Stiftung Tierärztliche Hochschule Hannover
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Application of antibiotics in livestock via medicated feed, common compound feeds or via drinking water – aspects of interest!

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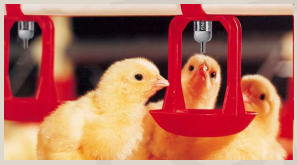


Toulouse, 16th September 2015

Arrangement

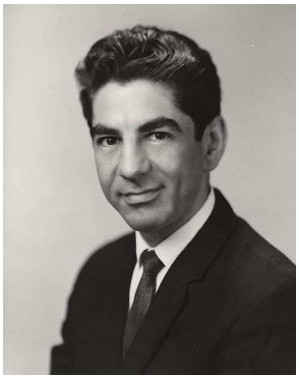
- **Use of antibiotics in livestock**
- **Challenge No. 1: Development of resistance**
- **Feed legislation / Drug legislation**
- **Definitions / Termini / Characterization**
- **Risks due to the use of antibiotics in livestock**
  - Application via feeds (all species)
  - Application via liquid diets (calves, pigs)
  - Application via water for drinking (all species)
- **Consequences / Conclusions**
- **Summary**

§

Times change

'The book of infectious diseases can now ultimately be closed.'

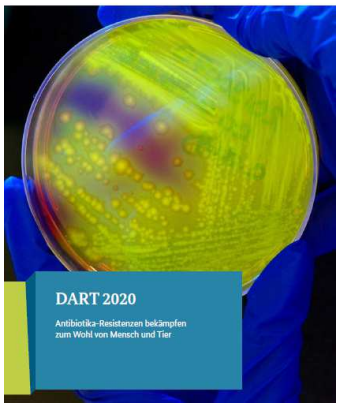
Steinfeld, Surgeon General, 1972



Jesse Leonard Steinfeld

nach Pletz, 2013

Resistance: The threat of human beings



Intensive efforts by governments to reduce the risks for human beings as well as for animals.

May, 2015

Use of antibiotics in livestock → determining the head lines in public media

- **comparing the amounts used in different countries of Europe (2011/2012) in food producing animals:**
  - Germany: 1734 t/year
  - France: ~ 1000 t/year
  - Netherlands: 514 t/year
- **neglecting the number of animals/produced amounts of food! (considering the produced food: Germany next to Denmark!)**
- **starting new efforts to reduce the amounts used in livestock**
  - monitoring the use on each farm in details
  - survey on conditions/indications/type of antibiotics
  - optimizing the application („prudent use“)

Main reasons/indications for use of antibiotics in livestock (based on epidemiological studies/surveys in Germany; KREIENBROCK et al. 2011)

Cattle	
- respiratory diseases	62 %
- diseases of the alimentary tract	17 %
- mastitis/udder health	2.5 %

Pigs	
- respiratory diseases	40 %
- diseases of the alimentary tract	40 %
- further reasons (MMA ...)	20 %

Poultry	
- gastrointestinal diseases	50 %
- respiratory diseases	25 %
- further reasons	25 %

Av. number of antibiotic treatments per animal in the production cycle:	
- pigs[1)]	5.9
- dairy cows	2.5
- fattening calves	2.3
- poultry[2)]	?

[1)] from birth up to end of fattening

[2)] turkeys +++ / broilers +; high variation due to the different length of the cycle

Aspects of legislation/official recommendations regarding application of medical products via feed/water:

- **Guidelines for the oral application of medicinal products to livestock via feed or water, 3rd edition, March 2014**
  Ministry for Food and Agriculture, Germany
- **Guidelines for the prudent use of antibiotics in veterinary medicine**
  BTK; January 2015 (Federal Chamber of Veterinarians)

➡ **risks: cross contamination/residues in food/inducing resistance in bacteria/adverse effects in/on the environment**

Legislative aspects related to drinking water quality

- **Code of Practice on Good Animal Feeding (2004):**
  "When there is a reason to be concerned about contaminations of animals from the water, measures should be taken to evaluate and minimize the hazards" §
- **EU-Directive 183/2005** (→ food producing animals):
  " … water for drinking … should be of appropriate quality for the animals being produced!" §
- **Further regulatory requirements have to attract attention:**
  → application of feed additives/biocides/drugs/vaccines via water §

