CleanMed Europe 2018

Creating Healing Environments

Health Care Without Harm

Radboudumc

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CleanMed Europe 2018
Creating Healing Environments

INTERREG Deutschland Nederland

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MEDUWA

D4 & E4: MEDUWA-Vecht(e)

D4: **Alfons Uijtewaal,** The EU INTERREG-VA MEDUWA-Vecht(e) project, a general introduction, post@huizeaarde.nl

D4: **Ad Ragas,** Estimation and prioritization of hospital pharmaceutical (API) emissions, a.ragas@fnwi.ru.nl

E4: **Paul Leenders**, Plasma Activated Water Treatment, paul.leenders@vitalfluid.nl

E4: **Martien Graumans,** The use of plasma activated water and UV/H2O2 for the degradation of cyclophosphamide in wastewater, martien.graumans@radboudumc.nl

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Potential conflict of interest	**None/see below**
Relationships with commercial companies	**Company names:**
• Sponsorship / research money • Fee or other financial compensation • Shareholder • Other relationship, (please specify)	• none • none • none • none

The EU INTERREG-VA MEDUWA-Vecht(e) project, a general introduction

CleanMed October 12 2018, Nijmegen, Netherlands

Presentation by Alfons Uijtewaal,
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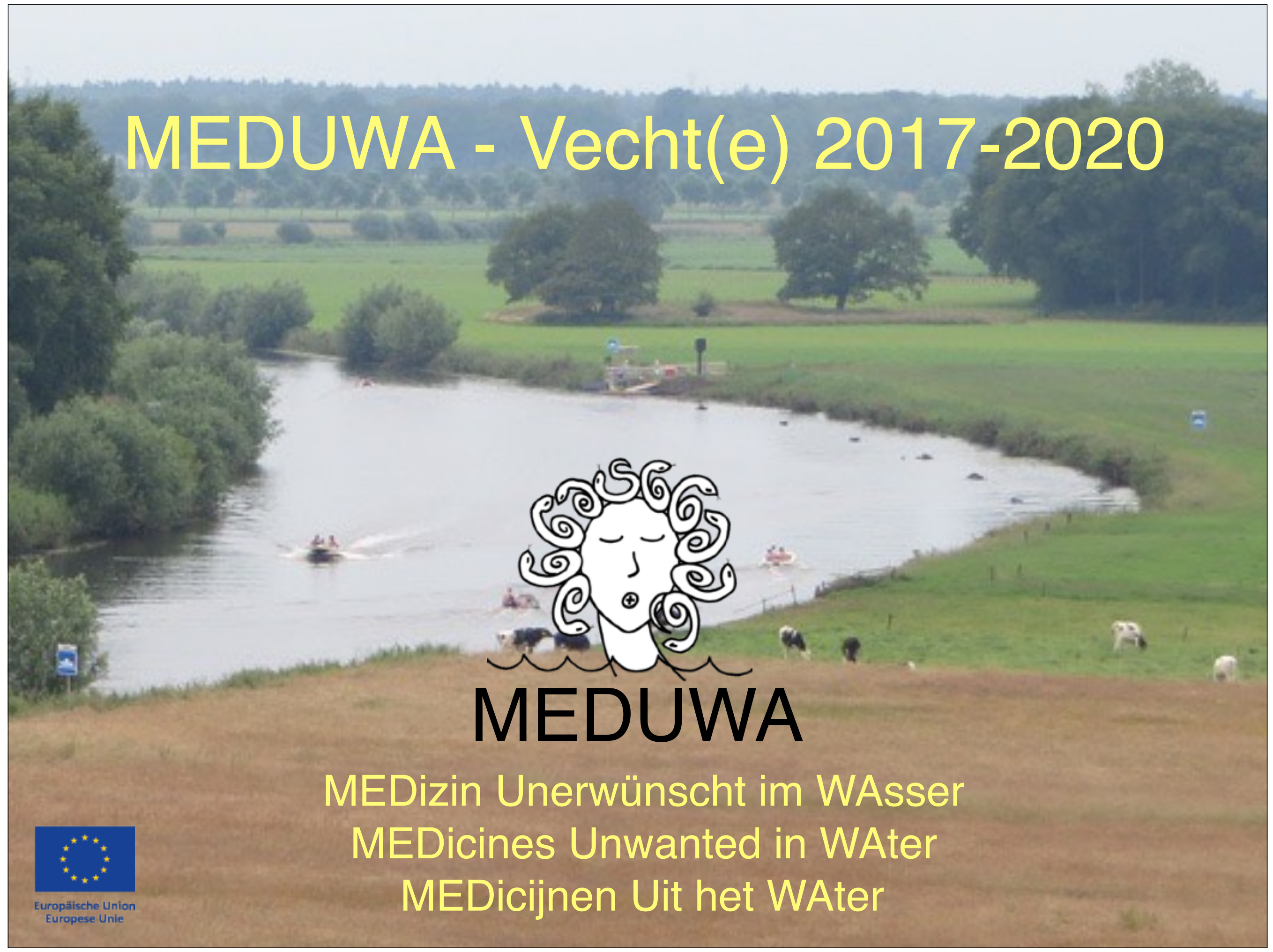
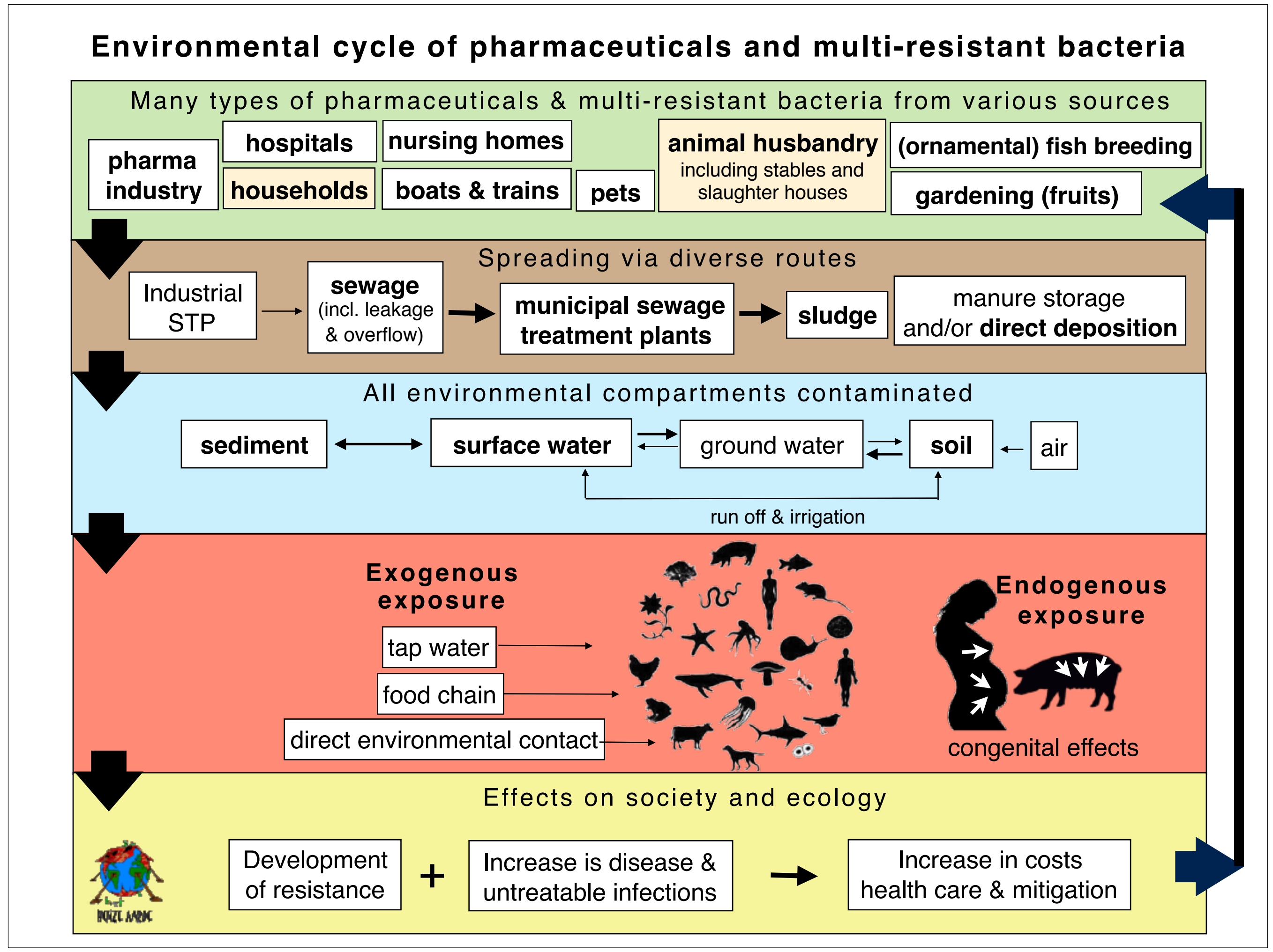


