egg (5 ppb/egg).[9] Although there is a general zero-tolerance policy for unlawful ELDU in the United States, the FSIS reports a total fipronil tolerance (parent compound plus metabolites) of 0.03 mg/kg/egg (30 ppb/egg).[10] Results of studies[11–13] involving fipronil residues in poultry products have been summarized **(Table 1)**, with most reported fipronil residues exceeding both the EU maximum residue limit and US FSIS tolerance. Those high fipronil residues in poultry tissues correlate with the lipophilicity of the pesticide and give credence to concerns about the potential for violative residues even after extended time periods have elapsed. Therefore, serious consideration should be given to whether eggs produced by layers that have been exposed to fipronil should ever enter the food chain.

Currently, the United States imports eggs from only 2 countries—Canada and the Netherlands—but an internal industry communication from the FSIS maintains that the United States has not received egg products from the Netherlands since July 21, 2017.[2,14] A constituent update published by the FDA in November 2017, reported that, in fiscal year 2015, 98% of domestic and 90% of imported foods tested were compliant with federal pesticide residue limits.[15] Although those foods were tested prior to the fipronil contamination incident, those high compliance rates highlight the diligence in testing and adherence to established residue limits by both US producers and regulatory agencies.

Mechanism of Action and Selectivity of Fipronil

Fipronil is a broad-spectrum phenylpyrazole antiparasitic agent that interferes with activation of insect-specific $GABA_A$ receptors, ultimately resulting in neuronal hyperexcitation and death in fleas and ticks.[16,17] The strong selectivity of fipronil for insect GABA receptors is the result of differences in receptor structure and binding affinity as well as pharmacological profiles between insects and humans. The selectivity of fipronil for insect $GABA_A$ receptors is 500-fold that for human $GABA_A$ receptors and is me-

Table 1—Summary for the residues of fipronil and its metabolites detected in various tissues of egg-laying hens.

		Residue information		
Reference	**Fipronil dosage**	**Matrix**	**Time after initiation of dosing (d)**	**Concentration (ppb)**
11	10 ppm, PO (prior to feeding), q 24 h for 28 d	Egg yolk	28.975	30,000
		Peritoneal fat	28.975	56,000
		Skin	28.975	17,000
11	2 ppm, PO (prior to feeding), q 24 h for 28 d	Egg yolk	28.975	7,020
		Peritoneal fat	28.975	12,000
		Skin	28.975	3,900
11	0.5 ppm, PO (prior to feeding), q 24 h for 28 d	Egg yolk	28.975	180
		Peritoneal fat	28.975	290
		Skin	28.975	100
12	0.103 ppm, PO (in feed), q 24 h for 42 d	Egg	41	96*
		Fat	42	191*
12	0.031 ppm, PO (in feed), q 24 h for 42 d	Egg	41	24*
		Fat	42	54.3*
12	0.01 ppm, PO (in feed), q 24 h for 42 d	Egg	41	10*
		Fat	42	13*
13	10 ppm, PO (in feed), q 24 h for 14 d	Egg (partially formed)	14.96	8,700†
		Omental fat	14.96	8,800†
		Liver	14.96	4,100†
13	2 ppm, PO (in feed), q 24 h for 14 d	Egg (partially formed)	14.96	1,550†
		Omental fat	14.96	1,610†
		Liver	14.96	1,020†
13	0.05 ppm, PO (in feed), q 24 h for 14 d	Egg (partially formed)	14.96	58†
		Omental fat	14.96	58†
		Liver	14.96	38†

*Mean. †Mean total radioactive residues.
ppm = Parts per million.