Definitions / termini / characterization -
The different ways for application of medicinal products to livestock:

1.”Finished Medicinal Products“ for oral application relevance↑↑↑
- medicinal product prescription → vets → farmer
- veterinary practitioner is responsible for correct application

feed | water | feed and water

- veterinarians / farmers are *not licensed* to use *premixes* but complete medicinal products („finished medicinal product“)

2. “Compound feed“ containing the medicinal product(s) (”medicated feedingstuff“/”medicated feed”) relevance ↓
- produced in specific facilities under specific conditions (premixes)
- veterinary prescription to the producing factory
- fed as delivered (without mixing etc. by the farmer)

3. ”Medicinal products“ for further ways of application (injection etc.) relevance ↑

Official recommendations regarding the application of medical substances in livestock via the feed or the water for drinking
Ministry BMELV, 19th June 2009

1. „finished medicinal products“ for oral application via feed and/or water

- use of „dosing apparatus“ (DIN norm 10529 – 1/2)

or (alternatively)

2. „medicated feed“ (produced in specific factory)

- principals to minimize diverse risks in the interest of animal welfare, consumer protection and food safety

There is a need for differentiation:

„Medicinal products“ for oral application (via feed / water)

- **individually (pets +++ / livestock +)**
- **one group of animals (pen of pigs, calves, poultry)**
  (in one trough, dosing done by hand)
- **groups of animals (lots of pens / boxes in one barn)**
  primary purpose of automatic dispensers for medicinal products, application via feed (mash diets) or drinking water
  (feeding system of the whole barn / technique for offering drinking water to all animals in one barn/one extra water dispenser per box)
- **individual groups of animals in one barn**
  (two pipelines for water: one for offering the „normal“ water for drinking, one for application of medicinal products)

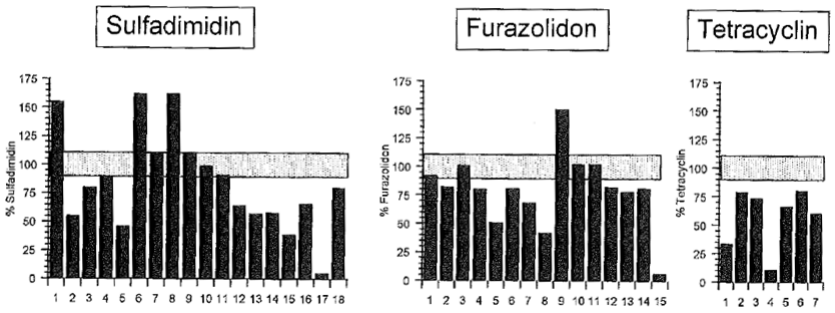
How to manage/handle „oral application“ of a finished medicinal product to livestock?

- by hand on the offered amount of feed into the trough ”top dressing” → individuals/some groups of animals in one barn
- by hand: adding the powdery or liquid product into the blender, in which the diet is prepared (under the supervision of the vet)
- automatically (“dosing apparatus”) on/into the “feed stream” (mash diet/pelleted diet (?)/granulated diet (?)
- automatically (“dosing apparatus”) via water for drinking to all animals in one pen[1)] or in one barn (several groups)
- automatically (dosing apparatus) via water into the liquid diet of individual groups (it is not an application via water for drinking; impossible for animals fed liquid diets)

[1)] by hand or when two different pipelines for drinking water are available

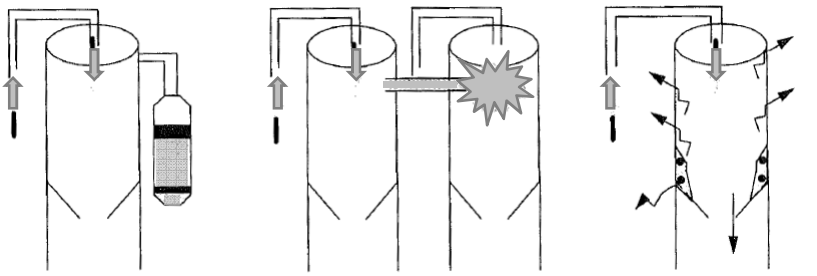
Measured concentrations of antibiotics in pelleted compound feeds for pigs in comparison to expected/calculated values