The EU INTERREG-VA project MEDUWA-Vecht(e) addresses a common challenge: the environmental cycle of human and veterinary medicines and multi-resistant bacteria that are transferred via drinking water, food and air back to humans and animals.

Because of its complexity, this problem could paralyze us - as did the Greek mythological Medusa. What makes this issue so complex?



1. Medicines and multi-resistant bacteria that left the body reach the environment, and through the environment they return to us.

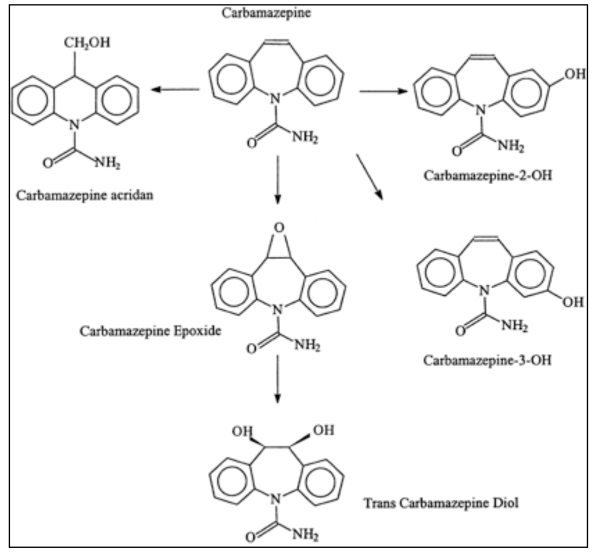
Dispersal of the problem

2. Through sewage water treatment, and manure application to land, medicines and multi-resistant bacteria are spread to different environmental compartments.

In the NL sludge is being incinerated; but in many countries sludge is reused as a fertilizer (biosolids). As do other countries, the NL imports food grown on contaminated soils.

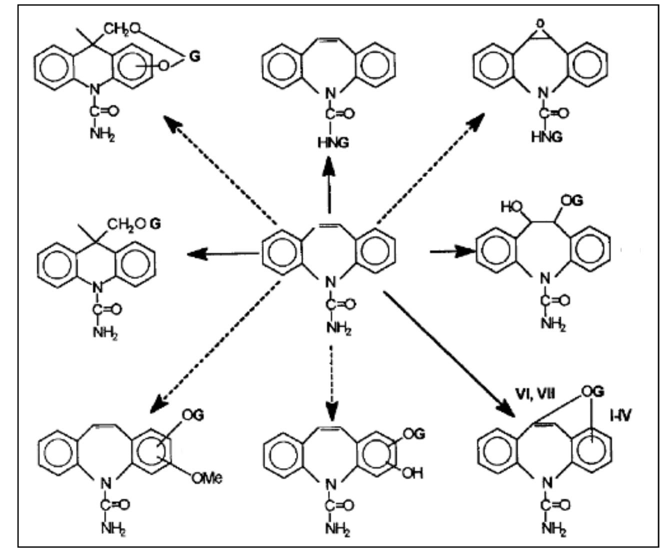
Monitoring, toxicology, risk assessment, risk management major challenge

in total 33 phase-I-metabolites of CBZ

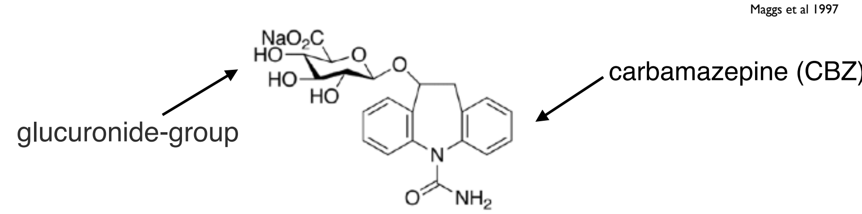


Reith and Cannel 2006

phase-II-metabolites of CBZ (G= glucuron)



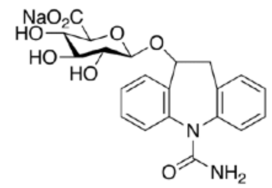
Maggs et al 1997



3. Through their high number and many transformations, monitoring, toxicology, risk assessment and management of these contaminants is very challenging.

In our body these metabolised molecules are made more soluble and by that better excretable with a body molecule. Through this so called conjugation proces there are hundreds of different forms of each medicine formed. They are not being analysed and by that invisible for water managers.

Medicines are very persistent molecules



Carbamazepine in STP (ng/L)

