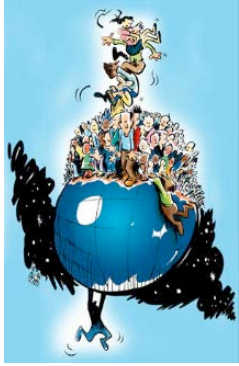
Pharmaceuticals in the Environment

Fabio Kaczala, PhD
Ass. Prof. in Env. Sciences
Kalmar Municipality
Service and Adm. Department
Mobile: +46 (0)72 537 4129
Phone: + 46 (0) 480 5802
Email: fabio.kaczala@kalmar.se



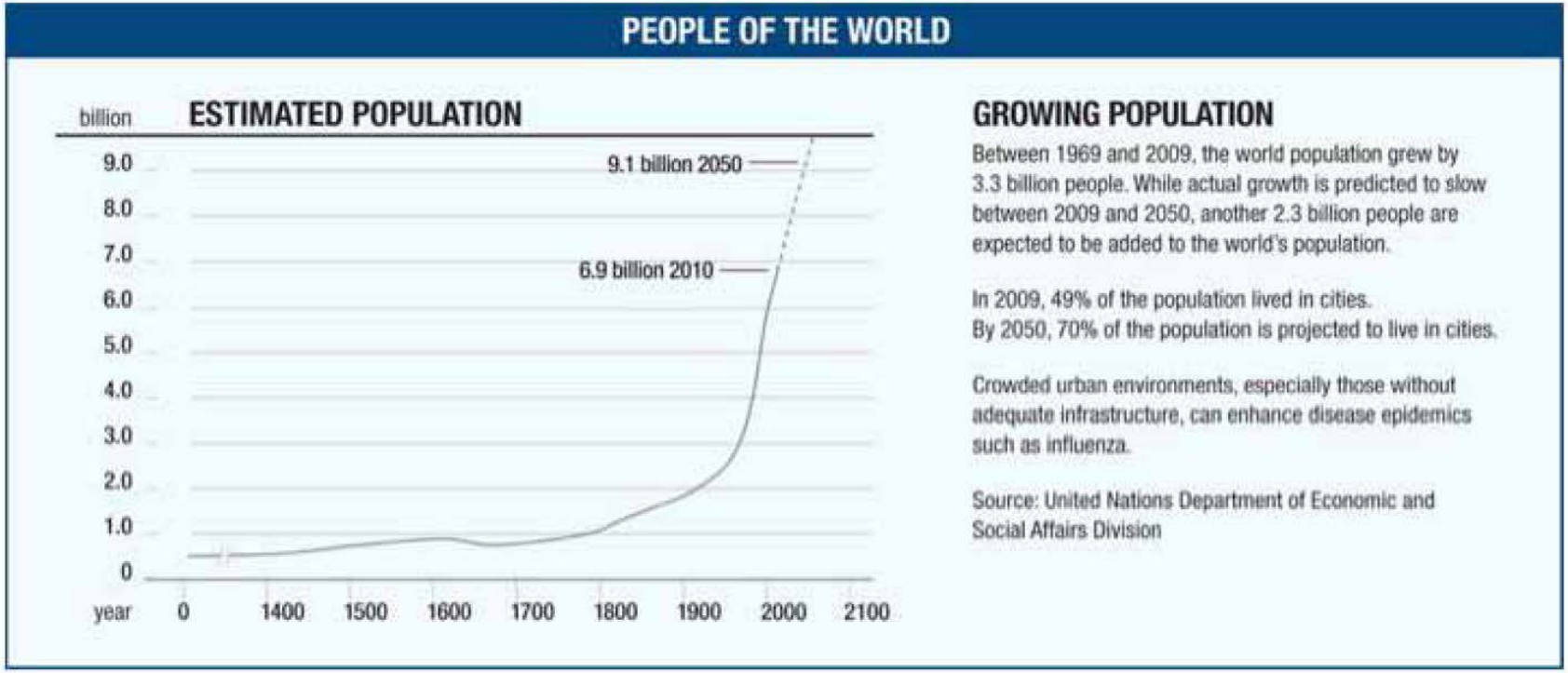
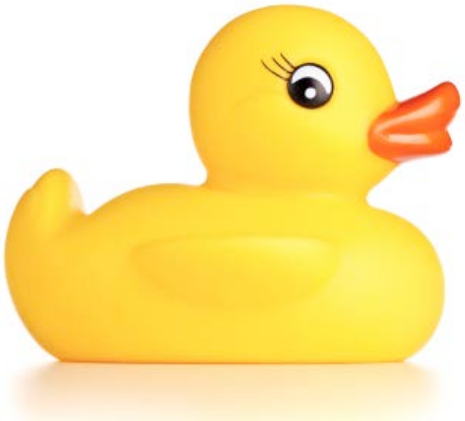


Figure 1. Estimated population of the world from approximately the last 2000 years through 2050. (Reprinted with permission from: Roth, J. A., Galyon, J., Stumbaugh, A. Causes and Consequences of Emerging and Exotic Diseases of Animals: Role of the Veterinarian. *In* Emerging and Exotic Diseases of Animals, 4th Edition, 2010, Rovid-Spickler, A., Roth, J.A., Galyon, J., Lofstedt, J. Editors. Center for Food Security and Public Health, Ames, IA. USA.

Our modern life style and daily use products…

Emerging contaminants

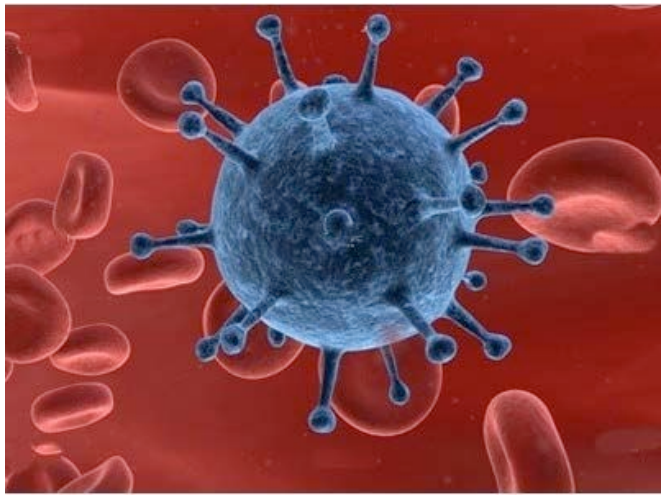
Contaminants of Emerging concern



Plasticizers – Phtalate esters

Per- and polyfluoroalkyl substances (PFASs) – Aqueous fire fighting foams

Flame retardants



Microorganisms (Antibiotic-resistant bacteria, Fungi etc)

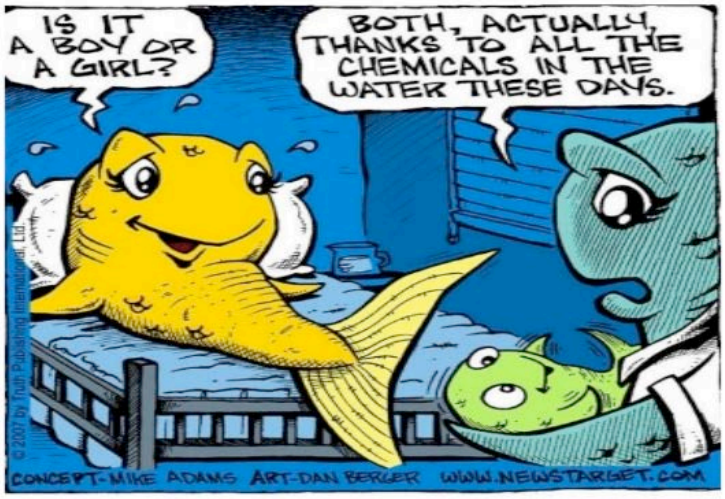
Personal Care Products

- Fragrances
- Parfum
- Deodorants
- Shampoo
- Shaving foam
- Make up
- Tooth paste

PHARMACEUTICALS

Environmental occurrences started to be known….

