LARAS
LATIN AMERICAN
RISK ASSESSMENT
SYMPOSIUM

Chemical Risk Assessment regarding Veterinary Drug Residues

David Schumacher
Susanne Rath
Eloisa Dutra Caldas

What we already know …

News reports:

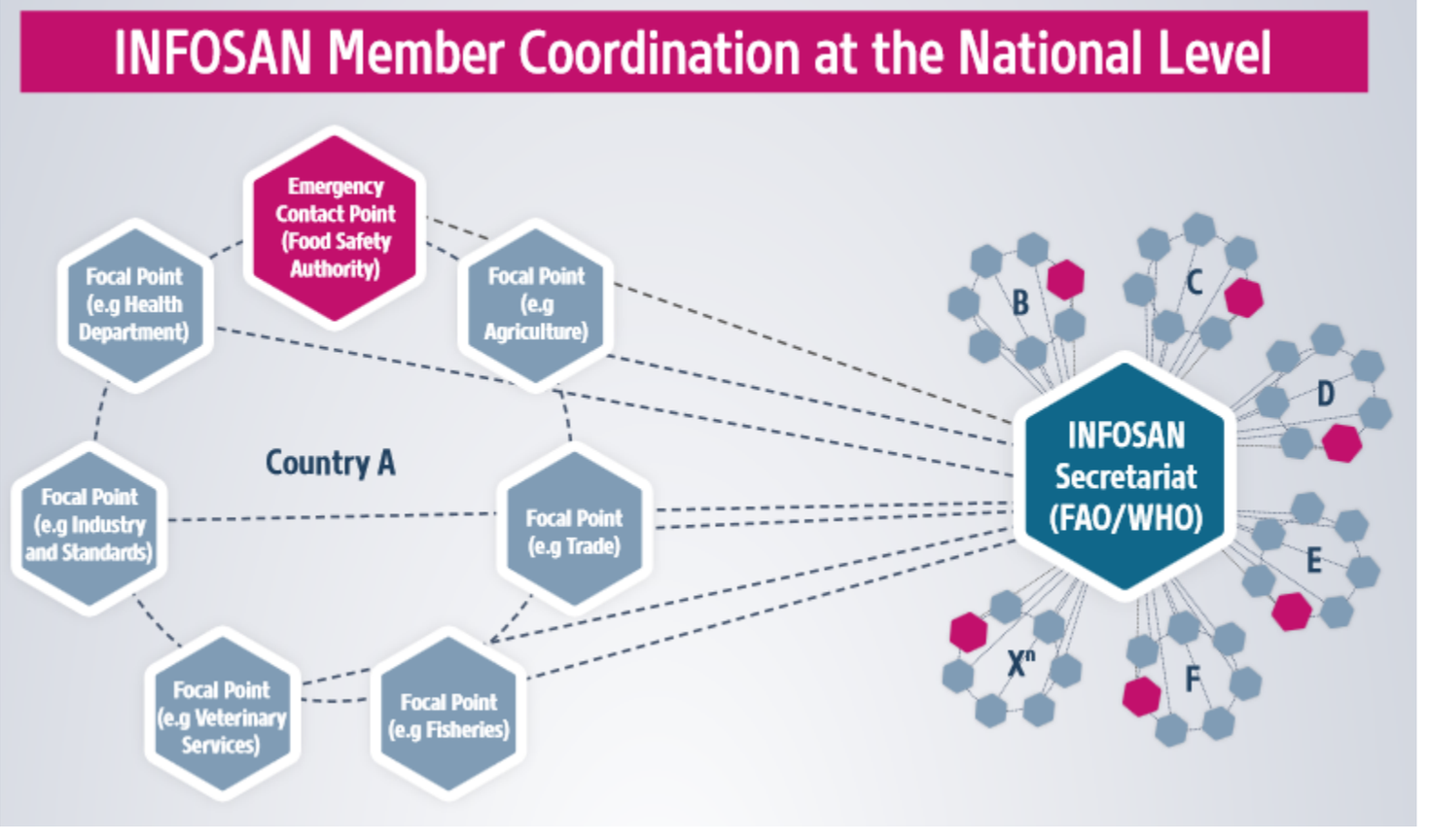
A shipment of cattle meat was stopped at Amsterdam harbour.