(losses of tetracyclines due to thermal challenge)



KAMPHUES 1996

Risks for contamination of feeds due to processes at filling, storing or emptying of bins/silos



1. „dust collector“ (of one bin)
2. „bypass“ (between two bins)
3. „dead zones“ (within one bin)

risks primarily related to “medicated feedingstuff”

KAMPHUES 1996

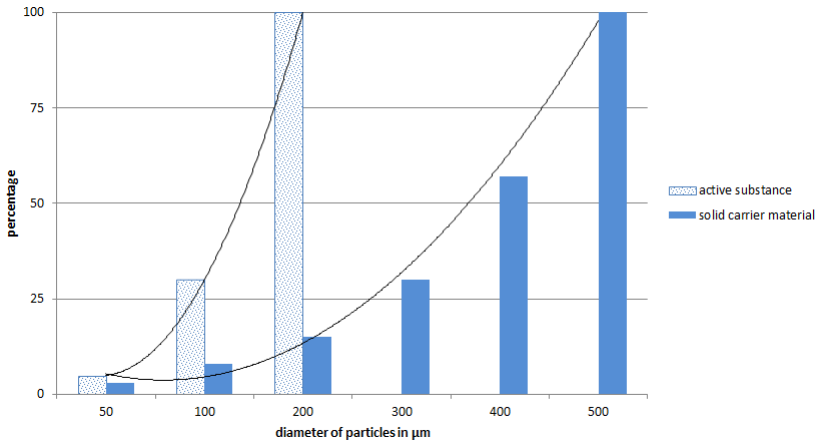


Fig.: The distribution of particle sizes within the active substance and within the solid carrier material: Only in the case of “parallel curves” stable blends can be produced!

The contamination of compound feeds by the coccidiostat nicarbacin due to the production in one line only

compound feed	mg/kg diet	
• intended dosage • observed dosage	125 118.7 ± 5.90	 (128)[1)]
• 1st following batch • 2nd following batch • 3rd following batch	5.87 ± 4.97 0.78 ± 0.74 0.30 ± 0.27	(14.8)[1)] (2.19)[1)] (0.72)[1)]

[1)] max. values; residues in egg yolk: > 2 mg/kg diet

DORN et al. 1988

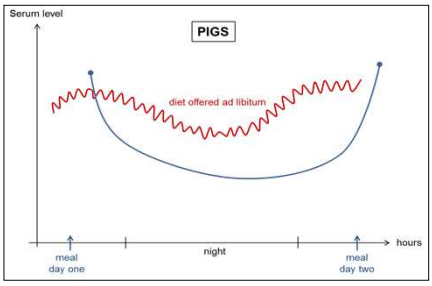
Contamination/cross contamination due to the use of medicated feeds/compound feeds containing antibiotics for livestock

step	contamination of	relevance
production of medicated feed		
- elevators	next feed batch	+++
- blender	dust sampler	+++
- pelletizing plant	next feed batch	(+)
transport to the farm		
- truck	next batch of feed	(+)
- emptying	surrounding area via dust	(+)
storing at the farm		
- store (itself)	internal surfaces (adherence)	+
- „dead zones“	non flowing feed material	+++
- dust sampler	fines of the feed („dust“)	++
offering the feed		
- transport to the animals (pipelines)	following feed batch	(+)
- dust of the feed	air, technical equipment	++
- „refused feeds“	trough / following feed batch	- / +++
ingestion by animals		
- „refusals“ (→ litter)	floor, litter material	- /++
- feces, urine, excreta	manure / slurry	- / +++

Risks due to a direct contact (skin), inhalation (respiratory tract) and entrance in the body (for example: eyes) at handling of medicated feeds

Risks due to direct contact with feeds containing medical substances	
step	**precautions**
production of substances	high grade
production of premixes	high grade
transport/storing of feeds	different grades
compound feed production	different grades
offering the feed(s)	low grade
dust within stables	not established
cleaning of technical equipment	not established
emissions leaving the stable (manure, air, dust, etc.)	possible, but not common