- 1990s - Surface waters in the U.K. - feral fish with altered reproduction strategies and high incidences of hermaphrodism (Sumpter and Johnson 2008)
- Male fish were undergoing feminization or endocrine disruption.
- The presence of ova within males and the occurrence of the egg yolk precursor protein, vitellogenin, in the blood of male or juvenile fish.



Environmental occurrences started to be known….

- The death of millions of vultures in Asia due to:
  - the use of the anti-inflammatory pain killer diclofenac in livestocks

- 95% of vultures population disappeared in the 90´s

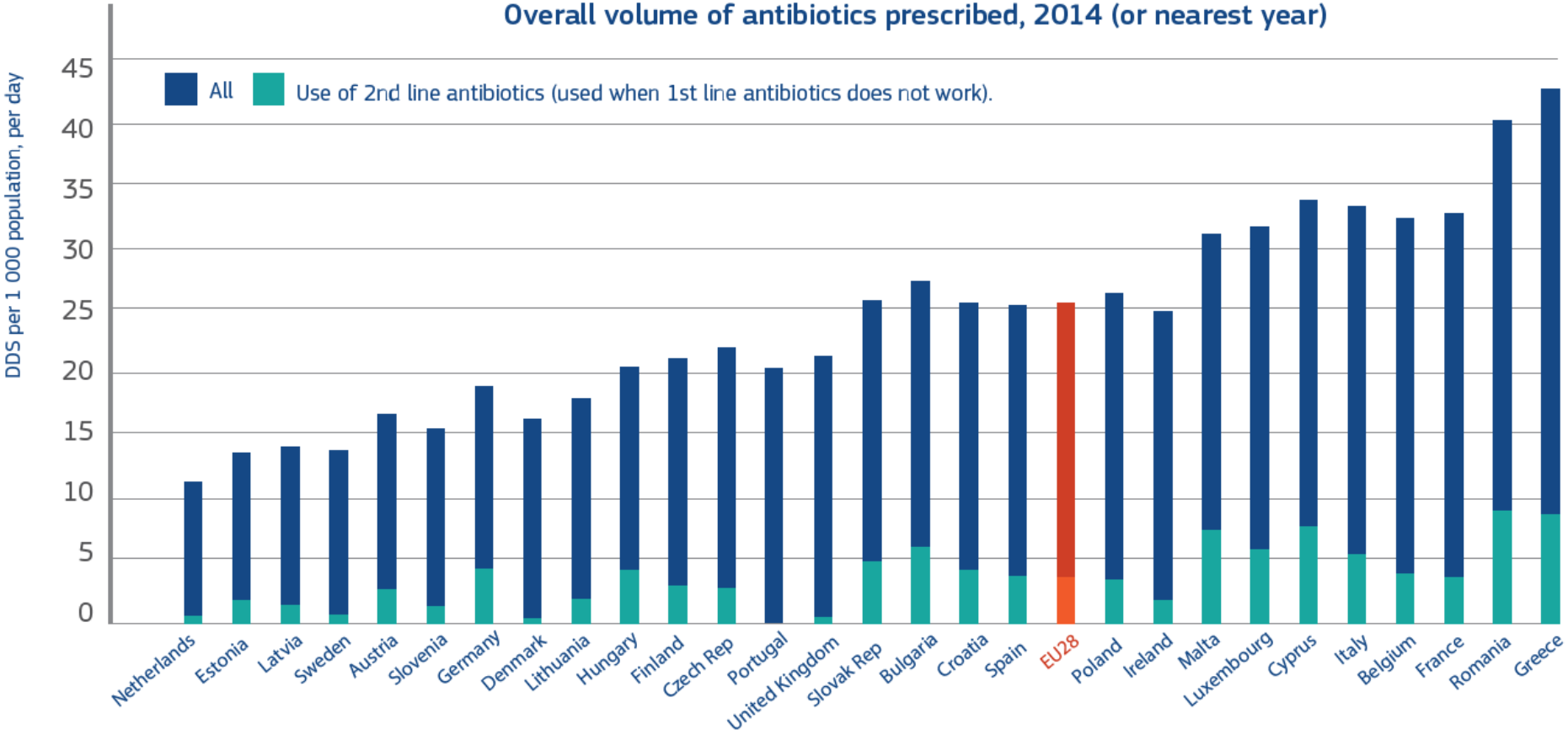
Is it getting worse?

An increased use and diversity of pharmaceuticals

More than 3000 prescription pharmaceuticals are registered for use in the U.S. and EU - Small sub-set of these have been monitored in water.

Nearly 10,000 drugs currently on the market - bio accumulative, persistent, and toxic to wildlife and possibly humans

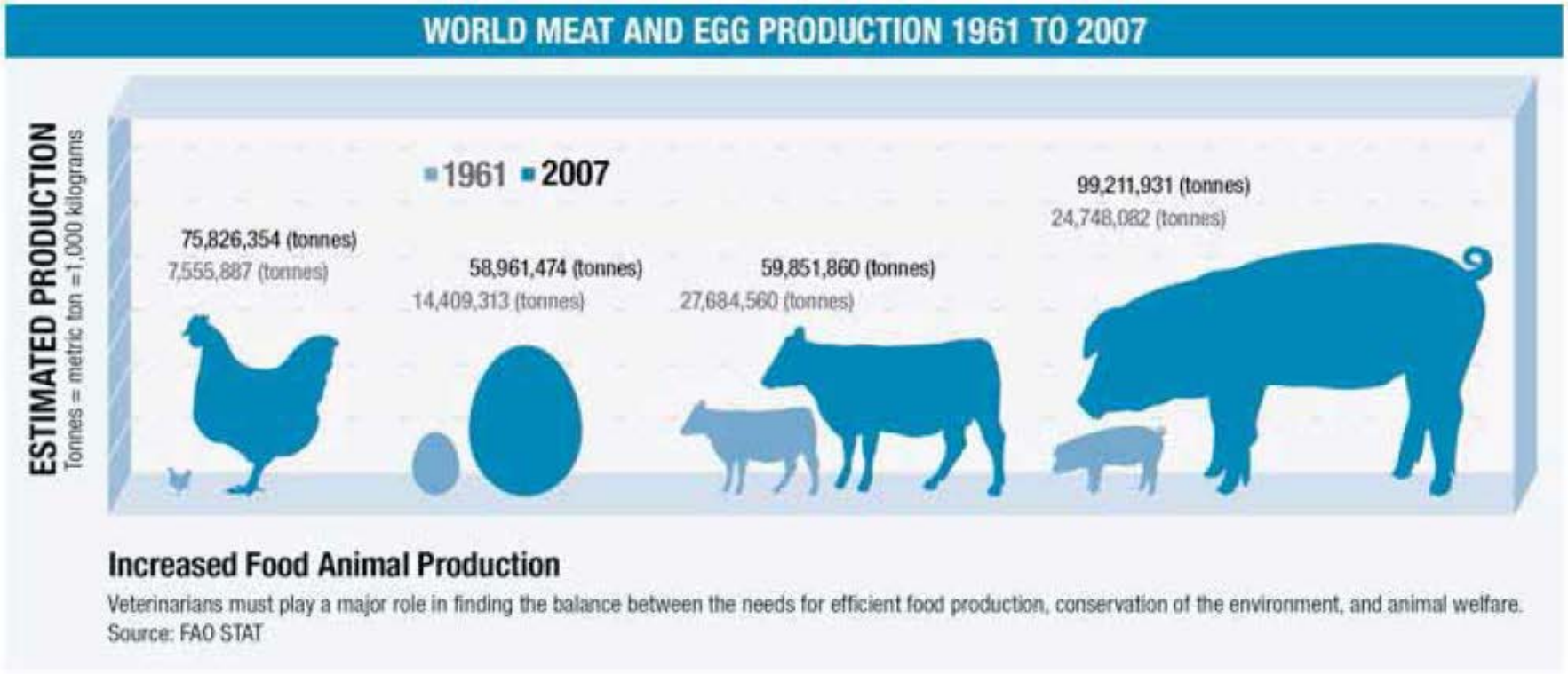
In 2007, the market for prescription and non-prescription medicines for human use in the EU was worth around €214 billion compared to €48 billion in 1990 (Bio IS, 2013).