The shipment was sent from Poyais. Poyais exports mainly cattle meat to EU.

What would you do now?

- Ignore it.
- Deny it.
- Call a friend in Amsterdam and ask for background.
- Call a friend in EU Commission and ask for background.
- Liaise with official contact point and ask for background.

Information exchange networks
International Food Safety Authorities Network



https://www.who.int/activities/responding-to-food-safety-emergencies-infosan

Graphics: https://www.who.int/docs/default-source/food-safety/member-roles-and-responsibilities-en.pdf?sfvrsn=d76c44fb_2

Codex alimentarius

Guidelines for the exchange of information between countries on rejections of imported food (CAC/GL 25-1997)

Annex: Standard format for exchange of information between countries on rejections of imported food

- Identification of the food concerned
- Importation details
- Details of rejection decision
- Reason(s) for rejection
- Action taken

http://www.fao.org/3/X4489E/x4489e06.htm

Information received from the contact point

The cattle meat (muscle) contained ivermectin.

The amount detected was 100 µg/kg.

The shipment originated from Poyais and had a size of 100 tons.

The shipment will not be imported but will be rejected.

Reason: The ivermectin amount in the sample exceeded the maximum residue limit (MRL)

What is ivermectin?

- An antiparasitic drug.
- A non-steroidal anti-inflammatory drug.
- An antimicrobial drug.
- A pesticide.
- I do not know.