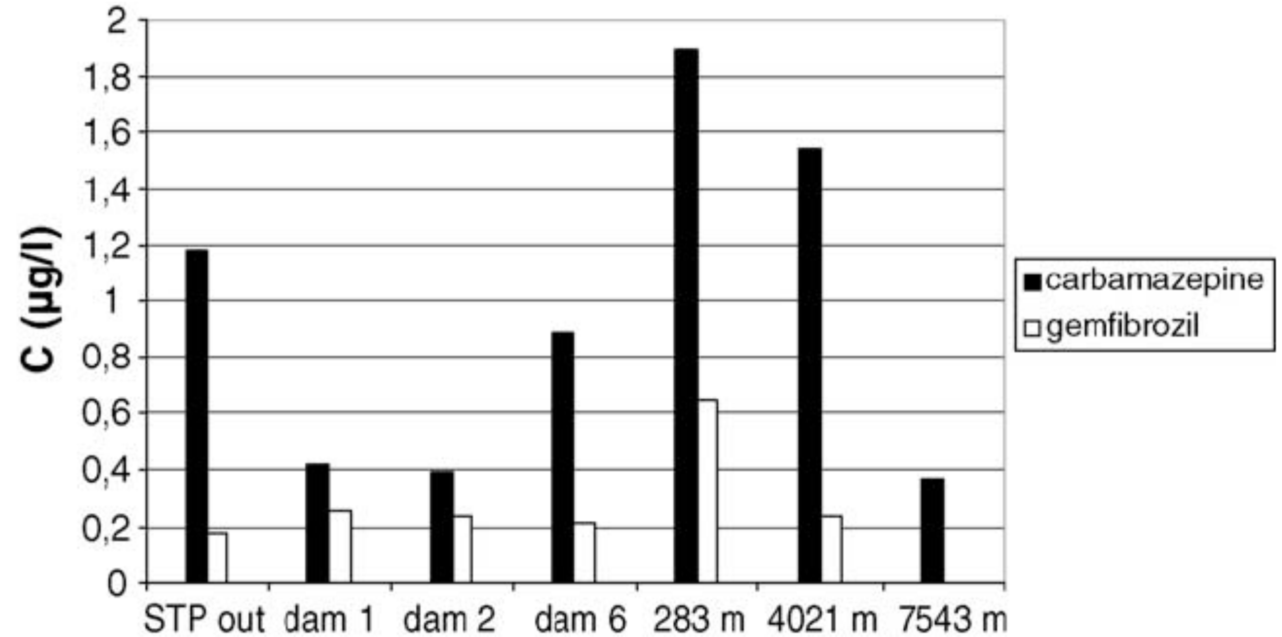
analyte	influent	effluent
CBZ	368.9 ± 5.3	426.2 ± 6.1
CBZ-EP	47.2 ± 1.8	52.3 ± 1.2
CBZ-DiOH	1571.7 ± 31.0	1325.0 ± 12.2
CBZ-2OH	121.0 ± 1.6	132.3 ± 2.1
CBZ-3OH	94.8 ± 2.2	101.5 ± 0.3
CBZ-10OH	8.5 ± 0.6	9.3 ± 0.4

Miao et al 2003 Photo sewage by jlj4774 Flickr.com

4. Medicines are very persistent molecules

In the sewer, the sewage treatment plant and in surface water, bacteria attack the conjugates and the original molecule is released again. That's why wastewater treatment plants seem to release more medicines than they receive via the influent.

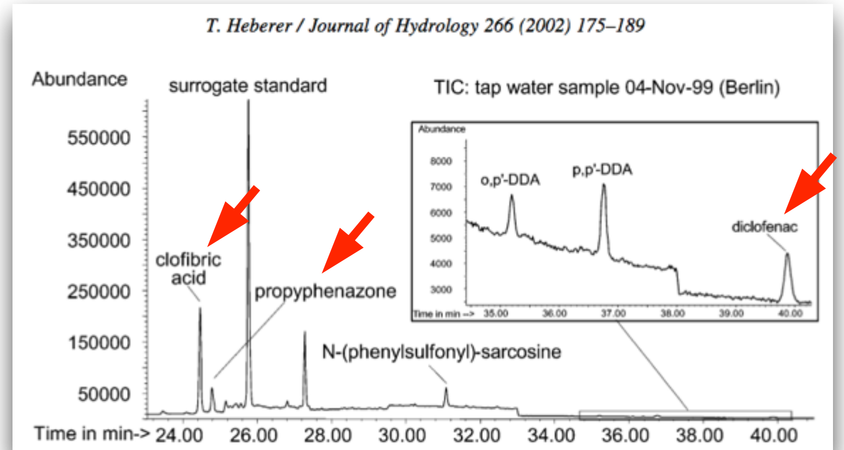
Deconjugation continues after emission



Bendz et al 2005, corrected for dilution. Dam1,2,6 = reservoirs for effluent after treatment (total average residence time is three days). The data do not include metabolites and drugs bound to suspended matter.

5. Deconjugation continues to determine the fate of various medicines in surface water at a large distance from the sewage treatment plant.

Massive exposure to medicines via tap water



1994: 4 million inhabitants of Berlin (Stan et al. 1994)

2007: 28 million Americans (Benotti et al. 2009)

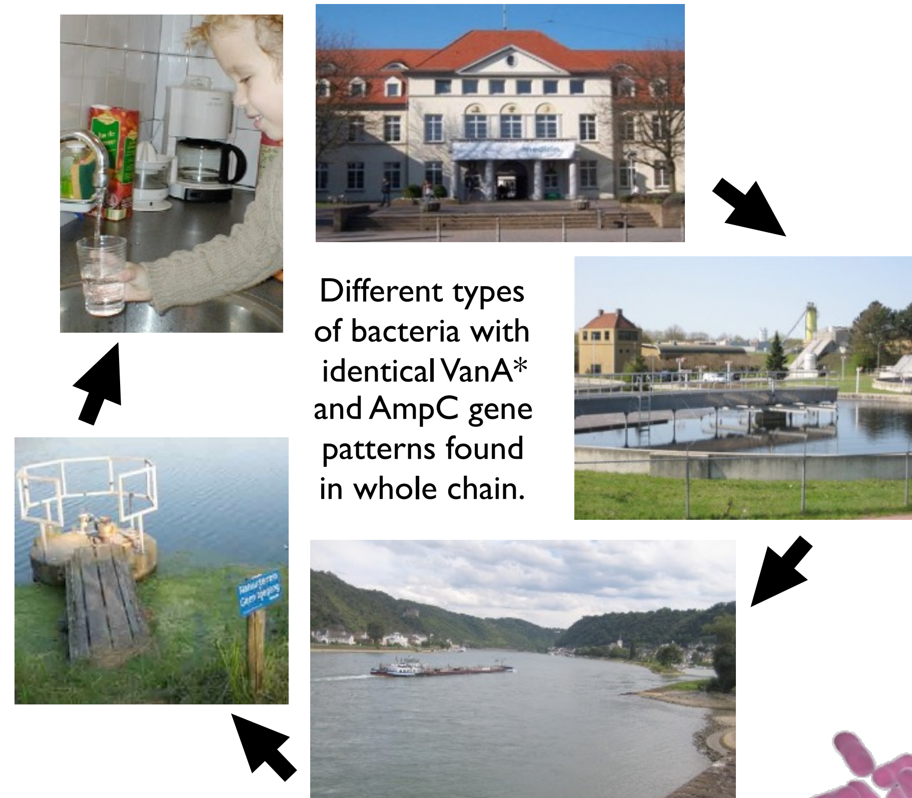
2014: > 6,7 million Dutch (Laak ter et al. 2010, Wuijts et al 2012, CBS 2014)

HUIZE AARDE

6. Despite high-tech water treatment, via tap water also people are being exposed massively to medicines and multi-resistant bacteria