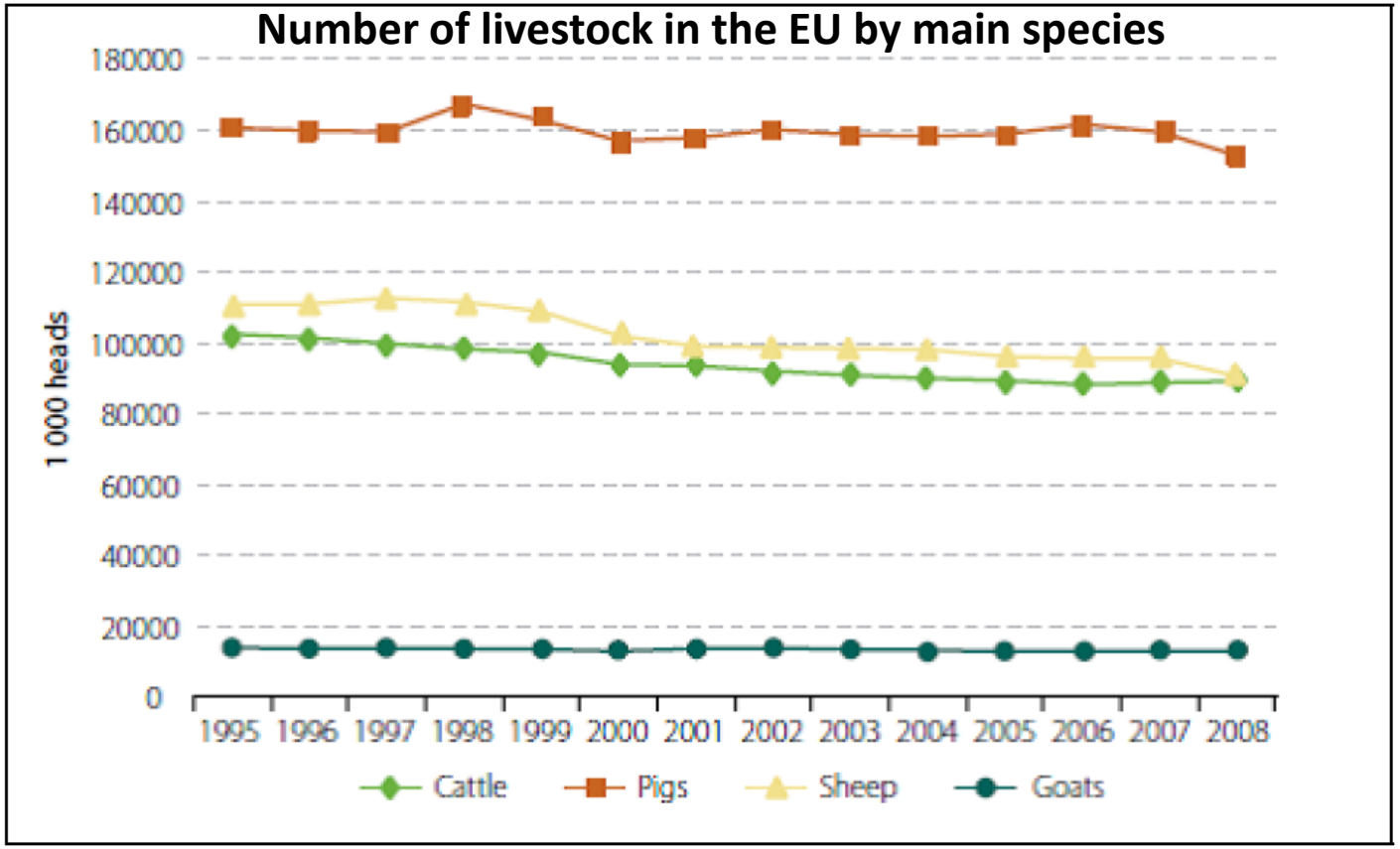
Sources:

- ECDC Data and reports: Antimicrobial resistance and consumption, 2017
- EMA: Latest figures on sales of veterinary antibiotics, October 2016
- Jim O'Neill: Tackling Drug-Resistant Infections Globally - Final Report and Recommendations, May 2016
- OECD: Antimicrobial Resistance – Policy insights, November 2016
- OECD: Health at a Glance: Europe 2016: State of Health in the EU, 2016
- World Bank: Drug-Resistant Infections - A threat to Our Economic Future, September 2016

Veterinary Pharmaceuticals



Estimated world meat and egg production in 1961 and 2007. (Roth J.A, Galyon, J., Stunbaugh, A. Causes and Consequences of Emerging and Exotic Diseases of Animals. Role of the Veterinarian. In Emerging and Exotic Diseases of Animals. 4th Ed. 2010.



Source: Eurostat 2009a.

- EU - one of the major livestock producing regions in the world.
- In 2008, the value of livestock production amounted to 152 billion Euro
- 40 % of the total EU agricultural output.