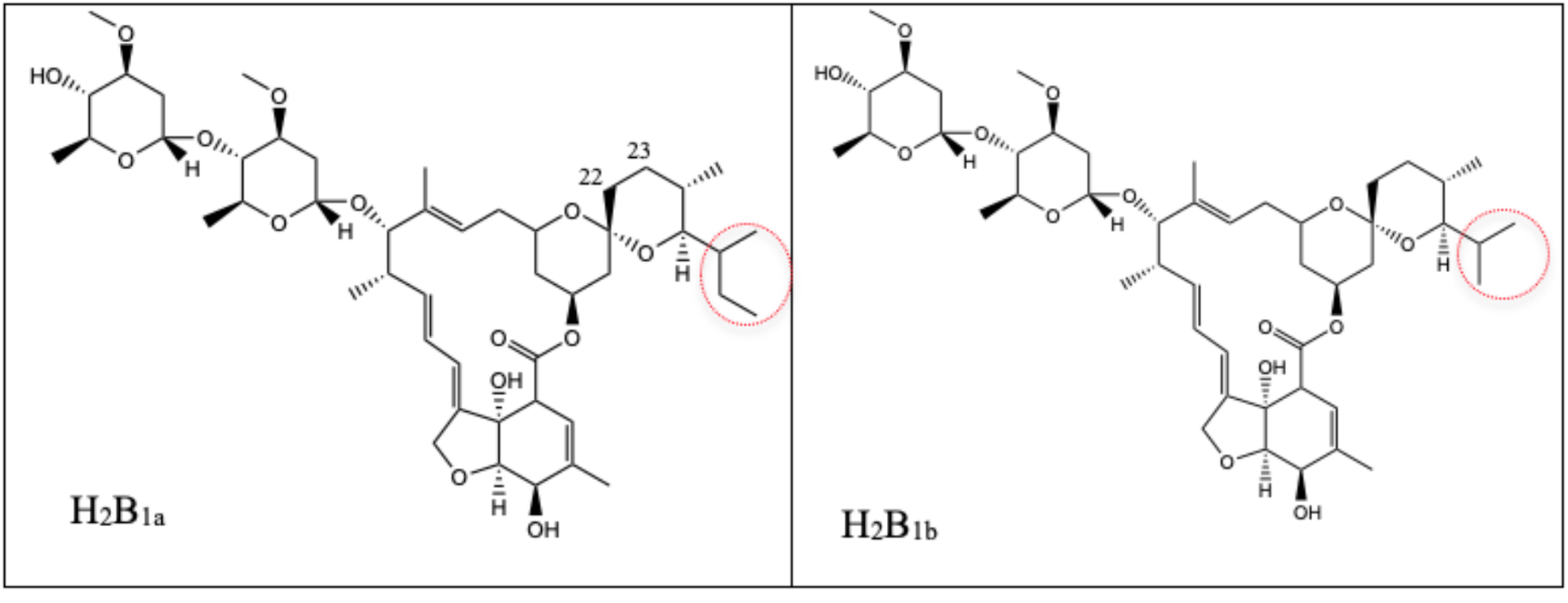
Ivermectin

In veterinary medicine ivermectin is used in cattle, sheep, goats, pigs, horses and reindeer as an antiparasitic, administered subcutaneously, topically or orally as a single dose treatment only.

In human medicine ivermectin is used for the treatment of onchocerciasis.

Ivermectin is a chemically modified fermentation product of *Streptomyces avermitilis*, consisting of a mixture of two homologous compounds

- 22,23-dihydroavermectin B1a (H_2B_{1a}, not less than 80%) and
- 22,23-dihydroavermectin B1b (H_2B_{1b}, not more than 20%).



Risk assessment – toxicity

- No drug-related effects (physical signs, body weight, ocular lesions, haematology, serum biochemical parameters, or necropsy findings) were noted in treated rhesus monkeys with ivermectin at doses of 0.3 to 1.2 mg/kg bw.

- Genotoxicity – negative

- Ivermectin is a drug also used in human medicine (oral doses of ivermectin of up to 120 mg were well tolerated by human subjects). The NOAEL for acute oral toxicity of ivermectin was identified as 120 mg (equivalent to 1.5 mg/kg bw based on the median body weight of 77.9 kg), the highest dose tested.

- Expsoure (injection site): ARfD of 200 µg/kg bw, based on a NOAEL of 1.5 mg/kg bw, the highest dose tested in a safety, tolerability and pharmacokinetics study in healthy human subjects, with application of an uncertainty factor of 10 for intraspecies variability.

WHO Food Additive Series 72, 2016

Maximum Residue Limit

Is the maximum concentration of a veterinary drug residue that is legally permitted or recognized as acceptable in or on a food as set by a national or regional regulatory authority. The term ‘tolerance,’ used in some countries, can be, in many instances, synonymous with MRL.

Acceptable Daily Intake

It is the amount of a substance that can be ingested daily over a lifetime, without appreciable health risk to the consumer. The ADI most often will be set on the basis of the drug’s toxicological, microbiological or pharmacological properties. It is usually expressed in micrograms or milligrams of the chemical per kilogram of body weight.

Acute reference dose

It is the estimate of the amount of substance in food, expressed on a body weight basis, that can be ingested over a short period of time, usually during one meal or one day, without appreciable health risk to the consumer on the basis of all known facts at the time of evaluation.

MRLs currently defined for ivermectin residues in cattle meat

Jurisdiction	ADI (µg/kg bw)	Muscle (µg/kg)	Liver (µg/kg)	Fat (µg/kg)	Kidney (µg/kg)	Injection site (µg/kg)
Codex	0-10	30	800	400	100	
US	5	650	1600			
Canada	1	10	70	100	140	
EU	10	30	100	100	30	1300
Japan	1	10	100	40	10	10
Australia	1	40	100	40	10	
New Zealand	1	10	100	40		

Marker residue: ivermectin H_2B_{1a}

Sample:
100 µg/kg

Injection site

Ivermectin is a lipophilic drug.

Main administration route in mammalians: subcutaneous injection.

High invermectin concentrations at the injection site.