1) one meal per day vs. ad libitum feeding



2) light determines feed intake

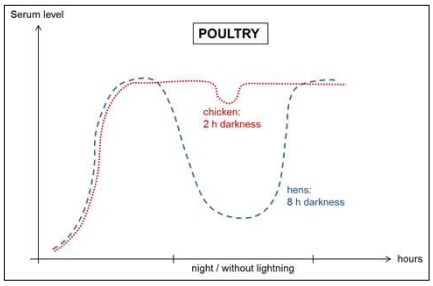
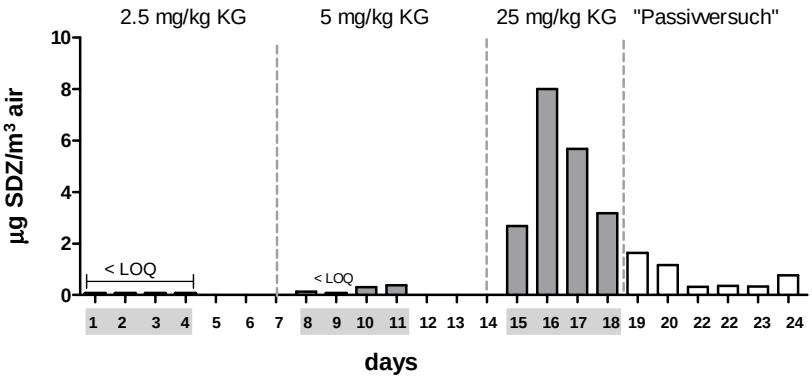


Fig.: The rhythm of feed and water intake is determining the level of medical substances in the serum of treated animals (KIETZMANN 2015)

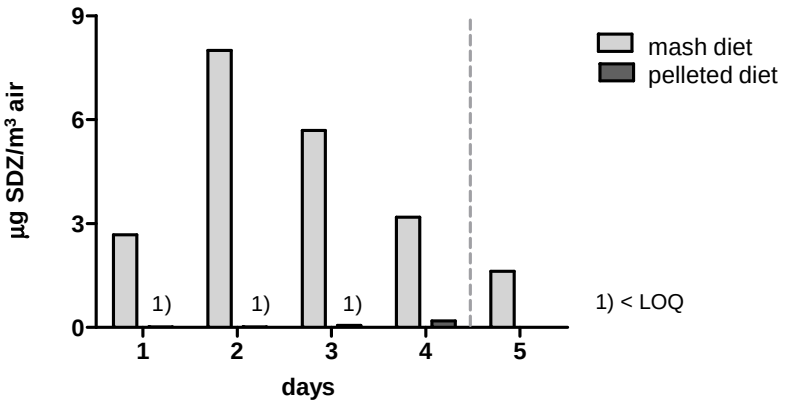
The contamination of the air by sulfadiazin due to its application via non-pelleted compound feed



Sulfadiazine content in the dust of the air in a pig stable after treatment of pigs (different dosages; four days; two meals per day)

Kietzmann 2015

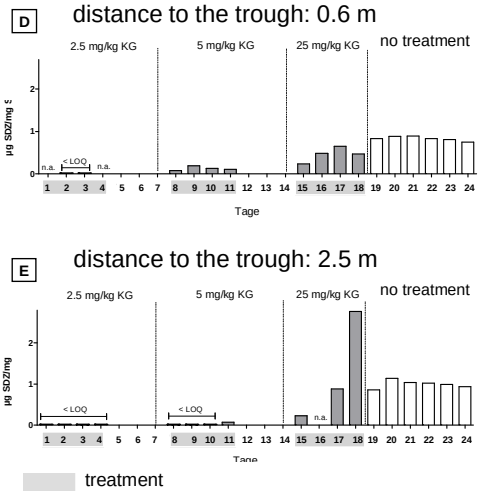
Contamination of the dusty deposits in a stable for pigs treated with sulfadiazine, applicated via feed (mash vs. pellets)