Veterinary Pharmaceuticals

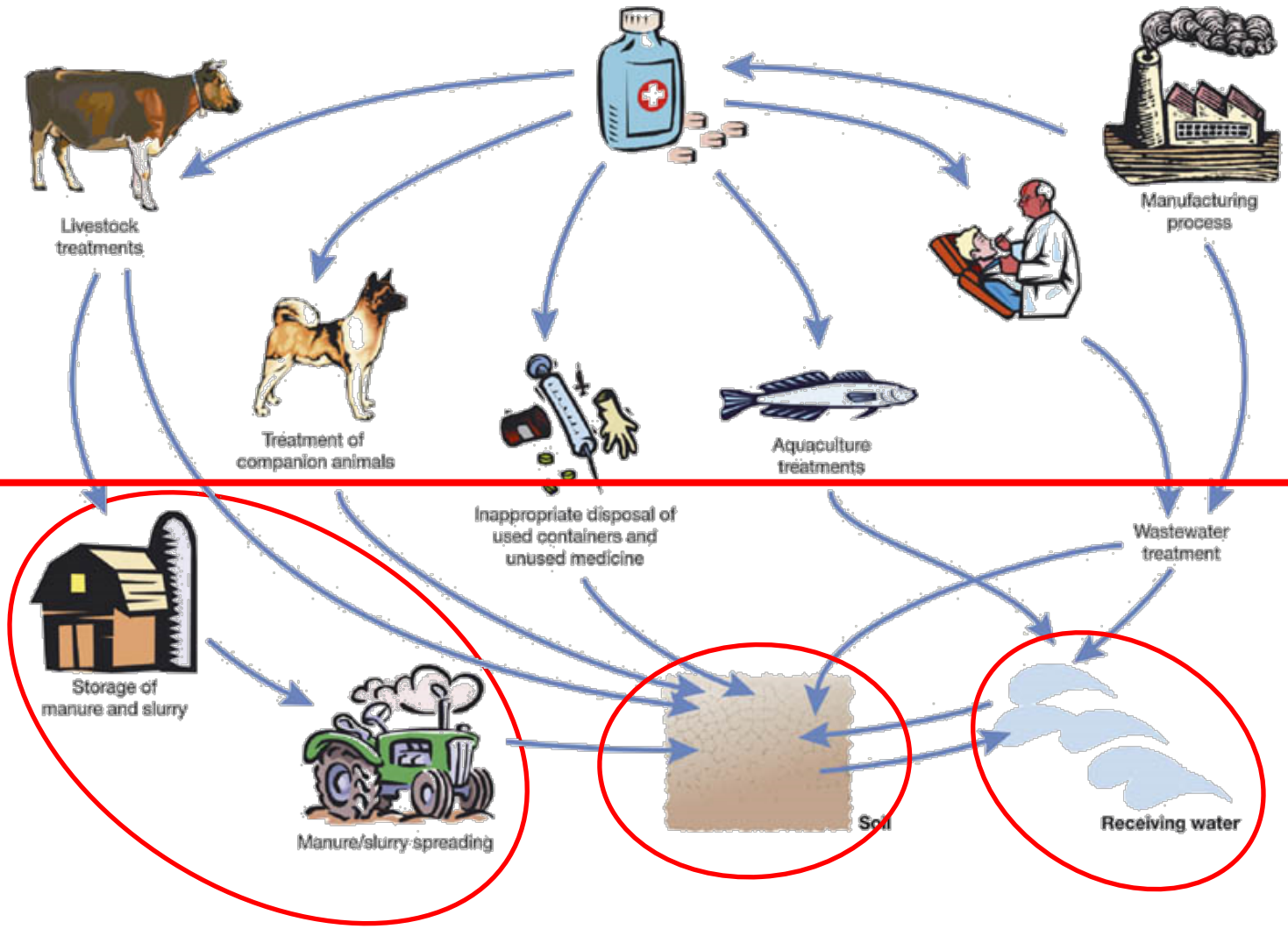
- The European Federation of Animal Health (FEDESA) - 4700 tons in veterinary medicine back in the year of 1999 in the European Union.
- One-third of antibiotics consumption in Europe is related to veterinary use more precisely for poultry and pigs livestock.
- Europe reports total sales of animal health products in the European market of 4.3 billion Euro in 2008. (*European Commission, Directorate General for Health and Consumers Evaluation of the EU Legislative Framework in the Field of Medicated Feed.* ***Final Report 2010)***
- Vaccines (26.3 %), antimicrobials (19.9 %), parasiticides (27.4 %), topical products (6.8 %) and other products (19.6 %).

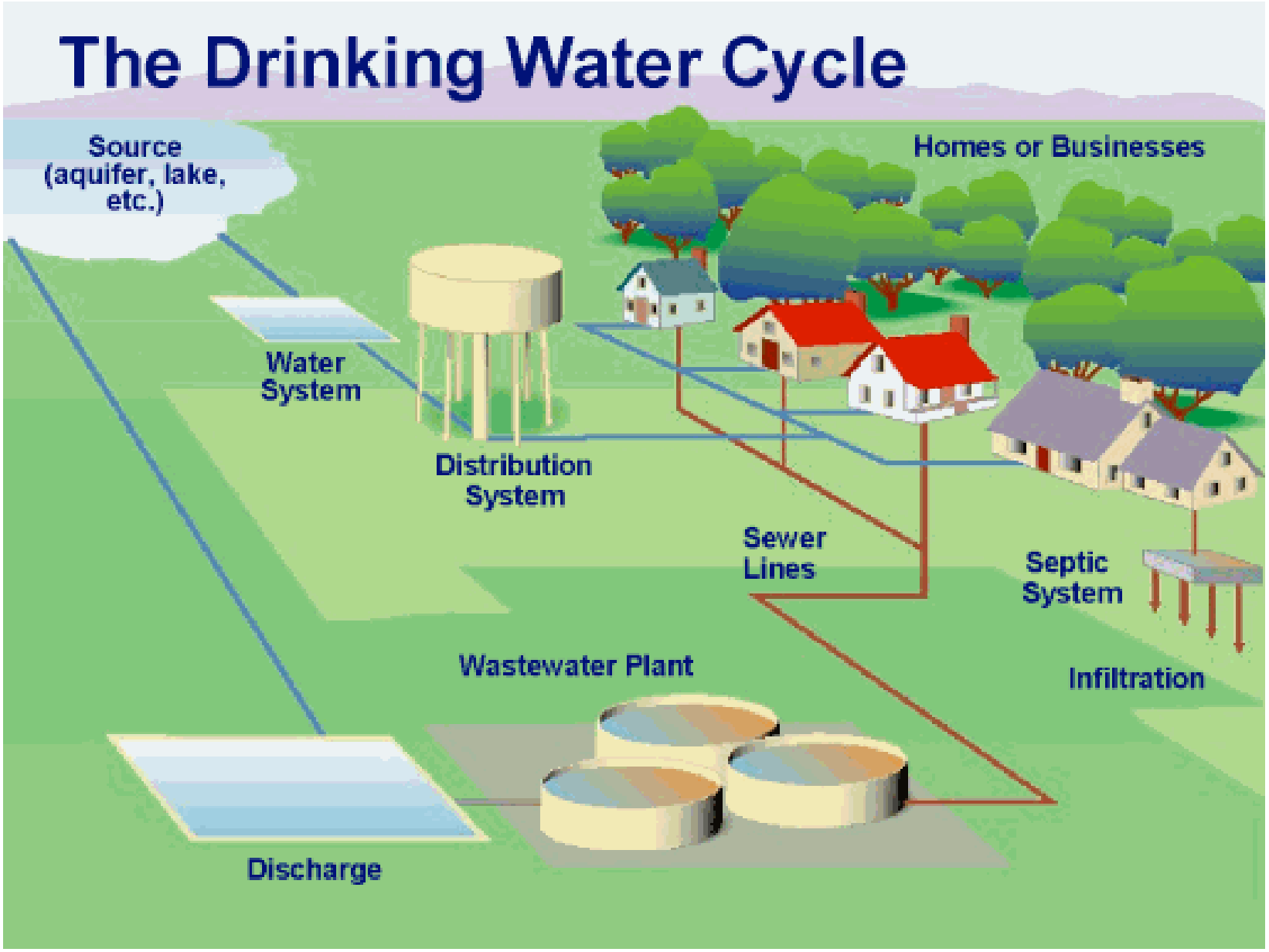
Veterinary Pharmaceuticals

- USA and Korea - top of the list with 11,148 tons year-1 and 1,533 tons year-1 respectively.

