14.5.
Case report: intentional endosulfan poisoning of domestic animals

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INTRODUCTION
Endosulfan is a chlorinated insecticide used in many Countries. It is usually provided as a mixture of two steroisomers, α- and β-endosulfan, that are partly metabolized and excreted in urine and feces as oxidation products, such as endosulfan-sulphate, endosulfan-alcohol, endosulfan-ether and endosulfan-lactone. Endosulfan presents moderate toxicity for mammal, but is frequently in malicious poisonings. It is highly toxic to fish and some bird species and was reported to have oestrogenic effects on humans. Two indipendent cases are reported here involving a cat and a dog, both treated for severe seizure symptoms. In both cases, they died within few hours. Liver and gastric content samples were sent to our laboratory in order to investigate over possible poisoning.

MATERIALS AND METHODS
The analysis were performed by gas-chromatography-mass spectrometry (GC-MS). After sample preparation. 4 g of each homogenised liver and gastric content were treated with the QuEChERS approach. All the extracts were evaporated under nitrogen and dissolved in 100 μl methanol. 1 μl was then injected in the GC-MS system.

RESULTS
Cat's gastric content resulted positive to α-endosulfan and β-endosulfan, while liver sample contained endosulfan-sulphate and endosulfan-ether (the former more abundant than the latter). No endosulfan-lactone was formed from its precursor endosulfan-sulphate (probably because of the short time elapsed from ingestion to death),
The dog's gastric content contained the same quantities of α- and β-endosulfan. Unlike in cat's sample, the same compounds were present also in the liver, where β-endosulfan concentration was about one fifth of the α-form. In the liver sample, also endosulfan sulphate and endosulphan ether were identified.

CONCLUSIONS
Ingestion of endosulfan by animals leads to its identification in the gastric content only when their death occurs shortly after ingestion. On the other hand, unmodified endosulfans can be detected in liver samples only at low concentration, because of its biotransformation. Endosulfan-sulphate and endosulfan-ether can therefore represent useful target analytes to disclose fatal conditions of endosulfan poisoning.

14.6.
Dog susceptibility to drug toxicosis and MDR1: the contribution of veterinary pharmacovigilance

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INTRODUCTION/OBJECTIVE
P-glycoprotein (PgP) is a membrane efflux pump. As PgP is ubiquitary, it minimizes the body exposure to potentially toxic xenobiotics. In some dog breeds, a mutation in the MDR1 gene results in a non-functional PgP, rendering them susceptible to some drug adverse effects. A lot of drugs interact with PgP (as substrates, activators or inhibitors) while susceptibility reactions are not systematically described in dogs with the gene deletion. Guidelines and warning comments on the use of some drugs in dogs with the MDR1-1Δ mutation were developed on www.collie-online.com. If toxicity is well documented for a few drugs (eg. avermectines) in breeds known to have the MDR1 gene mutation, there are few bibliographic data to support recommendations on a lot of other drugs (e.g. metoclopramide). In this context, data from veterinary pharmacovigilance concerning these drugs may provide additional information on the susceptibility to drug in connection with the mutation in the MDR1 gene.

MATERIALS AND METHODS
We have compiled a list of drugs for which the site www.collie-online.com references a susceptibility for dogs with the gene deletion but for which there is no specific mention on the summary product characteristics for corresponding veterinary products. A literature review and analysis of data from veterinary pharmacovigilance were conducted to look for over representation of breeds at risk or more severe symptomatology in dogs of these breeds.

RESULTS
Simple knowledge of type of interaction between a drug and PgP does not allow relevant conclusions to be drawn. Also, all PgP substrates do not cause toxicity in dogs with the MDR1 gene mutation. Some drugs like spinosad induce susceptibility only with some specific substrates of PgP (eg. ivermectin but no milbemycin). For other drugs like metoclopramide, experimental data collected in other species point to a possible susceptibilty to these drugs for breeds known to have the MDR1 gene mutation, but data from veterinary pharmacovigilance do not support this view.

CONCLUSIONS
Data from veterinary pharmacovigilance provide insight into recommendations developed on the web.