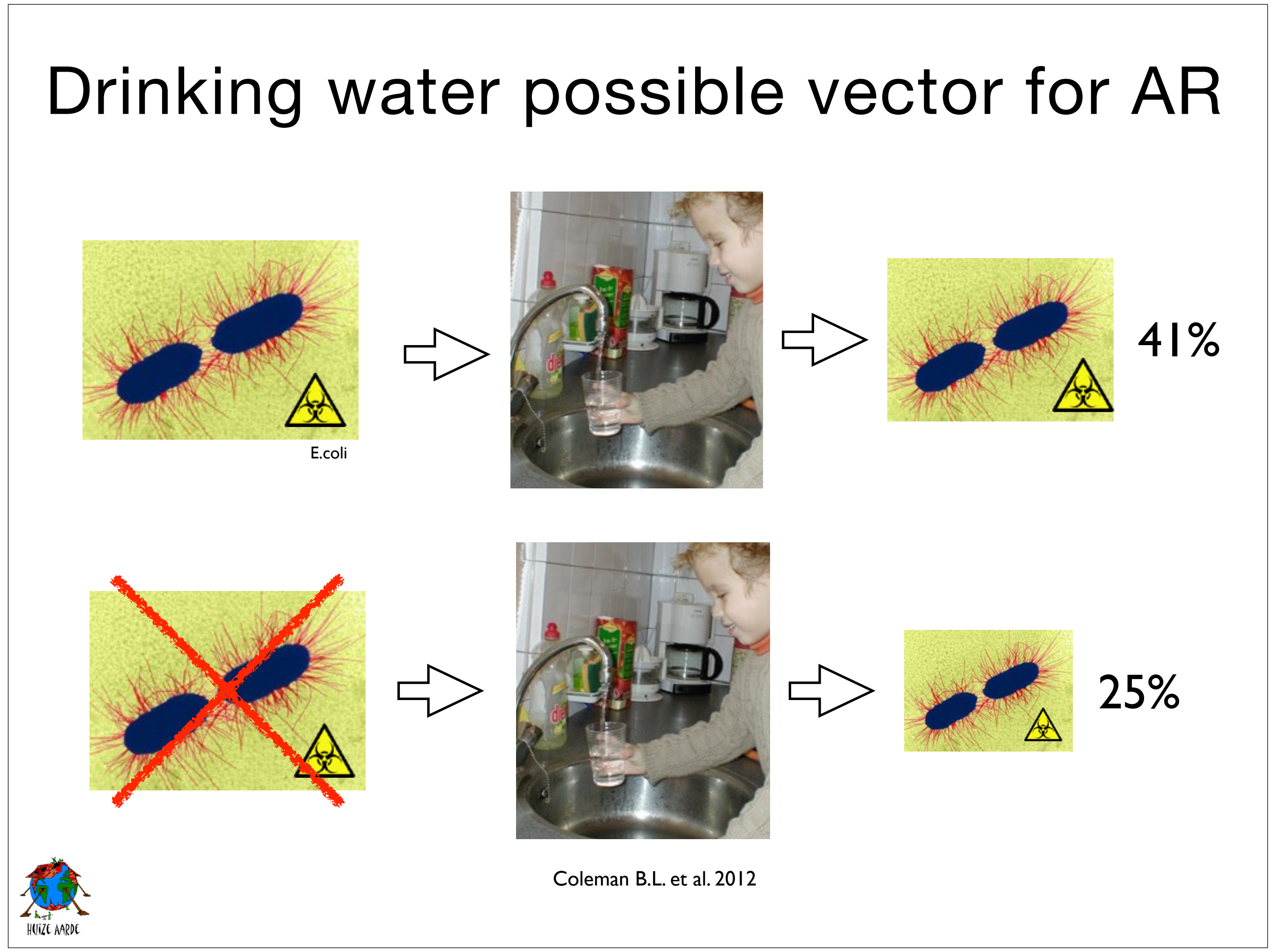
AR genes move through whole water chain

*multi-resistant VanA	
vancomycin	100%
tetracycline	100%
erythromycin	100%
ampicillin	62%
gentamycin	59%
imipenem	51%
amoxicillin	33%



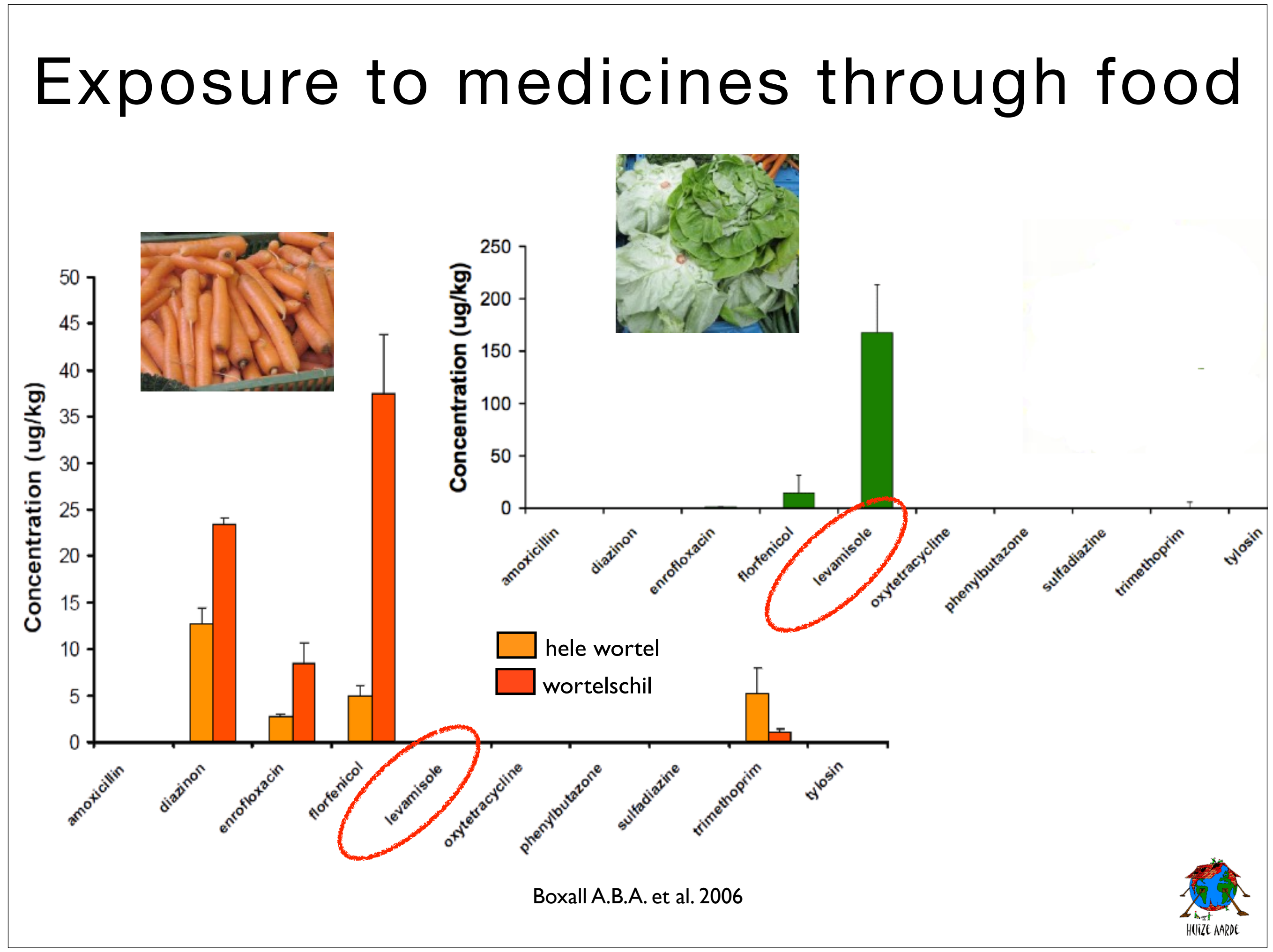
Schwartz T et al, 2003

7. Also multi-resistant bacteria are difficult to monitor as a result of their transfer of multi-resistence-genes to other species.