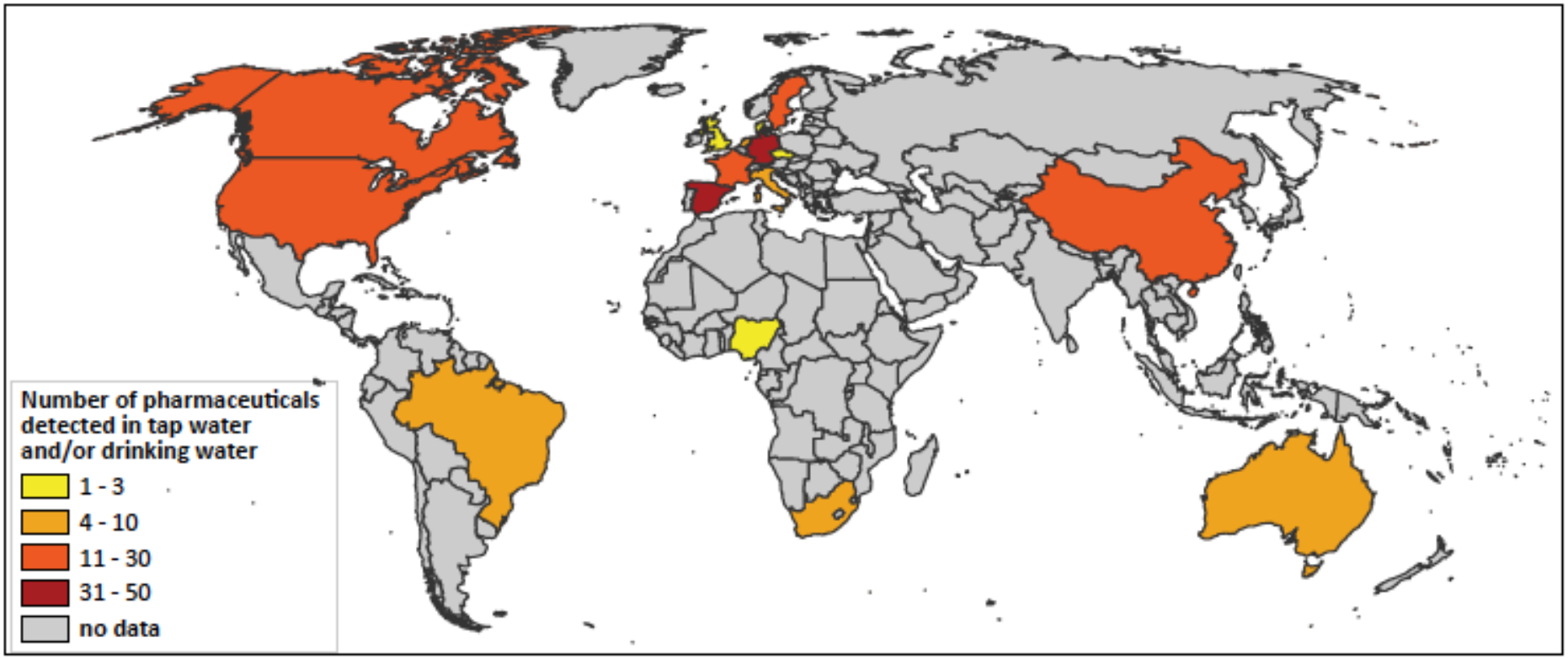
- About 70 % of antimicrobials used in the U.S. are fed to chickens, pigs, and cattle for nontherapeutic purposes (Mellon et al. 2001).

Pathways of pharmaceuticals




The Drinking Water Cycle
Source (aquifer, lake, etc.)
Homes or Businesses
Water System
Distribution System
Sewer Lines
Septic System
Wastewater Plant
Infiltration
Discharge

Number of pharmaceuticals found in drinking water worldwide



(Notes:
1. Caffeine is excluded, because although it is used in some pharmaceutical formulations, it is ubiquitous due to its presence in coffee and tea.
2. In addition, this map excludes drugs which are also used recreationally, and therefore, for example, cocaine and its metabolite, benzoylecgonine, are not included.)
(See IWW Water Centre 2014; http://pharmaceuticals-in-the-environment.org).

How Antibiotic-Tainted Seafood From China Ends Up on Your Table

You might want to pass on the shrimp cocktail.

by **Jason Gale**, **Lydia Mulvany**, and **Monte Reel** 15 December 2016, 10:00 GMT+1

From **BloombergBusinessweek** | Subscribe | Reprints

Future Outlook

Conscious use and disposal of drugs – Not pour them down the drain or in the flush toilets

Take back programs - Germany is a country with a national unused-pharmaceutical take-back program

A recent study by Gerard Vollmer of the European Union's Joint Research Centre, showed that in Germany, 364 tons per year of avoidable Pharmaceutical loads was observed

United Kingdom in 2003 - 22% of excess pharmaceuticals were returned to pharmacists; (Bound & Voulvoulis, 2005).

In Australia - Return Unwanted Medicines (RUM) Project. Estimates have shown 2010–2011, more than 34 tonnes of unwanted medicines were collected monthly by community pharmacies across Australia and subsequently incinerated according to guidelines (RUM, 2011).

In the USA "Great Lakes Earth Day Challenge", which collected 4.5 million pills for safe disposal.

.

Future Outlook

Reduction of environmental footprint by medical doctors - The Swedish Association of the Pharmaceutical Industry (LIF)

Swedish doctors can offer their patients information about the potential environmental impact of the prescription options.

For treatments for which there are many — patients and doctors can choose medications that don't have harmful consequences for the environment.

EU’s environmental legislation will consider pharmaceuticals for <u>the first time ever</u> in the revised Water Framework Directive

Pharmaceuticals and hormones proposed to be added in the watch list

Inclusion is confirmed!

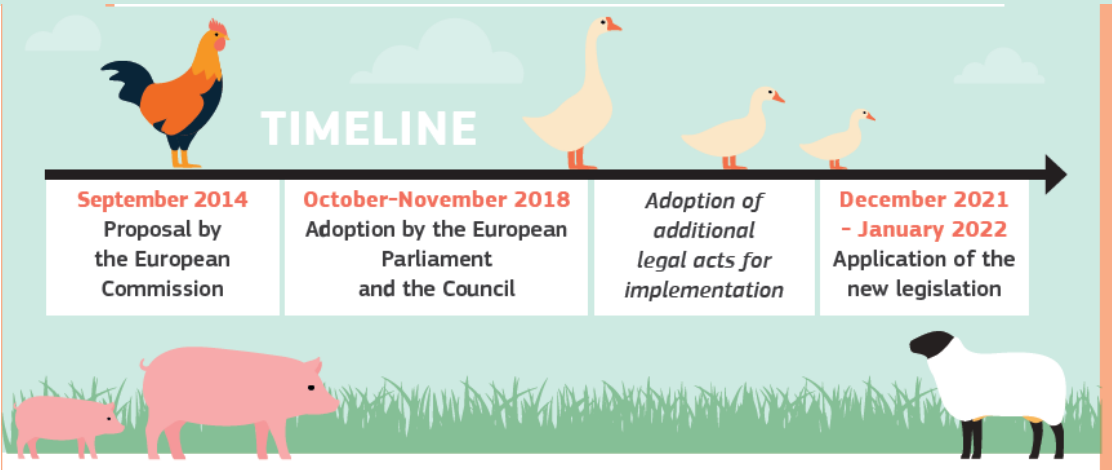
Compound	CAS	Use
17∝-ethinylestradiol	57-63-6	Contraceptive
17β-estradiol	50-28-2	Estrogen hormone
Diclofenac	15307-79-6	Anti-inflammatory
Ibuprofen	15687-27-1	Anti-inflammatory
Carbamazepine	298-46-4	Antiepileptic

- monitor in surface waters and report to European Commission (mandatory)
- Monitor in wastewater effluents (voluntary)

European Commission

NEW EU RULES ON VETERINARY MEDICINAL PRODUCTS AND MEDICATED FEED

TIMELINE



September 2014
Proposal by the European Commission

October-November 2018
Adoption by the European Parliament and the Council

Adoption of additional legal acts for implementation

December 2021 - January 2022
Application of the new legislation

VETERINARY MEDICINAL PRODUCTS: WHAT'S NEW?