Acute dietary exposure

Acute reference dose: ARfD 200 µg/kg bw

MRL at the injection site???

Is this sample a serious health risk?

- Yes.
- No.
- I do not know.
- I do not have sufficient information.

Sample:
100 µg Ivermectin per kg cattle meat

Risk assessment

At the 81st JECFA meeting, an ADI of 0-10 µg/kg bw was established on the basis of a NOAEL of 0.5 mg/kg bw per day for neurological effects (mydriasis) and retardation of weight gain in a 14-week dog study, with the application of an uncertainty factor of 50.

The Committee also established at this meeting an ARfD of 200 µg/kg bw, based on a NOAEL of 1.5 mg/kg bw in humans and an uncertainty factor of 10 (WHO, 2016).

ADI x ARfD

Risk assessment

ADI: 10 µg/kg bw

ARfD: 200 µg/kg bw

Exposure assessment with EFSA‘s PRIMO (acute exposure):

Results for children

No. of commodities for which ARfD/ADI is exceeded (IESTI): ---

IESTI

Highest % of ARfD/ADI	Commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
0,4%	Bovine: Muscle/meat	0,1 / 0,1	0,72

Results for adults

No. of commodities for which ARfD/ADI is exceeded (IESTI): ---

IESTI

Highest % of ARfD/ADI	Commodities	MRL / input for RA (mg/kg)	Exposure (µg/kg bw)
0,3%	Bovine: Muscle	0,1 / 0,1	0,57

EFSA‘s PRIMO (chronic exposure)

Calculated exposure (% of ADI)	MS Diet	Expsoure (µg/kg bw per day)
4%	SE general	0,44
1%	FR child 3 15 yr	0,15
1%	ES child	0,14

Risk assessment

ADI: 10 µg/kg bw

ARfD: 200 µg/kg bw

Exposure assessment with TMDI/EDI:

0.5 µg/kg bw (60 kg bw, 300 g meat)

JECFA‘s GEADE (acute exposure):

Adults: 2.54 µg/kg bw (consumption: 25.4 g/kg bw/day)

Children: 2.54 µg/kg bw (consumption: 25.4 g/kg bw/day)

Consumption data from FAO/WHO (2014). *Residue evaluation of certain veterinary drugs*. JECFA Monographs 15. http://www.fao.org/3/a-i3745e.pdf

Where did the sample come from?

- I do not know.
- It is impossible to answer this question.
- I do not have sufficient information.
- This can be solved quite easily.
- From Poyais

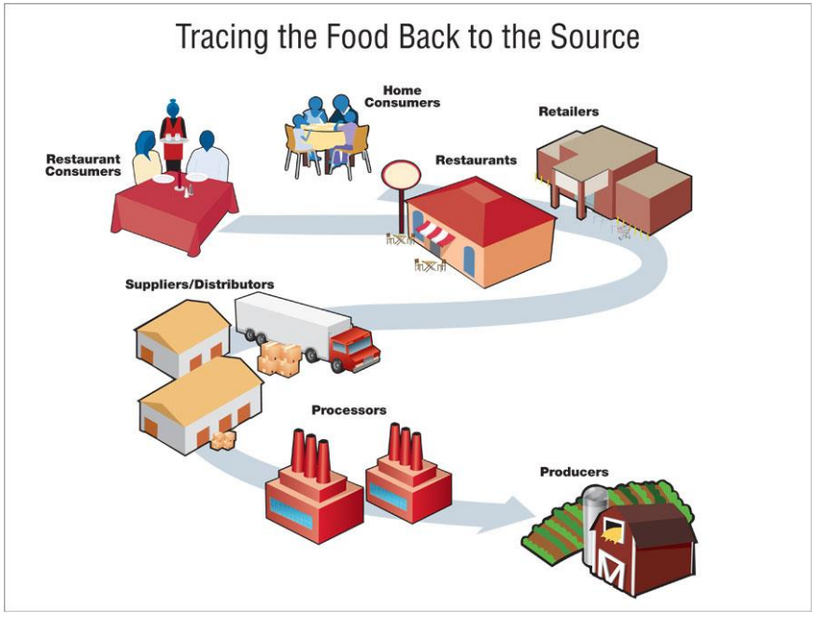
Traceability

Based on the documentation it should be possible to trace back where the meat / animals came from:

