Veterinary drug residues and food safety

David Schumacher
Outline

- Veterinary drugs
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  - Residues

- Food safety
  - General principles
  - Information network
  - Example
Introduction
Veterinary medicinal products
Selected information requirements for veterinary medicinal products

Summary
- Administrative information
- Pharmaceutical information
- Quality of active substance and product

Safety tests
- Identity
- Pharmacology
- Toxicology
- User safety
- Environmental risk assessment

Residue tests
- Metabolism and residue kinetics
- Residue analytical methods

Pre-clinical and clinical trials
- Pharmacology
- Development of resistances
- Pharmacokinetics
- Tolerance in target animal species
- Efficacy
Authorisation and maximum residue limits

Different procedures to authorise veterinary medicinal products exist:

- Centralised procedure
- Decentralised procedure
- Mutual recognition procedure
- National procedures

To establish maximum residue limits (MRL), a respective application needs to be submitted to European Medicinal Agency (EMA). The Agency sends the Committee for veterinary medicinal Products (CVMP) opinion on the MRL application to the European Commission, which adopts a Commission Regulation confirming the classification of the substance.

Involved organisations (centralised procedure)

Applicant → Dossier → European Medicines Agency

- Member States
- Competent Authorities

European Medicines Agency
- Committee for Veterinary Medicinal Products (CVMP)
- Working parties of the CVMP

Opinion

European Commission
Risk assessment

Hazard identification

Hazard characterisation

Exposure assessment

Risk characterisation

Problem formulation

Communication
Hazard assessment

- Single dose toxicity
- Repeat-dose toxicity
- Tolerance in the target species
- Reproductive toxicity including developmental toxicity
- Genotoxicity
- Carcinogenicity
- (Special studies)
- Observations in humans

Health-based guidance values:
- ADI – Acceptable Daily Intake
- ARfD – Acute Reference Dose
Risk assessment

- Hazard identification
- Hazard characterisation
- Exposure assessment
- Risk characterisation
- Problem formulation
- Communication
Exposure assessment

Residue assessment
- Pharmacokinetics in food producing species
- Depletion of residues
  - Identification of marker residues
  - Ratio of marker residue to total residues
- Monitoring and exposure data
- Validated residue analytical method
- Appropriate measure for the amount of residue in the food
  - e.g., median, 95th percentile, MRL

![Diagram showing concentration over time for liver and muscle tissues.](image)
Exposure assessment

Consumption data
- Model diet
- Consumption surveys


Adults

<table>
<thead>
<tr>
<th></th>
<th>meat</th>
<th>liver</th>
<th>eggs</th>
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<tbody>
<tr>
<td>food basket</td>
<td>300</td>
<td>100</td>
<td>200</td>
</tr>
<tr>
<td>chronic (mean)</td>
<td>500</td>
<td>200</td>
<td>400</td>
</tr>
<tr>
<td>chronic (97.5)</td>
<td>600</td>
<td>250</td>
<td>500</td>
</tr>
<tr>
<td>acute (97.5)</td>
<td>700</td>
<td>300</td>
<td>600</td>
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</tbody>
</table>

Consumed amount (g/person per day)
Risk assessment

Hazard identification

Hazard characterisation

Exposure assessment

Problem formulation

Risk characterisation

Communication
Food safety

General food law (Regulation (EC) No 178/2002)

aims at a “… high level of protection of human health and consumers' interest in relation to food, taking into account in particular the diversity in the supply of food including traditional products, whilst ensuring the effective functioning of the internal market.”

“… shall apply to all stages of production, processing and distribution of food and feed. It shall not apply to primary production for private domestic use or to the domestic preparation, handling or storage of food for private domestic consumption.”
(Selected) reasons for non-compliance

- fraud
- exceedance of MRLs
- dangerous food
- non-allowed ingredients
- hygiene
- labelling
- production
- ...

Compliant vs. non-compliant

Criminal offence
Administrative offence
Warning/caution
Article 14

Food safety requirements

1. Food shall not be placed on the market if it is unsafe.

2. Food shall be deemed to be unsafe if it is considered to be:
   (a) injurious to health;
   (b) unfit for human consumption.

3. In determining whether any food is unsafe, regard shall be had:
   (a) to the normal conditions of use of the food by the consumer and at each stage of production, processing and distribution, and
   (b) to the information provided to the consumer, including information on the label, or other information generally available to the consumer concerning the avoidance of specific adverse health effects from a particular food or category of foods.

4. In determining whether any food is injurious to health, regard shall be had:
   (a) not only to the probable immediate and/or short-term and/or long-term effects of that food on the health of a person consuming it, but also on subsequent generations;
   (b) to the probable cumulative toxic effects;
   (c) to the particular health sensitivities of a specific category of consumers where the food is intended for that category of consumers.

5. In determining whether any food is unfit for human consumption, regard shall be had to whether the food is unacceptable for human consumption according to its intended use, for reasons of contamination, whether by extraneous matter or otherwise, or through putrefaction, deterioration or decay.

6. Where any food which is unsafe is part of a batch, lot or consignment of food of the same class or description, it shall be presumed that all the food in that batch, lot or consignment is also unsafe, unless following a detailed assessment there is no evidence that the rest of the batch, lot or consignment is unsafe.
of 6 May 2009

(Text with EEA relevance)

Article 23

Placing on the market

Food of animal origin containing residues of a pharmacologically active substance:

(a) classified in accordance with Article 14(2)(a), (b) or (c) at a level exceeding the maximum residue limit established pursuant to this Regulation; or

(b) not classified in accordance with Article 14(2)(a), (b) or (c), except where a reference point for action has been set for that substance pursuant to this Regulation and the level of residues does not equal or exceed that reference point for action;

shall be considered not to comply with Community legislation.