FIGHTING ANTIMICROBIAL RESISTANCE

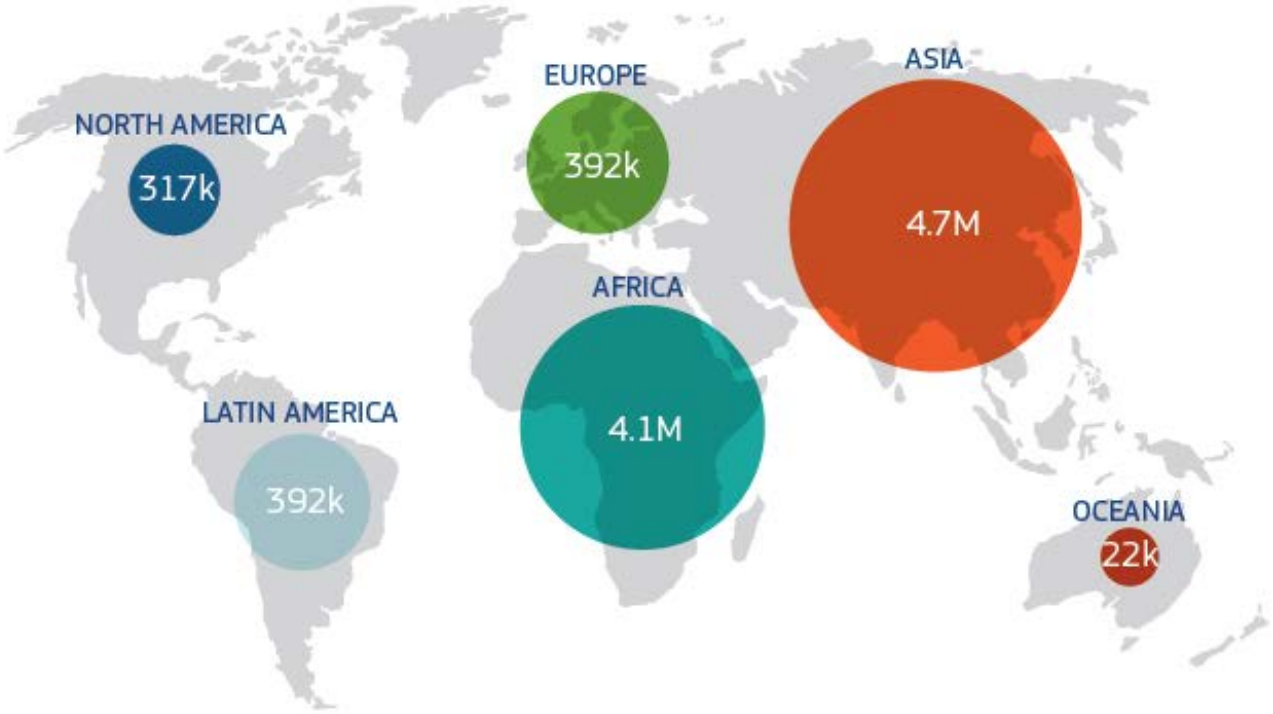
BAN on **preventive use of antibiotics** in **groups of animals**

REINFORCED BAN on the use of antimicrobials for **promoting growth and increasing yield**

RESTRICTIONS on metaphylactic use of antimicrobials (**control treatment** preventing a further spread of infection)

Possibility to **RESERVE certain antimicrobials for humans** only

OBLIGATION for Member States to **collect data on the sale and use** of antimicrobials



Number of deaths per year attributable to AMR by 2050 if current resistance rates increased by 40%

EU- 1.5 Billion Euros each year due to health care costs and productivity losses due multi-resistant bacteria.

Losses to trade and Agriculture – Norway 2015, 20% of chicken sales reduction due to resistant strain of *E.coli* found in chicken meat.

A more sustainable way of designing pharmaceuticals…

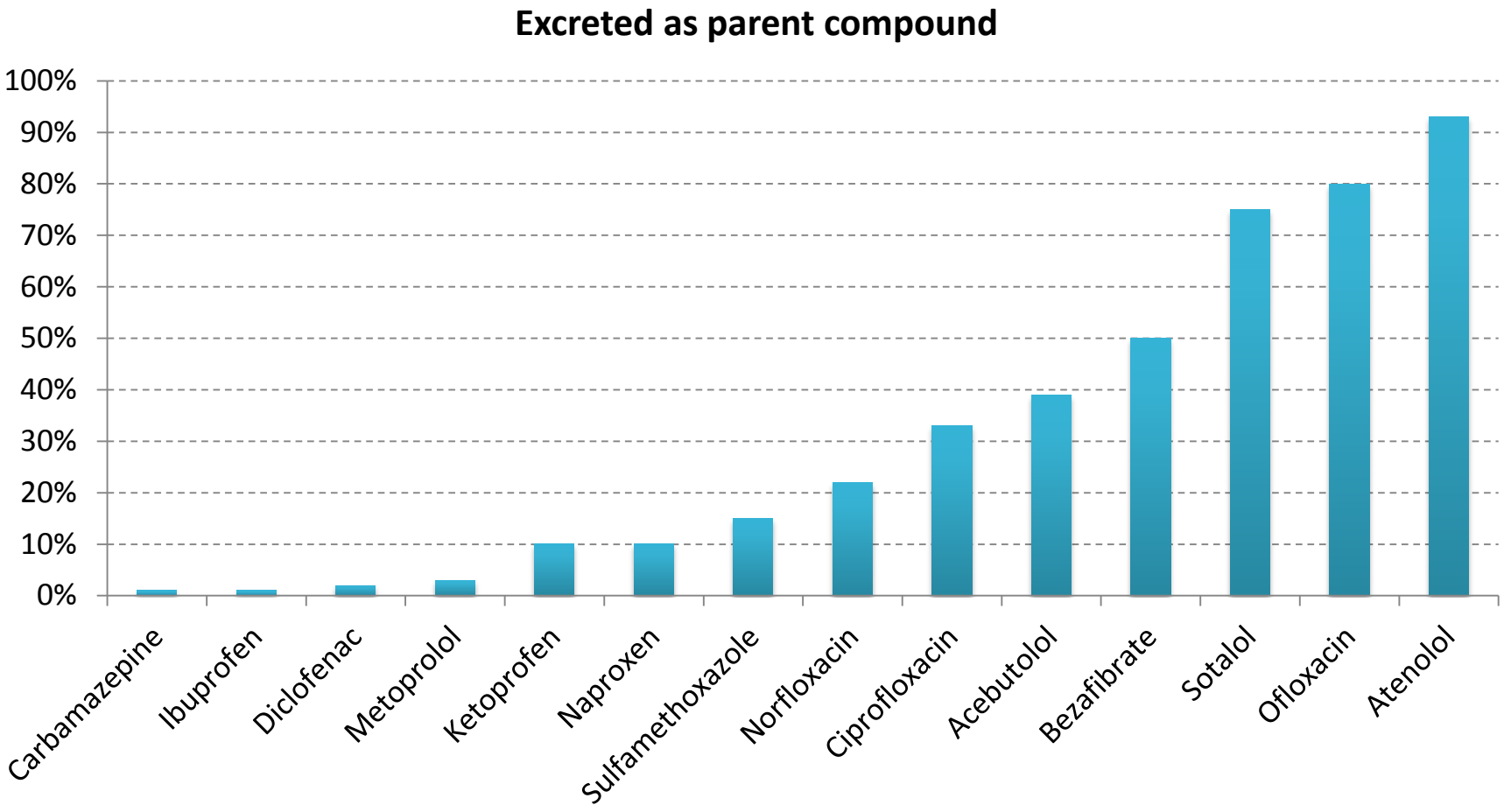
Green design of pharmaceuticals Benign-by-design

One of the easiest ways to reduce the impact of drugs in the environment.

Medicines before design and implementation would be examined for:

- persistence
- Toxicity
- Bioaccumulation
- solubility
- bioavailability
- genotoxicity
- pharmacokinetics
- and carcinogenicity before it went into optimization.