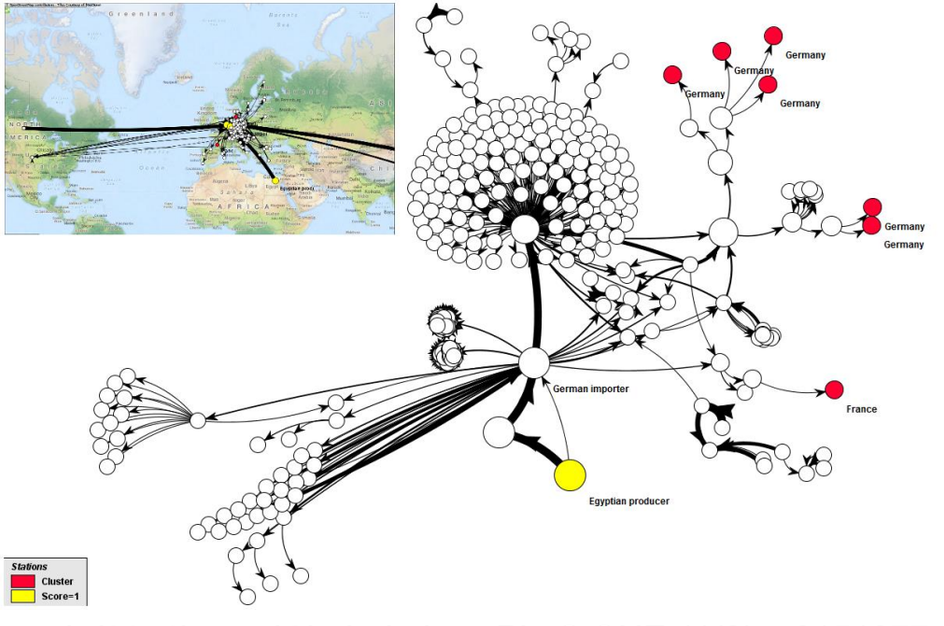
Shipment → Slaughter house → Farm

Based on these information, it should be possible to determine where else the meat or the animals were delivered?

Farm → (other) slaughter houses → distributors → retailors



https://www.cdc.gov/outbreaknet/investigations/figure_traceback.html



Weiser et al. (2016) FoodChain-Lab … PLoS ONE 11(3): e0151977. https://doi.org/10.1371/journal.pone.0151977

Traceability

- The shipment originated from one slaughter house.
- The slaughter house checked their logs: the meat from this shipment was derived from cattle of one farm.
- The farmer indicated that at that time he had a flock of young cattle with parasites and wanted to treat these animals. This should be done by subcutaneous injection with an ivermectin-containing drug.
- The farm hand remembered, that he gave the drug to the older cattle. These animals were brought soon thereafter to the slaughter house and were slaughtered 1-2 days after treatment. He administered 1 mg/kg bw as requested by the farmer.

The drug label states a withdrawal period of 42 days and recommends a dose level of 200 µg/kg bw.
There are neurological symptoms in cattle dosed with 4 mg/kg bw.

How can such a situation be prevented to re-occure?

- I do not know.
- It is not possible to prevent such situations.
- Competence of farmers and veterinarians.
- More official enforcement and official controls.