diated through the β_3 subunit on that receptor.[18–20] Fipronil's major metabolites, fipronil sulfone and fipronil desulfinyl, have less selectivity for insect receptors, compared with the parent drug.[18,21] Fipronil is the active ingredient in numerous EPA-registered topical flea and tick preventative products for use on cats and dogs and has a broad spectrum of activity against fleas, ticks, mites, and lice.[16] It is also available as an insect bait to remove cockroaches, ants, and termites and is used in the agricultural industry for soil treatment, seed coating, and crop protection.[18] Fipronil products, such as Frontline,[a] work by sequestering the drug in sebaceous glands, which act as a reservoir and slowly release the drug resulting in a minimum duration of action of 30 days.[22] Regardless of formulation, fipronil is extremely lipophilic, and thus, prefers tissues with a high lipid content such as fat. High lipophilicity leads to wide and complete distribution of the drug following absorption, and plasma fipronil concentrations are unlikely to accurately reflect the overall fipronil concentration in the body. Although many fipronil metabolites may be present in the tissues of exposed animals, fipronil sulfone is the predominant metabolite identified in egg yolk, skin, and liver, whereas the fipronil parent compound is the predominant form of the pesticide identified in milk and fat.[23] Fipronil desulfinyl is a photodegradation rather than a mammalian metabolite and is often detected in eggs, milk, and other tissues prior to metabolic conjugation; therefore, it represents another residue marker to consider.[23] 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 those compounds tend to have extremely long half-lives. Serious consideration should be given to whether exposed animals should enter the food chain because violative residues are likely to persist for prolonged periods of time.

Toxicity Profile of Fipronil

The WHO classifies fipronil as a moderately hazardous (class II) pesticide because it can exert toxic effects following inhalation or ingestion.[24] Although fipronil is highly selective for insect GABA receptors, it also has activity on human GABA receptors and can induce neurologic symptoms such as seizures, dizziness, sensory impairment, and agitation.[25] The fipronil LD_{50} is 92 mg/kg (42 mg/lb) for rodents,[24] whereas that for houseflies is only 0.13 mg/kg (0.06 mg/lb),[19] which indicates that insects are more susceptible to fipronil toxicosis than mammals. Results of an in vitro study[26] involving a human neuronal cell line (SHSY5Y) indicate that even fairly low concentrations of fipronil can cause mitochondrial injury by uncoupling phosphorylation, which can lead to cell death. In murine models, fipronil is toxic to the reproductive system and causes thyroid enlargement and cancer as well as hepatocyte damage leading to hepatomegaly and hepatocellular carcinoma.[27] In dogs and mice, oral administration of fipronil was associated with neurologic damage, including developmental delays.[27] Although some adverse effects associated with fipronil require chronic exposure and time to develop, as of August 2017, the USDA Foreign Agricultural Service considers fipronil contamination to be "more of an economic…issue…than a food safety and a health risk concern".[1]

FARAD Perspective and Comments on Withdrawal Intervals

Because FARAD exists to advise veterinarians on withdrawal intervals for food-producing animals administered FDA-approved medications in a legal extralabel manner, FARAD personnel cannot legally recommend withdrawal intervals for animals administered or exposed to EPA-registered products in an extralabel manner. In general, FARAD may attempt to provide withdrawal interval recommendations in cases of accidental exposure or contamination when pertinent supporting literature is available and a scientifically sound withdrawal interval can be elucidated. Unfortunately, the paucity of pharmacokinetic data for fipronil in layers and the innate characteristics of the pesticide make development of an appropriate data-driven withdrawal interval extremely difficult. Although EPA-registered products cannot be legally used in an extralabel manner, FARAD has received over a dozen calls since its founding regarding the administration of fipronil to poultry and has maintained a strict recommendation that layers and broilers exposed to that pesticide never enter the food chain or be consumed in any way by humans. This recommendation stems from the lack of comprehensive pharmacokinetic information regarding the adminis-tration of fipronil and its metabolites to poultry as well as the innate characteristics (lipophilicity) of the compound that will likely result in persistent violative residues in meat and eggs.

Acknowledgments

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Footnotes

a. Merial Ltd, Duluth, Ga.

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