…next important thing is human metabolism



Adapted from DWI, 2007

Green design of pharmaceuticals
Benign-by-design

Twelve principles which should be central to the planning and processes of pharmaceutical development and manufacture.

- Prevention
- Atom Economy
- Less hazardous chemical synthesis
- Designing safer chemicals
- Safer solvents and auxiliaries
- Design for energy efficiency
- Use of renewable feedstocks
- Reduce derivatives
- Design for degradation
- Real-time analysis for pollution prevention

Examples in the real world

Pfizer won an award from the UK Institute of Chemical Engineers for reducing the amount of organic process waste generated in the production of Viagra.

A cancer drug produced by Janssen (the pharmaceuticals arm of Johnson & Johnson) was re-evaluated by scientists to explore ways of making the synthesis process “greener”..

They discovered it was possible to:

- reduce raw material input by nearly two-thirds,
- water usage by more than three-quarters and,
- hazardous waste by 87 per cent.

How Pharmaceuticals behave in the environment/Treatment plants?

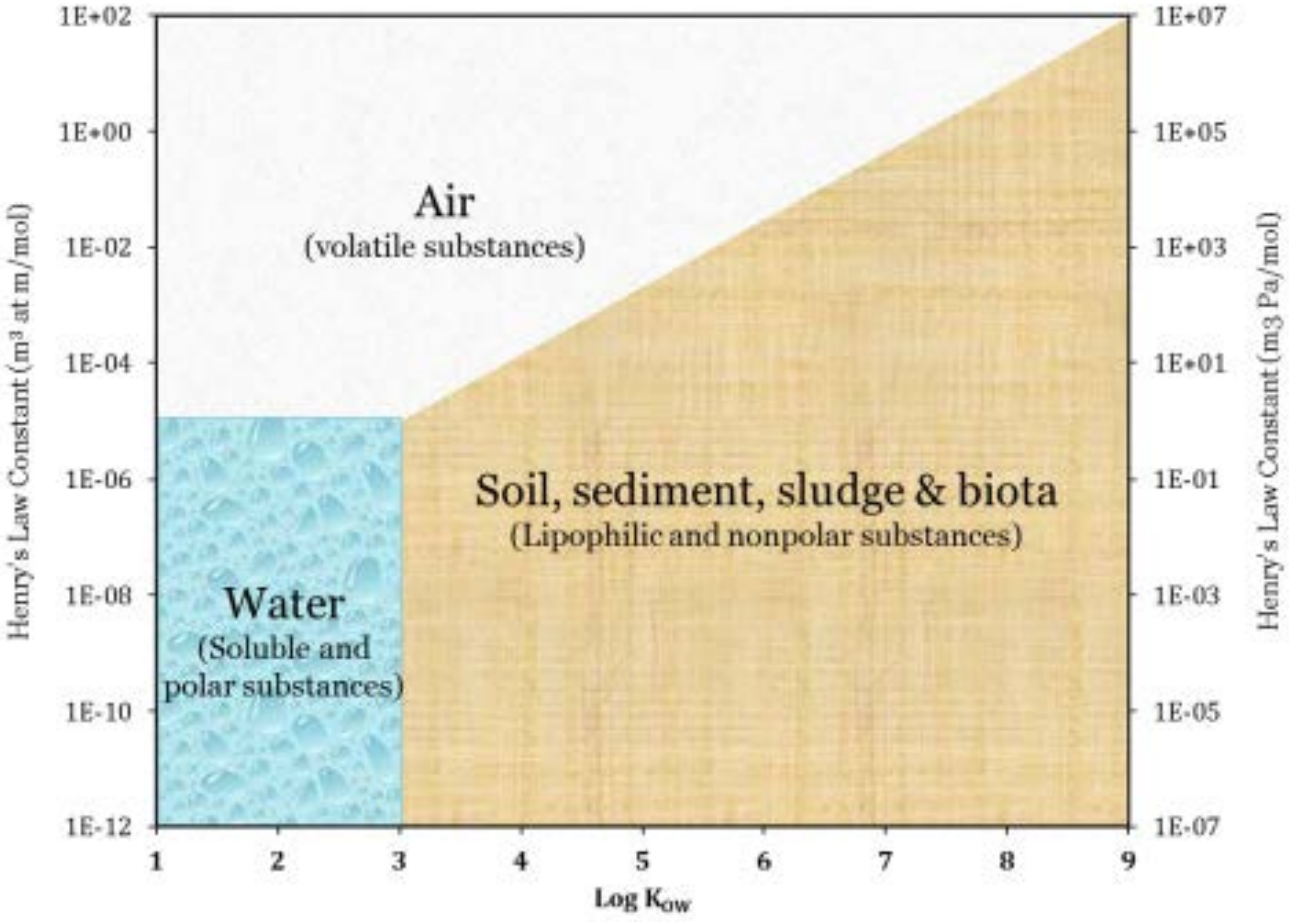


Table 7. Conventional and advanced wastewater treatment processes and their expected range of removal efficiency for pharmaceuticals

Treatment process	Removal range (%)	Water source	Areas studied	Reference
> Conventional wastewater treatment processes				
Activated sludge	11–99	Raw sewage	Australia	Watkinson, Murby & Costanzo (2007)
	7–100	Primary settled sewage	Europe, Japan	DWI (2007)
	< 20–80	Primary settled sewage	France	Gabet-Giraud et al. (2010)
	–193–86[a]	Primary settled sewage	Europe	Vieno, Tuhkanen & Kronberg (2007)
	8–98	Not specified	Brazil, Europe, Japan	Ziylan & Ince (2011)
Biological filtration	6–71	Primary settled sewage	Europe	DWI (2007)
Primary settling	3–45	Not specified	Brazil, Europe, Japan	Ziylan & Ince (2011)
Coagulation, filtration and settling	5–36	Not specified		
Sand filtration	0–99	Activated sludge effluent		
> Advanced wastewater treatment processes				
Ozonation	1–99	Activated sludge effluent	Brazil, Europe, Japan	Ziylan & Ince (2011)
	86–100	Secondary effluent	France	Gabet-Giraud et al. (2010)
Ozonation/ultrasound and sonocatalysis	23–45	Not specified	Europe, India, Japan, Turkey, USA	Ziylan & Ince (2011)
Ozonation and catalytic ozonation	> 9–100			
UV irradiation	29	Not specified	Brazil, Europe, Japan	Ziylan & Ince (2011)
Photolysis (UV/hydrogen peroxide)	52–100	Not specified	Europe, India, Japan, Turkey, USA	Ziylan & Ince (2011)
Dark and light Fenton	80–100			
UV/TiO_2	> 95			
Biomembrane	23–99	Treated effluent	Brazil, Europe, Japan	Ziylan & Ince (2011)
Microfiltration and reverse osmosis	91–100	Secondary treated effluent	Australia	Watkinson, Murby & Costanzo (2007)
Reverse osmosis	62–97	Secondary treated effluent	France	Gabet-Giraud et al. (2010)
Ultrasound	24–100	Not specified	Europe, India, Japan, Turkey, USA	Ziylan & Ince (2011)

UV, ultraviolet

[a] The removal of some pharmaceuticals appears to be negative. This has been attributed to the way in which removal is calculated, without hydraulic retention time being considered. This means that the effluent sample does not directly correspond to the influent sample. In the case of carbamazepine, the increase observed was consistent, and the most probable cause was reported to be conversion of carbamazepine glucuronides and other conjugated metabolites to the parent compound by enzymatic processes in the treatment plant (Ternes et al., 1999; Vieno, Tuhkanen & Kronberg, 2007).