8. Drinking water could increase antibiotic resistance in humans

A Canadian study showed that 41% of healthy people exposed to low concentrations of resistant E. coli bacteria via contaminated drinking water carry resistant bacteria in their guts, compared to 25% who did not acquire resistance bacteria due to pre-treatment of their drinking water.

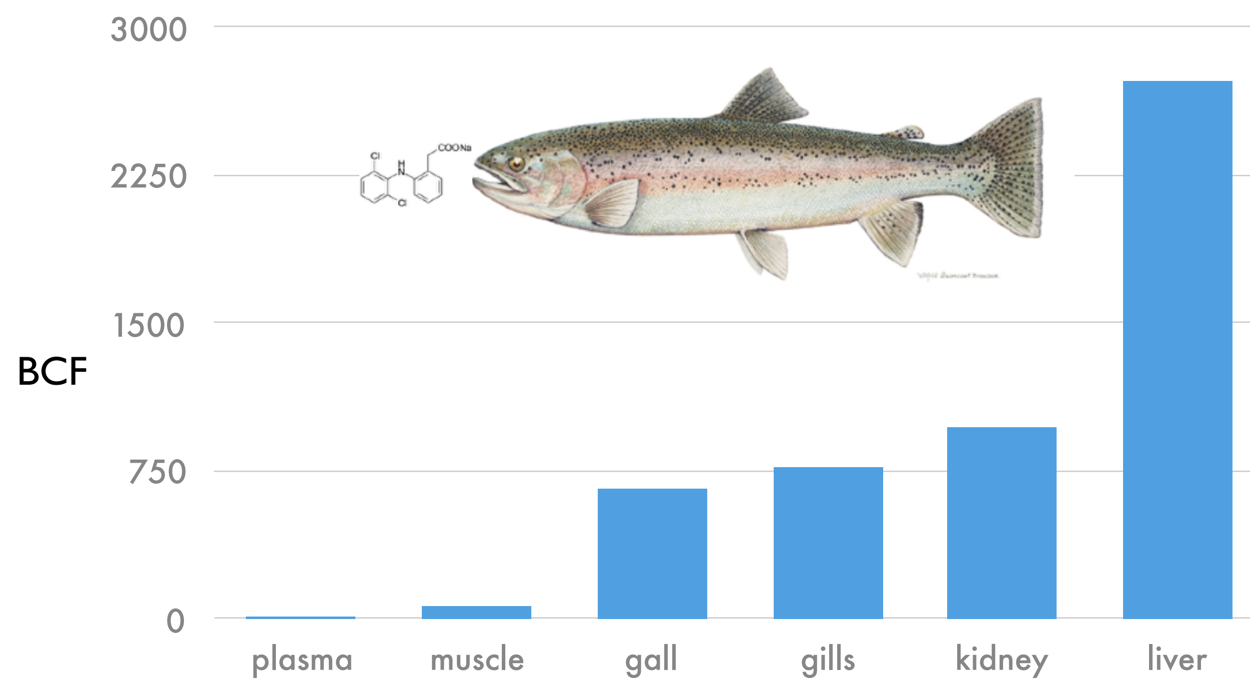


9. People are exposed to medicines via food

Medicines that end up in the soil accumulate in plants and therefore also in agricultural crops. The accumulation **differs per molecule, per plant species, and per type of tissue**. For example, the anthelmintic levamisol accumulates strongly in lettuce, while it was not absorbed by carrots. Some plant products that one eats raw, such as carrots and lettuce, allow one to obtain medicines in concentrations that can be 1000 to 10,000 times higher than in drinking water.

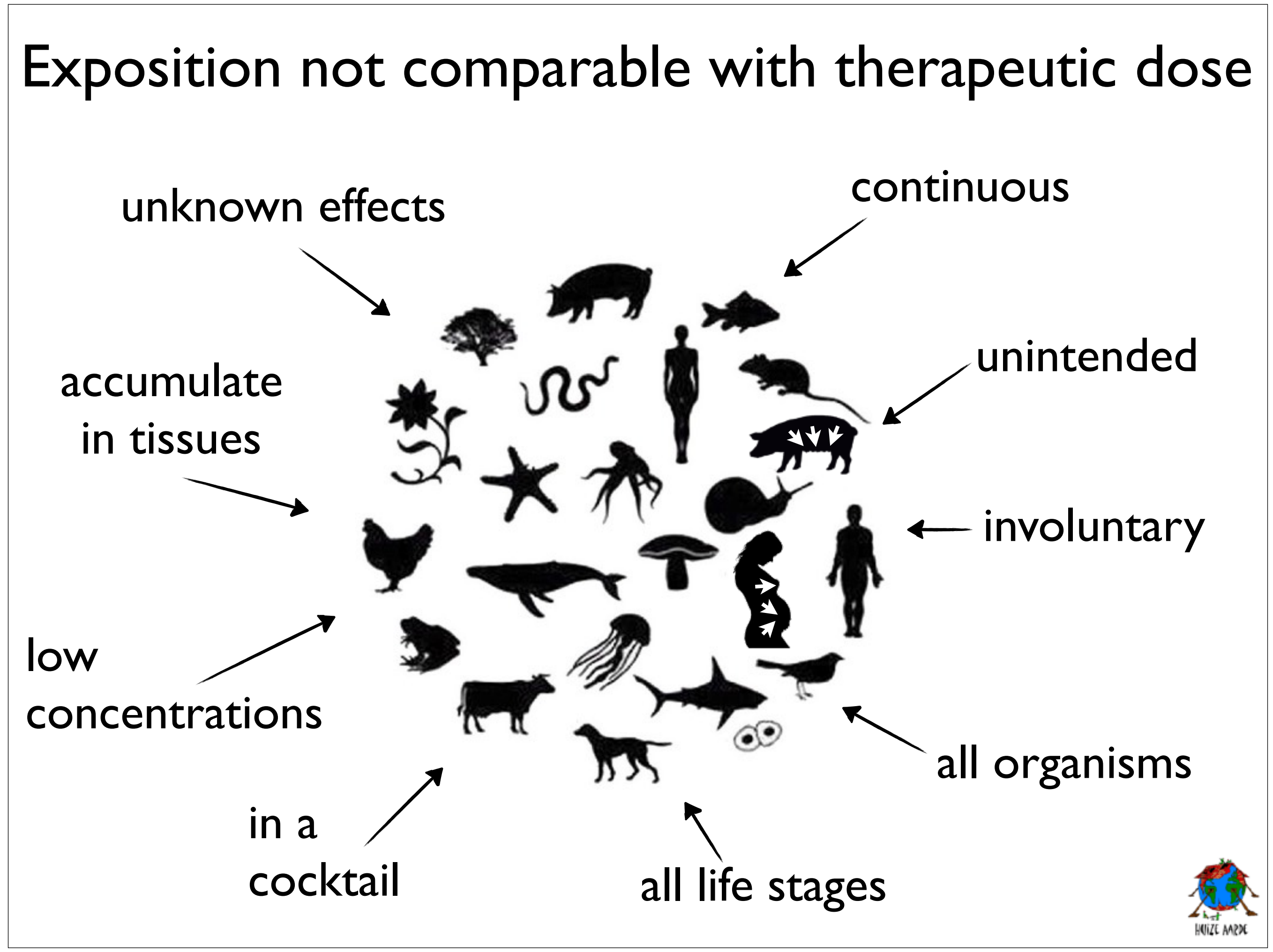
Tissue-dependent accumulation in organisms

diclofenac in fish



Schwaiger et al. 2004a (muscle, gills, kidney, liver), Mehinto et al. 2010 (gall), Brown et al. 2007 (plasma)