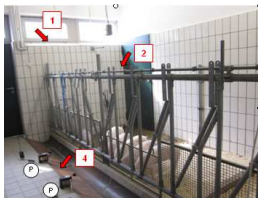


Treatment: 25 mg/kg bw; 2 meals per day; mash diet vs. pelleted diet;

Kietzmann 2015

The contamination of dust by sulfadiazine due to its application via non-pelleted compound feed for pigs





Kietzmann 2015

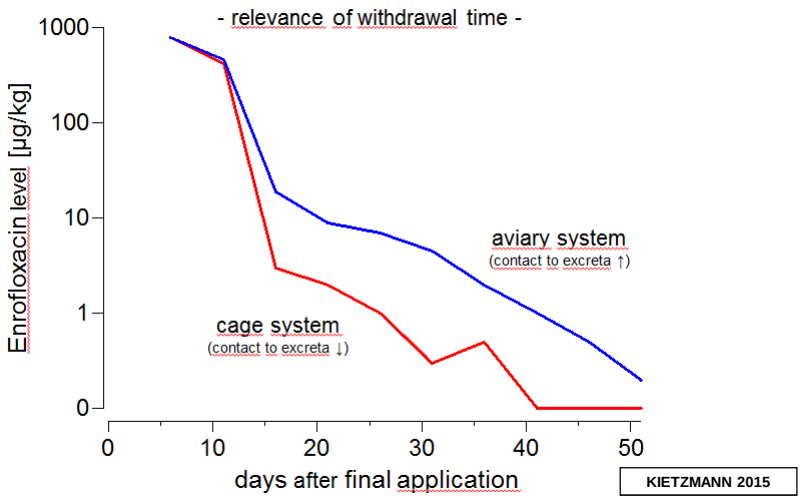


Fig.: Development of residue levels of enrofloxacin in laying hens after identical treatment but housed differently (cage system vs. aviary system)

Concentration of sulfonamides in feeds and slurry after treatment of sows (37.5 g Vetoprim® per sow and day during 8 days; LANGHAMMER et al. 1988)

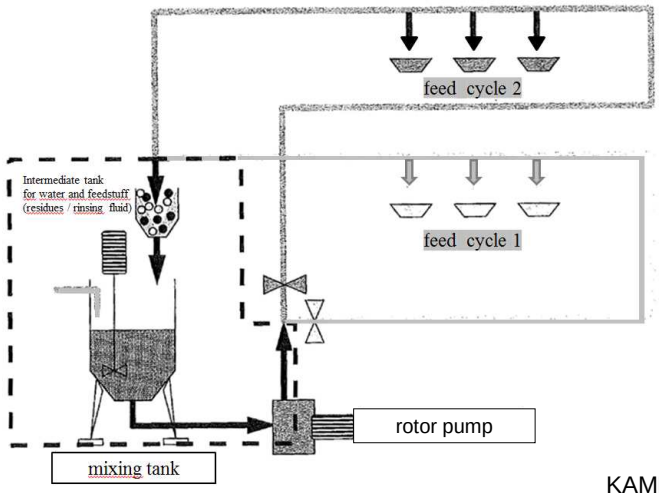
substrates analysed	concentration (mg/kg) SDM	STC	TM
diet (as fed)	600	600	240
slurry (wet)			
- directly after treatment	35 - 39	25 - 30	n.n.[1)]
- after 5 weeks of storing	~ 20	~ 10	n.n.[1)]
soil			
(1. day after application	0.05	0.04	-

1) lowest detection limit: 0.7 mg/l slurry

Specific challenges due to liquid feeding systems (calves, pigs)

- time between adding the drugs and feeding
- „demixing“ processes (or separation of liquid and solid phases/particles containing phase)
- one blender for different diets for different ages
- diverse moist ingredients of special composition
  - whey/CCM/food by-products (containing substances or preservation like org. acids, formaldehyde a. s. o.)