Monitoring

(Non-)targeted checks, whether the products are compliant

- at farm-level
- at slaughter house-level
- …
- (at market-level)

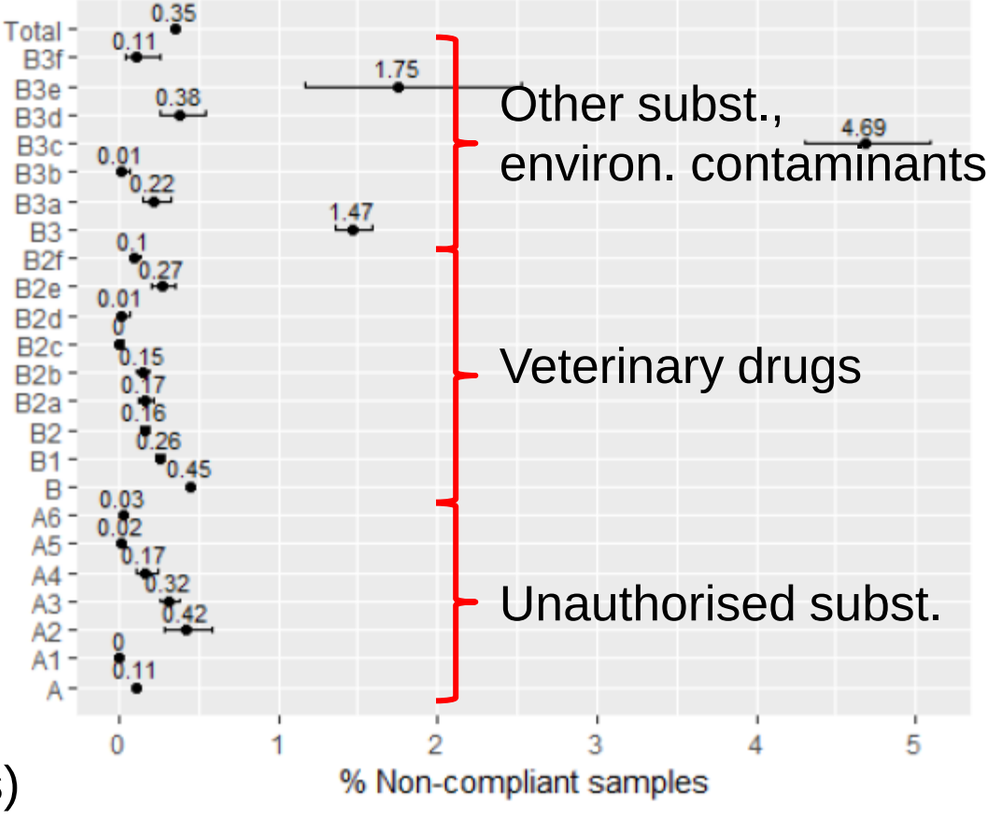
TECHNICAL REPORT

APPROVED: 8 February 2019

doi:10.2903/sp.efsa.2019.EN-1578

Report for 2017 on the results from the monitoring of veterinary medicinal product residues and other substances in live animals and animal products

European Food Safety Authority



360,293 samples (1,273 non-compliant samples)

Figure 1: Percentage of non-compliant samples in each substance group

How to prevent such situations?

- ✓ Proper use of veterinary drugs according to the label, e.g., correct dose levels and withdrawal periods.