Temporal Variation

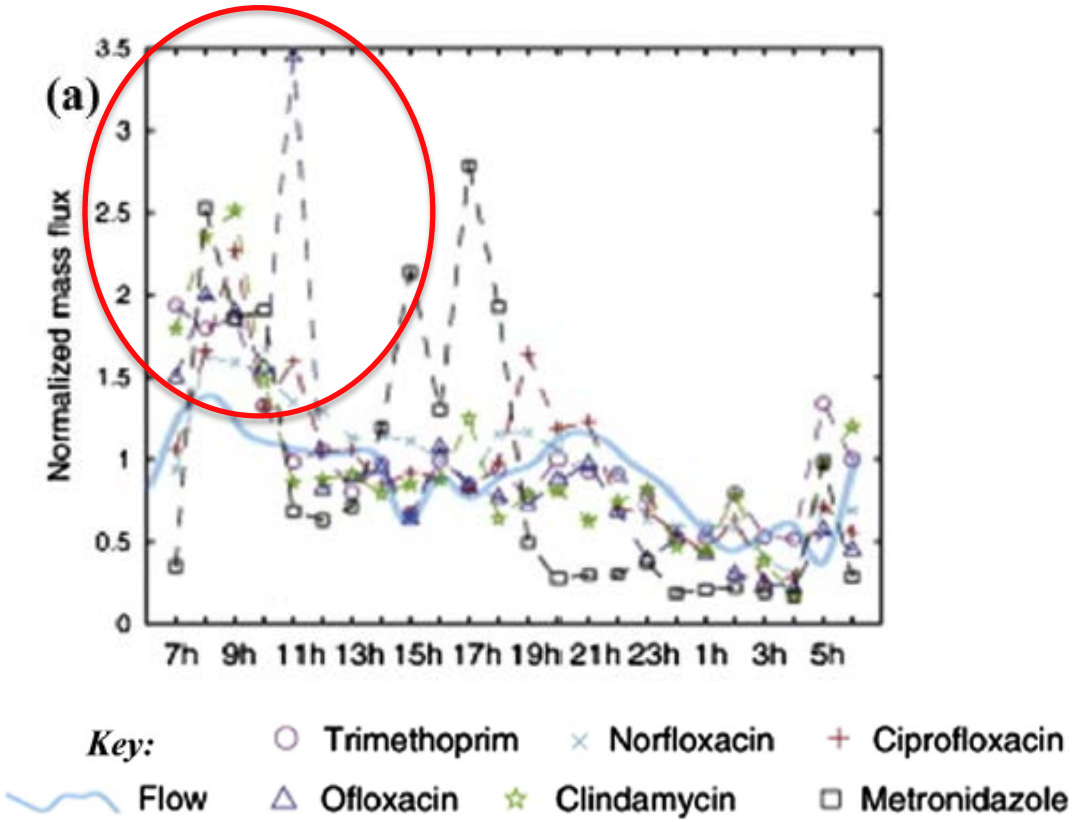
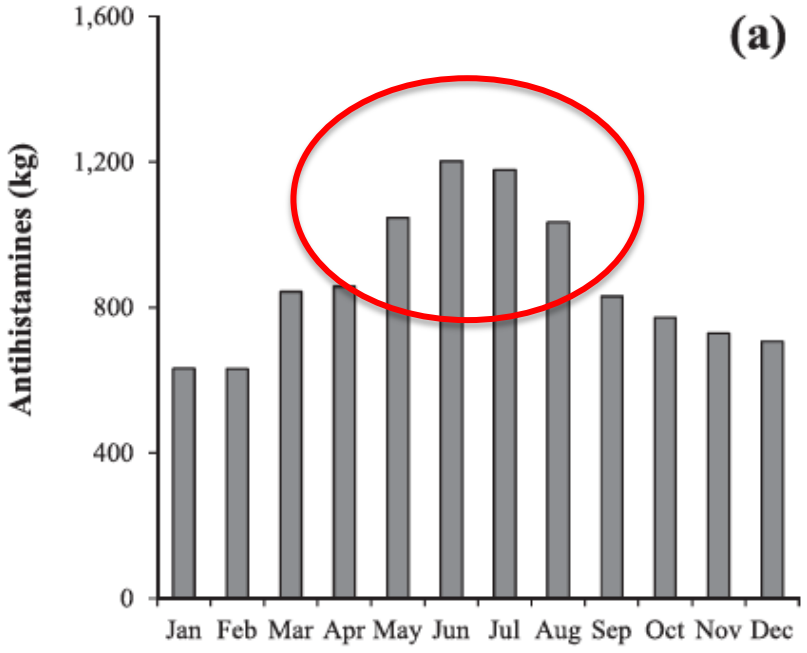
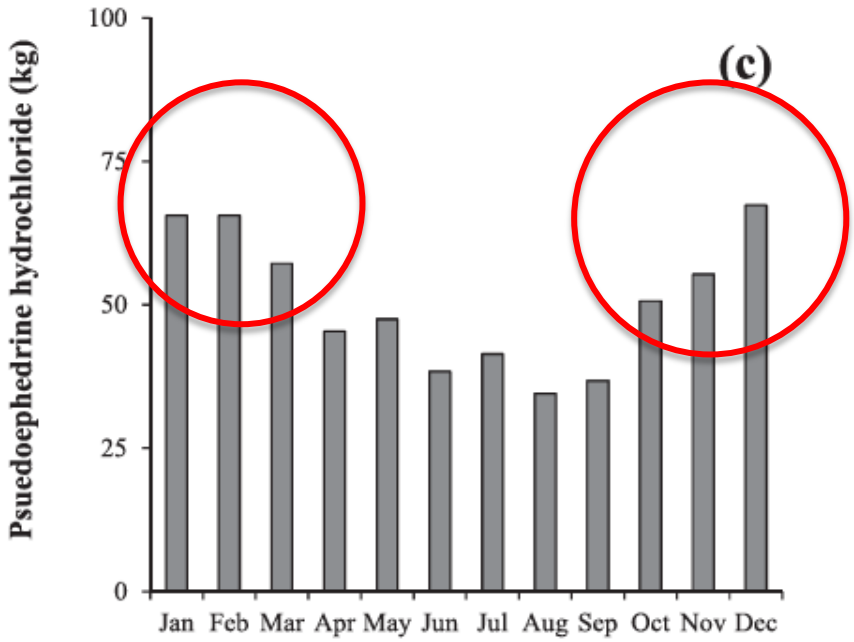


Fig. 1 – Fluctuations of mass flux for selected antibiotics in wastewater throughout a one day period (a) and during the course of a year (b) – adapted from Coutu et al. (2013).

High peaks observed between **7:00-9:00** in the morning – First flush of the day…

Explained by accumulation of medicines taken before sleep in the urine..





- A study conducted in UK - Antihistamines used to treat allergies peaked from May to August when pollen production is greatest (National Health Service, 2012).
- Generally, quantities prescribed were 100% greater in summer compared to winter months.
- In contrast, pseudoephedrine (used in nasal decongestants) showed an opposite trend
- Highest prescription observed during winter months

Additional Challenges

- Analytical Chemistry Procedures – Parent Compounds and metabolites
- Monitoring to improve exposure understanding – Water recipients, groundwater, soil, activated sludge.
- Hazard Identification – realistic exposure, metabolites, cocktail effects, realistic doses, synergism?, Antagonism?,
- Exposure assessment – main exposure routes, crop uptake, long-term exposure
- Organic farmings, use of probiotics?

Additional Challenges

- Monitoring strategies using surrogates are needed that can assure proper performance of treatment processes selected to remove pharmaceuticals.

- Communication to the public should be open, transparent, accurate and understandable.

- Water/Wastewater treatment design - final water and sludge quality should be based on human and ecological health endpoints, not simply on detection alone.

- Condition-specific legislations – environmental conditions, soil conditions, crops, climate conditions, physico-chemical properties


Thank you!