Risks for cross contamination in liquid feeding systems for pigs: one blender tank only and joint parts within two feed cycles



KAMPHUES 1996

Contamination (CTC, SDM) of the liquid diet for fattening pigs after treatment of grower pigs in the same stable (two feed circles) WANNER et al. 1996

pen No.	CTC[1)]	SDM[2)]	SDM[3)]
	← mg/kg liquid diet →		
26	n. d.	3.0	2.5
35	n. d.	2.7	2.2
43	n. d.	0.3	0.6
51	0.4	4.1	3.4
64	n. d.	n. d.	2.0

[1)] in the blender tank: 32 mg CTC (Chlortetracycline)/kg liquid diet
[2)] in the blender tank: 136 mg SDM (Sulfadimidine)/kg liquid diet
[3)] in water that cleaned the pipeline after treatment

Concentrations of CTC and SDM in the liquid diet in 7 troughs of 25 troughs for fattening pigs in one barn (WANNER et al. 1996)

active substance	blender tank	in troughs of 7 boxes min. value	in troughs of 7 boxes max. value
CTC (mg/kg)[1]	32	26	37
SDM (mg/kg)[1]	136	97	185

[1] CTC = Chlortetracycline; SDM = Sulfadimidine

Application of “finished medicinal products” via water (1)

- **presumed water : feed ratio?**
  - for example: 2 : 1 → 5 : 1 (in broiler: high temperatures)
- **water flow rate at individual drinkers**
  - in pens of pigs: < 100 ml/min. → > 1000 ml/min.
- **water losses at drinking**
  - depending on the technique/position/pressure
- **foster the water intake by stopping the water before supply for some hours before**
  - high initial intake for immediately high serum levels

Application of “finished medicinal products” via water (2)

- **test the technical facilities for water supply continuously**
  - parameters of water composition/formation of „biofilm“
- **cleaning after ending the treatment via water**
  - to avoid „delay of release from complexes in biofilm“
- **low doses of antibiotics (in the water pipeline, litter)**
  - risks for inducing resistance in bacteria
- **whereabouts of water that arise when watering technique is cleaned/rinsed**

Use of organic acids to lower the pH in drinking water for diverse purposes

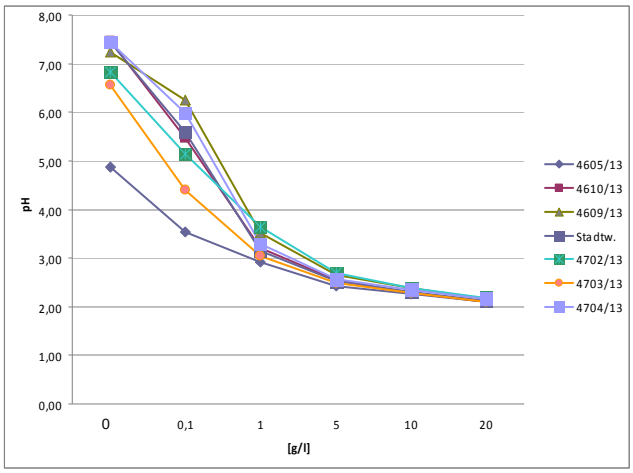


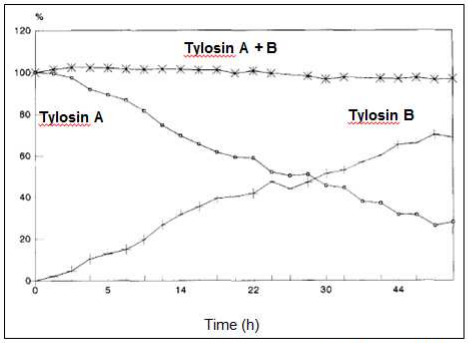
Fig 2: pH values in drinking water (field samples) after adding increasing amounts of formic acid (85 %) **KAMPHUES et al. 2013**