10. Medicines concentrates in organs. Accumulation varies by tissue type.



11. Environmental exposure to medicines is not comparable with a therapeutic dose

Because of the low environmental concentrations, human exposure via the environment frequently is compared to a therapeutic dose. And then it is concluded that there is no human health risk. However, **from a toxicological point of view** such a comparison is incorrect. There is a continuous unintentional and involuntary exposure of all organisms at all stages of life to a cocktail of medicines and other substances in low concentrations, that accumulate in tissues, with mainly unknown effects.

Environmental medicines: endocrine disruptors?

non-hormonal medicines with ED-effect

medicine group	sub group	examples	number studies
analgesics	NSAID	ibuprofen acetaminophen	11
antidepressants	SSRI	fluoxetin sertralin	10
anti-fungal agents	azoles	ketoconazole clotrimazole	7
cholesterol reducers	fibrates	bezafibrate clofibrate	5
antihypertensives	beta-blockers	salbutamol propanolol	4
anti-cancer agents	anti-estrogenics	tamoxifen	2
antihypertensives	diuretics	furosemide	2
antibacterial agents	antibiotics	amoxicillin erythromycin	1
antiepileptics	Na-blocker	carbamazepin	1
antiacids	H2-blocker	cimetidine	1

(based on 30 publications till February 2014)

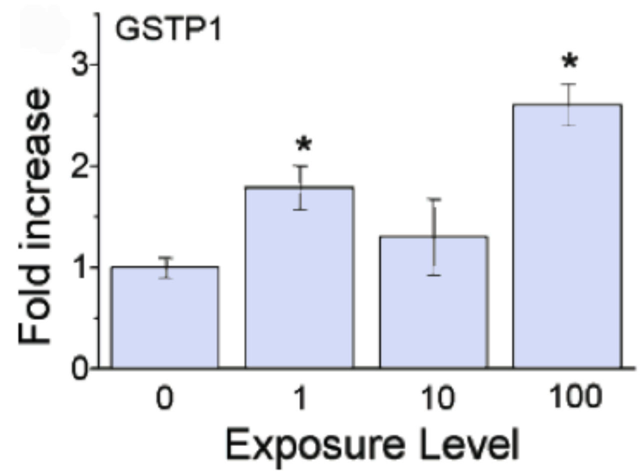
Zero tolerance for EDC
March 13 2013

12. Medicines in low concentrations could act as EDC's

A large number of non-hormonal medicines is suspected of endocrine disrupting effects. The table, which is based on 30 papers, shows that non-hormonal medicines like analgesics and antibiotics, have possible endocrine disrupting effects. From 2012 WHO and UNEP consider medicines in the environment as substances that may have a hormone effects. IN 2013 The European Parliament put endocrine disrupting substances high on their agenda. According to the Parliament, no environmental threshold should apply to these substances (zero tolerance).

Medicine mixture disturbs cell division

expression of genes related to
disturbed cell division



(0= blanco; 1,10,100 x dosis)

Photo: 5 weeks old human embryo by Euthman Flick.com

in human
embryonic cells

Mixture of atenolol, bezafibrate, carbamazepine, cyclofosfamide, ciprofloxacin, furosemide, hydrochlorothiazide, ibuprofen, lincomycin, ofloxacin, ranitidine, salbutamol, and sulfamethoxazole - each product in low environmental relevant concentration

Pomati F. et al. 2006

13. Individually, medicines in the environmental cycle have no harmful effect, but in a cocktail (here of 13 medicines) they seem to do so.

Medicine mixture activates gene sets

A mixture of: carbamazepine, fluoxetine and venlafaxine activates human-identical genes in young laboratory animals.

Table 4. Sets associated with human neurological disorders.

Set	Size	NES	p-value	FDR q-value
AUTISM_IDIOPATHIC	324	1.621	0.000	0.064
PARKINSONS	94	1.560	0.007	0.055
MS_GILLI	216	1.375	0.011	0.137
SCHIZOPHRENIA	23	1.232	0.181	0.364
MS_BOMPREZZI	28	1.199	0.201	0.326
ADHD_UP	30	1.187	0.222	0.275
DEPRESSION	23	1.137	0.307	0.293
ADHD_DOWN	20	−0.684	0.894	0.924
RETT	25	−0.784	0.798	1.000
ALZHEIMERS	237	−0.967	0.549	0.859
ASD_SECONDARY	39	−1.083	0.332	0.764
BIPOLAR	41	−1.172	0.217	1.000

Sets are described in Table 2; size refers to the number of genes in the set; NES is the normalized enrichment scores for the set; p-value is the nominal p-value associated with the NES; FDR q-value is the false discovery ratio rate.