Detailed rules on the maximum residue limit to be considered for control purposes for foodstuffs derived from animals which have been treated under Article 11 of Directive 2001/82/EC shall be adopted by the Commission in accordance with the regulatory procedure referred to in Article 26(2) of this Regulation.
RASFF - the Rapid Alert System for Food and Feed

https://ec.europa.eu/food/safety/rasff_en

A recent food incident in Europe

Source: PubChem

Fipronil
Reports of fipronil in hens eggs

### Notification details - 2017.1065

Unauthorised substance fipronil (between 0.0031 and 1.2 mg/kg - ppm) in eggs

<table>
<thead>
<tr>
<th>Reference</th>
<th>2017.1065</th>
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<tr>
<td>Notification date</td>
<td>20/07/2017</td>
</tr>
<tr>
<td>Last update</td>
<td>12/10/2018</td>
</tr>
<tr>
<td>Notification from</td>
<td>Belgium (BE)</td>
</tr>
<tr>
<td>Classification</td>
<td>alert</td>
</tr>
<tr>
<td>Risk decision</td>
<td>serious</td>
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- **Notification type:** food - alert - official control on the market
- **Action taken:** withdrawal from the market
- **Distribution status:** distribution to other member countries
- **Product:** eggs
- **Product category:** eggs and egg products
- **Published in RASFF Consumers' Portal:** has been published before

MRL for eggs: 0.005 mg/kg

Risk assessment

Hazard identification

- ADI: 0.0002 mg/kg bw
- ARfD: 0.009 mg/kg bw (EFSA, 2006)

Hazard characterisation

- UK infant: 166 % ARfD
- FR adults: 57 % ARfD

Exposure assessment

- EFSA PRIMO (version 3.1), acute
  - UK infant: 108 g / 8.7 kg bw
  - FR adults: 282.2 g / 66.4 kg bw

- Amount eaten

Communication

- Eggs: 1.2 mg/kg

- *

- Serious risk for infants/children
- Medium-severity symptoms
- Concentration of 0.72 mg/kg is the threshold

Problem formulation

- Acute dietary exposure. All consumer groups.
## Follow-up

<table>
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<tr>
<th>fup720</th>
<th>France</th>
<th>28/06/2018</th>
<th>additional information</th>
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<tr>
<td>fup721</td>
<td>Denmark</td>
<td>09/07/2018</td>
<td>outcome of investigations</td>
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### Hazards

<table>
<thead>
<tr>
<th>Substance / Hazard</th>
<th>Category</th>
<th>Analytical result</th>
<th>Units</th>
<th>Sampling date</th>
</tr>
</thead>
<tbody>
<tr>
<td>unauthorised substance fipronil</td>
<td>pesticide residues</td>
<td>between 0.0031 and 1.2</td>
<td>mg/kg - ppm</td>
<td>15/05/2017</td>
</tr>
</tbody>
</table>

### Countries/organisations concerned (D = distribution, O = origin)

- Afghanistan (D) - Angola (D) - Austria (D) - Belgium (D) - Bulgaria (D) - Canada (D) - Cape Verde (D) - Commission Services
- Congo (Brazzaville) (D) - Cyprus (D) - Czech Republic (D) - Denmark (D) - Equatorial Guinea (D) - Estonia (D) - Finland - France (D)
- Germany (D) - Greece (D) - Hong Kong (D) - Hungary (D) - INFOSAN - India (D) - Iraq (D) - Ireland (D) - Isle of Man - Israel (D) - Italy (D)
- Latvia (D) - Lebanon (D) - Liberia - Liechtenstein (D) - Lithuania (D) - Luxembourg (D) - Maldives (D) - Malta (D) - Montenegro (D)
- Netherlands (D) - Norway - Philippines (D) - Poland (D) - Portugal - Qatar (D) - Romania - Russia (D) - Saudi Arabia (D) - Singapore (D)
- Sint Maarten (D) - Slovakia (D) - Slovenia (D) - South Africa (D) - Spain (D) - Sweden (D) - Switzerland (D) - Turkey (D) - Ukraine
- United Arab Emirates (D) - United Kingdom (D) - United States (D)

Follow-up: ad-hoc monitoring program

5,439 samples taken between 1 September 2017 and 30 November 2017 (thereof 2,899 randomly taken) were analysed for up to 66 substances.

EFSA (2018): Occurrence of residues of fipronil and other acaricides in chicken eggs and poultry muscle/fat

David Schumacher, LARAS, 2019-08-27
Conclusion

- The food law aims at safe food while maintaining traditional products. The effective functioning of the market should also be ensured.

- There are specific rules for the different stages of production, processing and distribution. (E.g., authorisation of veterinary medicinal products; maximum residue limits)

- Food surveillance should ensure that the rules are complied with.

- Depending on the reason for non-compliance, different follow-up actions can be prudent.
Thank you for your attention

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Further reading

**Legislation on authorization of veterinary medicinal products**


Further reading

Legislation on maximum residue limits of pharmacologically active substances


Further reading

Guidance documents
Further reading

**General food law**
- Rapid alert system on food and feed [https://ec.europa.eu/food/safety/rasff_en](https://ec.europa.eu/food/safety/rasff_en)