Use of organic acids to lower the pH in drinking water for diverse purposes

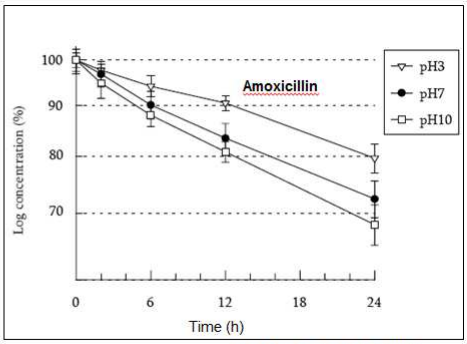
products used in the field to reduce pH in drinking water

samples of water, n	**7**
native pH (min. – max.)	**4.87[1)] – 7.45**
formic acid (85 %)	2.93 – 3.65
lactic acid (100 %)	2.68 – 3.33
propionic acid (99.5 %)	3.33 – 4.86 **!**
citric acid (85 %)	2.93 – 4.37
combination of formic acid/formate	3.19 – 3.33

1) **native pH value of Coca Cola = 2.5 – 2.7!**



PAESEN et al. 1995



JERZSELE and NAGY 2009

Fig.: Losses of active substances in aqueous solutions depending on parameters of the quality of water for drinking

Veterinary aspects concerning the quality of drinking water for poultry

Formation of "biofilm" in the water pipelines/watering technique

- **"biofilm" characterized by a solid build up at the inner surface of the pipelines/ technique consisting of anorganic and organic compounds settled with certain microorganisms**
- **favored by low water flow rates, high contents of minerals (Mn?), supplemented organic substances (substrate for bacteria within the system)**
- **consequences:**
  - **technical dysfunction/malfunction**
  - **continuous contamination of passing water**
  - **temporary binding/complexing of drugs**
  - **→ later on: release → residues of drugs (?)**

Specific challenges when substances are applicated via water for drinking

1. variation of water consumption in animals
   - temperature, dietary effects, performance
2. variation in the quality of drinking water
   - pH, inorganic constituents, microbial contamination
3. variation in the techniques for drinking water
   - animals adopted or not
4. variation in losses of water at drinking
   → non-metabolized drugs are released → contamination of litter, floor and equipment of pens
5. precipitation, sedimentation of soluble agents
   → due to formation of „complexes“ → losses in „availability“
   → new developments: emulsions

„side effects“ when medical substances are applicated via feed or water for drinking

- palatability of feed or water for drinking?
  → reduced water intake: risk of salt intoxication
- interactions between drugs and feed/water constituents?
  → cations like calcium etc. → formation of insoluble complexes
- interaction between medical substances and feed additives?
  → ionophores (coccidiostats) in the diet, therapy with tiamulin
- effects on the microflora of the alimentary tract?
  → long lasting treatment → vitamin K deficiency
- susceptibility for infections of the GIT?
  → higher risk of infections with *Salmonella* spp. after antibiotic treatment

„Residues“ in animals in spite of correct application and considering the withdrawal time exactly

- **in treated animals**
  - delayed metabolization (?)
  - unintended intake of contaminated feed
  - ingestion of feed refusals from the litter (poultry!)
- **in non-treated animals**
  - confounding feeds
  - contamination of feeds (on different steps)
  - contamination of the barn (equipment)
- **in both (treated and non-treated animals)**
  - antibiotics are bound in the „biofilm“ and released after a time lag (“delayed medication“)

Reasons for failure (the intended dosage is not achieved) when substances are applicated via medicated feeds / compound feeds with…

- **miscalculation/underdosed premixes**
  - drug concentrations in feed or in water
  - low price products?
- **lower feed intake than supposed**
  - individual day by day variation in feed consumption
  - reduced appetite (typical reaction at infection, disease, pain)
  - impaired palatability
  - demixing processes in nonpelleted feeds
- **inhomogenous distribution of drugs in feed**
  - insufficient mixing processes
  - demixing processes in feeds
- **processes resulting in losses of medical substances**
  - thermal treatment (conditioning / compaction)
  - formation of „complexes“ (interactions to feed constituents)
  - „inactivation“ due to pH, feed additives (?)
  - microbial activity / enzymes (?)

Consequences/conclusion

- **Antibiotics are definitively**
  - not “normal” additives for feed and water
  - not developed to hide lacks of management
- **The most important risk of antibiotics: each use**
  - is favoring **RESISTANCE** in bacteria
  - of diverse biotopes (including human beings)
- **To maintain successful therapy of human beings and animals in future times antibiotics should be used**
  - only in cases of absolute necessity
  - in a prudent way (minimizing diverse risks)