doi:10.1371/journal.pone.0032917.t004

Thomas MA & RD Klaper 2012; Kaushik G et al. 2016

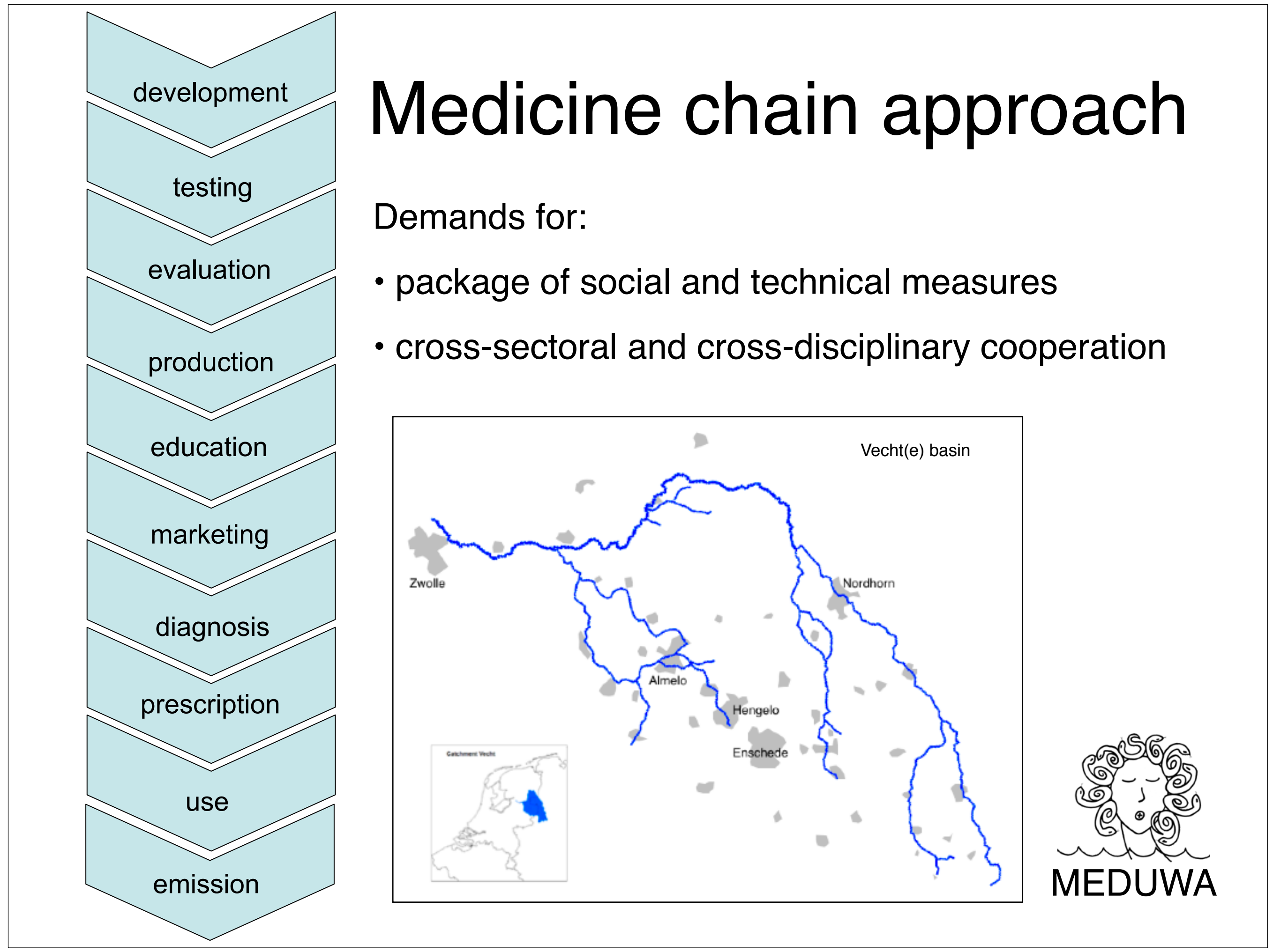
14. Effects possibly occur at gene level and could be expressed later in life or in next generations

In young animals a cocktail of three neuro-pharmacological agents, in low (environmentally relevant) individual concentrations, show gene activation patterns that encodes for autism, Parkinson's and multiple sclerosis in humans.

=> zero tolerance for the **emission** of medicines and multi-resistant bacteria

Ethically impossible or ethically necessary?

15. Medicines can't be simply prohibited or replaced because they are meant to be an essential tool for our wellbeing. But, because of the health hazard, as a society we have to develop strategies to stop the EMISSION of medicines and multi-resistant bacteria into the environment.



To develop a package of complementary technical and social measures in the whole life cycle of medicines, communication and collaboration is needed between different social sectors and disciplines.

With this vision from 2009 the MEDicines Unwanted in WAter or MEDUWA-project has been developed.
To foster regional ownership of the issue and its solutions, the project operates within the shared river basin of the Vecht(e) river. All products that will be developed within the project become exportable worldwide.

To execute the MEDUWA project from 2017 a cross-border German-Dutch coalition of 27 partners has been formed: 16 companies, 5 research institutes, 2 academic hospitals, 1 government, and 2 civil society organisations from the water, agricultural and (human & veterinary) health sectors, and sustainable development.

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Budget: € 8.5 million

Co-funders:

EUROPEAN UNION
European Regional Development Fund

provincie Gelderland

Niedersächsische Staatskanzlei

provincie Overijssel

Ministerie van Economische Zaken en Klimaat

PROVINCIE FLEVOLAND

Ministerium für Wirtschaft, Innovation, Digitalisierung und Energie des Landes Nordrhein-Westfalen

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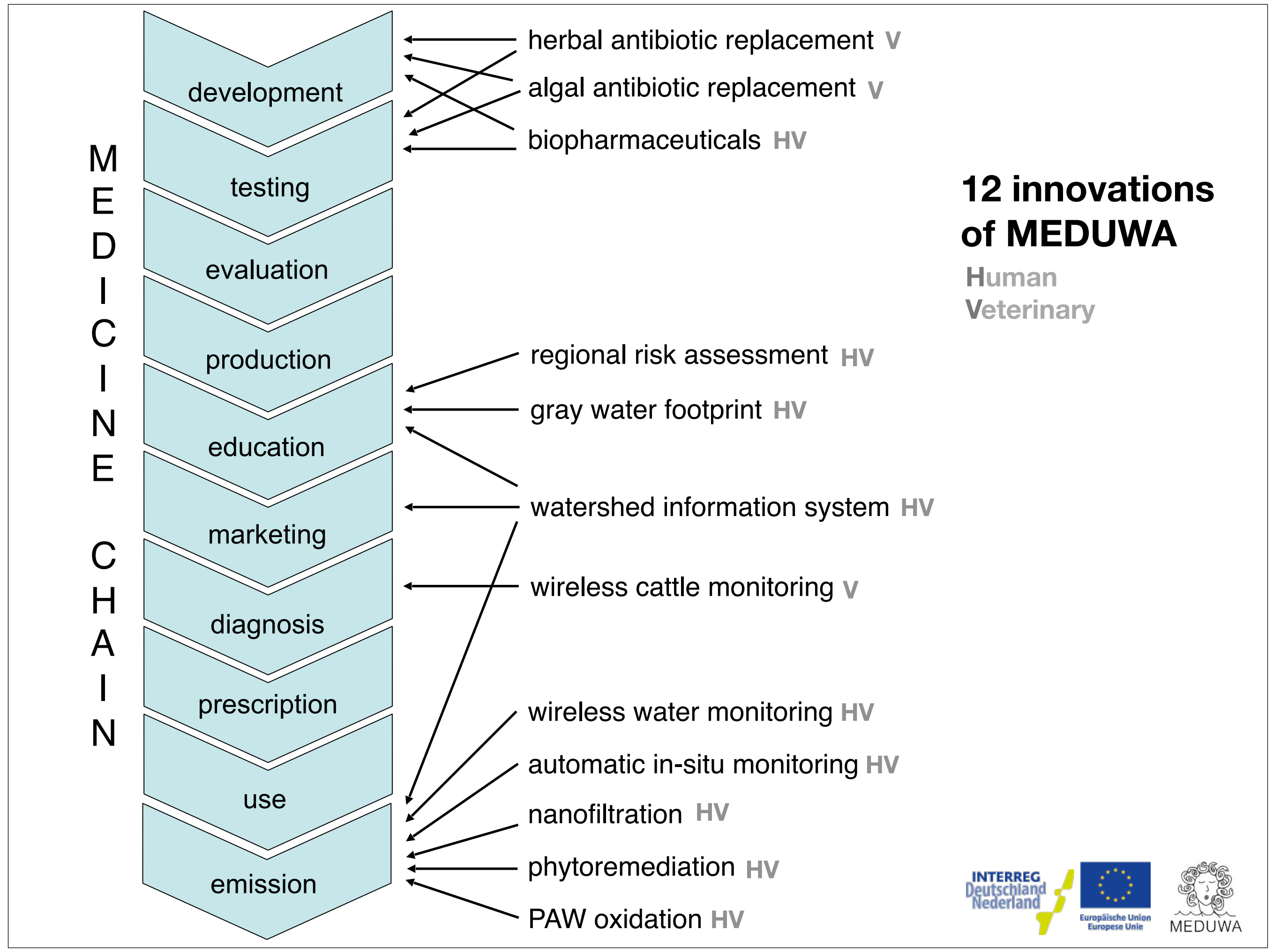
MEDUWA costs 8,5 million Euro. The project is for 50% subsidized by the EU Regional Development Fund (ERDF); for 20% by the regional INTERREG-VA Program Partners, and for 30% co-financed by the project partners themselves.