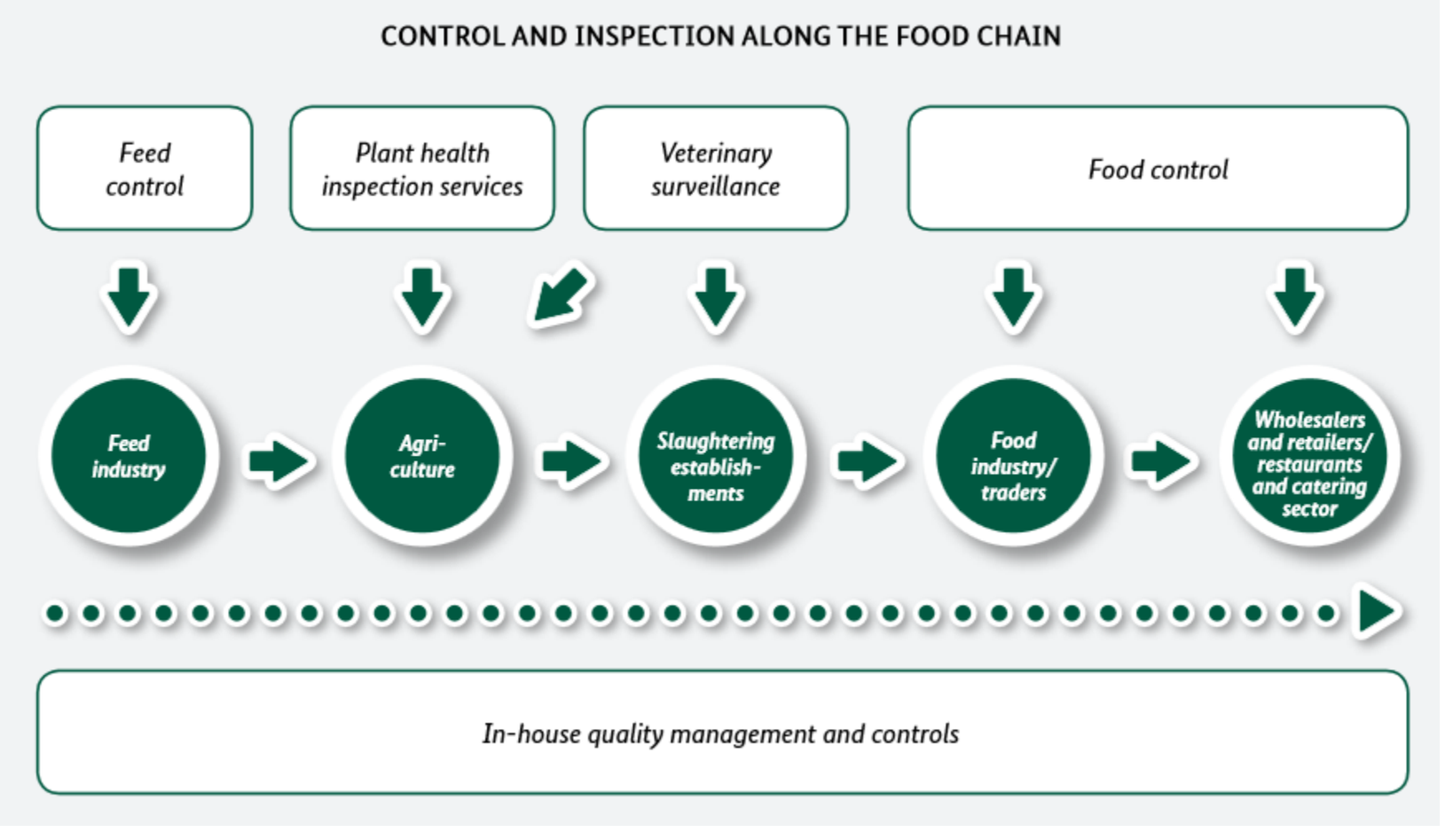
- ✓ Qualify farmers, veterinarians and all others handling food, but also of the personnel in the authorities.
- ✓ Continuous professional education of all persons involved.

- ✓ Official controls at farm, slaughter houses, warehouses and on the market regarding animal care, hygiene, residues, …
- ✓ Enforcement of the rules.
- ✓ Enforcement has more means, than punishment, such as follow-up investigations, more frequent visits, …

- ✓ Establish structures and networks.
- ✓ Organise your knowledge.

Safe food is a multidisciplinary task involving all levels of food production but also official controls

Move from reaction to prevention



Integrated surveillance – from farm to fork (table) – information sharing

Graphics: Federal Ministry of Food and Agriculture (2018): Understanding food safety https://www.bmel.de/SharedDocs/Downloads/EN/Publications/Understandingfoodsafety.pdf?__blob=publicationFile

Thank you for your contribution