MEDUWA is an attempt to put a life cycle approach into practice. 12 innovative products are being developed in several links of the human and veterinary medicine chain.

The project is characterized by the collaboration between research institutions and companies. In teams they collaborate on practical solutions. With 8 PhD-candidates and post-docs the project provides an opportunity to a new generation of scientists and stimulates co-production between disciplines.

Intervention classes of MEDUWA

WP	product	prevention	mitigation	measuring	simulation prediction	visualisation communication
1.1	Watershed info system				■	■
1.2	Gray water footprint				■	■
1.3	Risk assessment				■	■
2.1	Automatic in-situ monitoring			■		
2.2	Wireless water monitoring			■		
2.3	Nanofiltration		■			
3	PAW oxidation		■			
4.1	Phytoremediation		■			
4.2	Herbal antibiotic replacement	■	■			
4.3	Algal antibibiotic replacement	■	■			
5	Wireless cattle monitoring	■				
6	Biopharmaceuticals	■				

MEDUWA covers different intervention classes: prevention; mitigation; analysis; simulation of measures; prediction; visualization; and communication.

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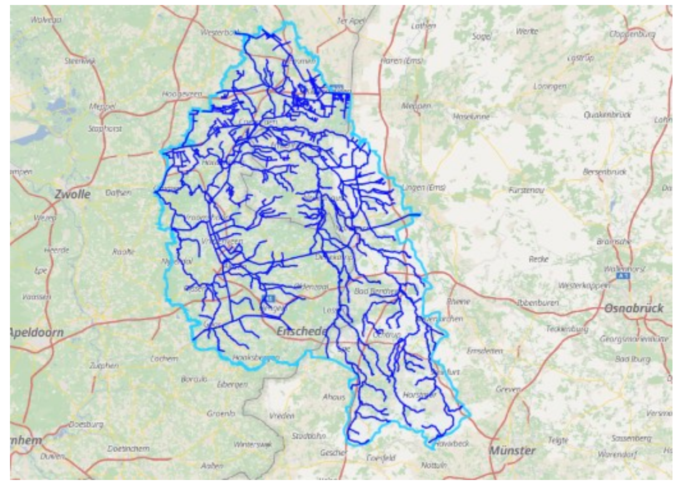
Example of a MEDUWA innovation:

Watershed Information System (WIS)



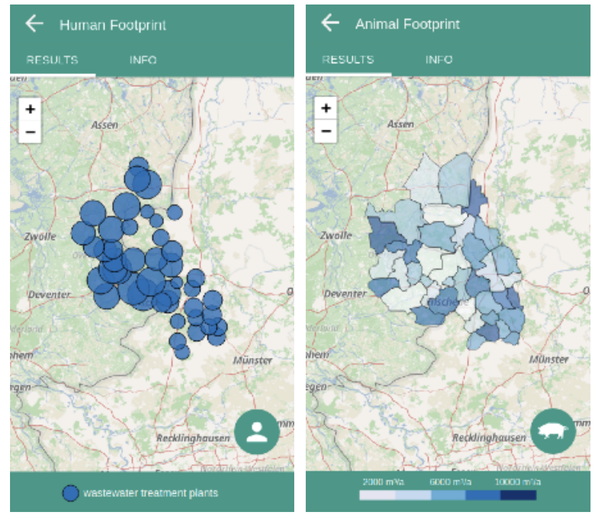
- Visualisation of chemical and biological contaminants.
- In the entire catchment area.
- Simulations of measures.
- Under different climate scenarios.
- Tool for communication, awareness and policy.

wetsus | UNIVERSITÄT OSNABRÜCK | GEOPLEX 3D & SOLAR

The watershed information system is mainly intended as a tool for communication, awareness and policy making on water quality in an entire river basin. This tool also can be used to simulate the effectiveness of a measure under different climate scenarios if it is implemented throughout the basin. With this functionality, participating companies can use the information system to test the efficacy of their product.

Example of a MEDUWA innovation:

Grey water footprint



- Visualisation of water pollution by veterinary and human medicine use.
- Per livestock farm (per head of livestock, per kilo of meat and per liter of milk).
- Per municipality (per inhabitant).
- Per hospital (per patient).

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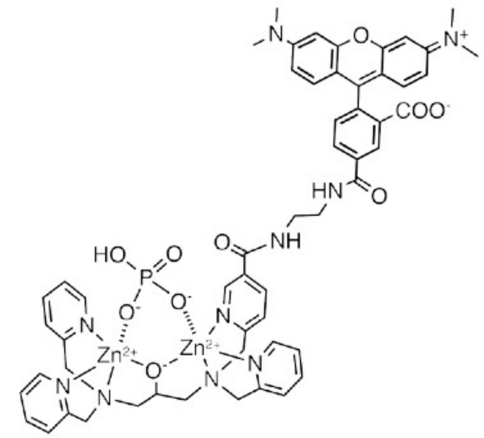
The grey-water footprint represents the amount of water contaminated by human and veterinary medicine use. This communication and marketing tool can be used to show how a sector, municipality, province, farm, institution, etc. performs in the field of socially responsible medicine use or in the field of sustainability.

Example of a MEDUWA innovation:

Biopharmaceutical : alkaline phosphatase (AP)



- Production and application of AP as a natural anti-inflammatory medicine.
- In humans: eg. to prevent steroid and antibiotic use against complications during cardiac operations.
- In animals: eg. against mastitis, colic and weaning diarrhea.

MEDUWA also stimulates innovations at the top of the product chain. Here the production and application of Alkaline Phosphatase as a natural anti-inflammatory medicine is developed. AP is a body enzyme that could prevent steroid and antibiotic use eg. during cardiac operations. And in farm animals it can be used against mastitis, colic and weaning diarrhea.

In session E4 another MEDUWA innovation, plasma water oxidation, wil be presented in more detail.

If you would like to get to know the MEDUWA innovations and be kept regularly informed about their progress, you can become a member of the MEDUWA Stakeholder Board.

MEDUWA Stakeholder and partner meeting, University of Osnabrück, March 2018

If you would like to get to know the MEDUWA innovations and be kept regularly informed about their progress, you can become a member of the MEDUWA Stakeholder Board. This Board is a way for the project to connect to society. Its members are amongst others, from the human and veterinary health and water sectors. As a member you will be invited to the annual stakeholder and partner days in 2019 and 2020.

For more info, see meduwa.eu

For for registration as a member of the **MEDUWA Stakeholder Board,**
please leave your business card behind
or write to: louisa.kistemaker@uni-osnabrueck.de

Thank you!