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

Stakeholder & Project Partner Meeting Jan 15 2019, Nordhorn

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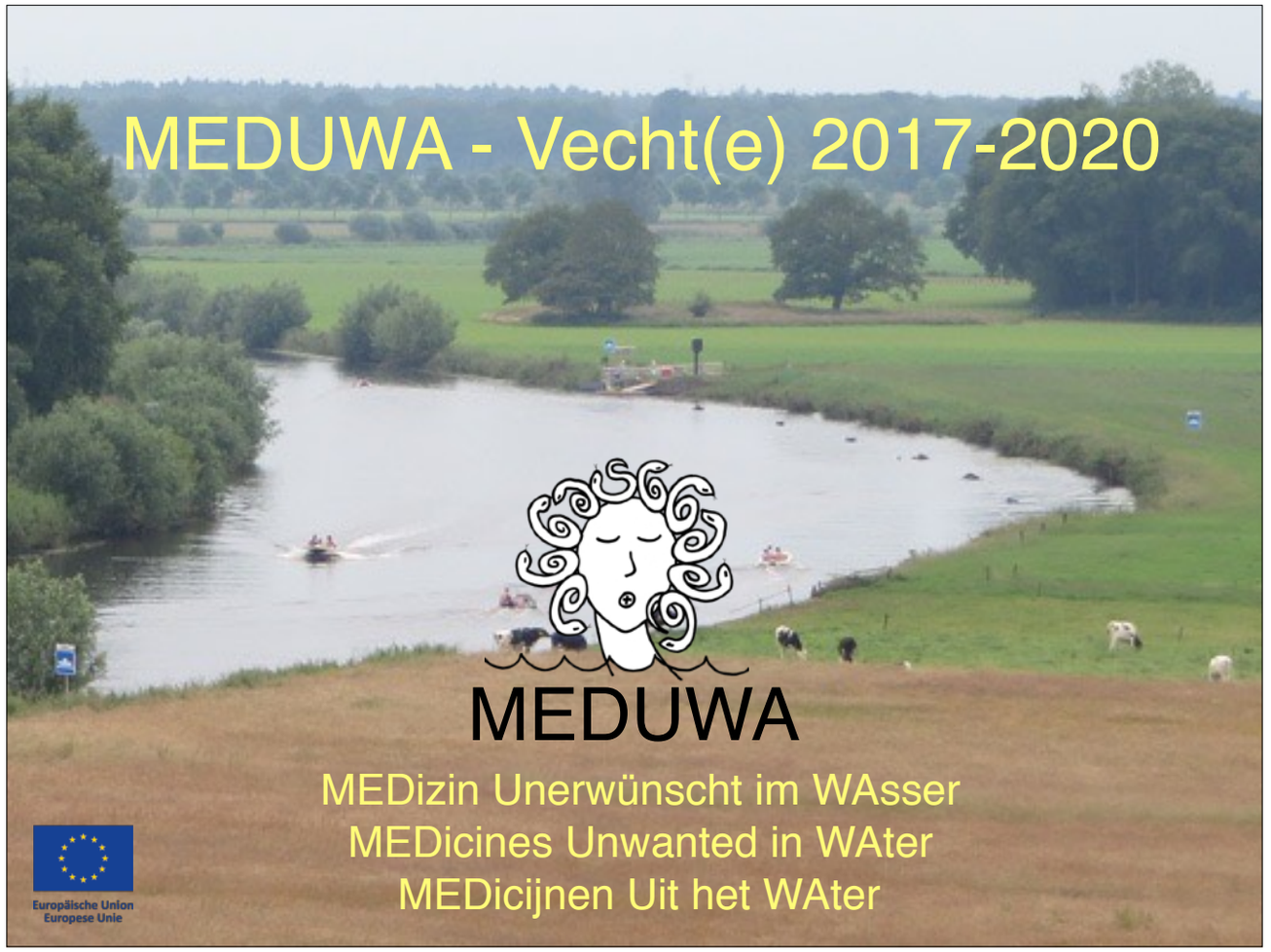
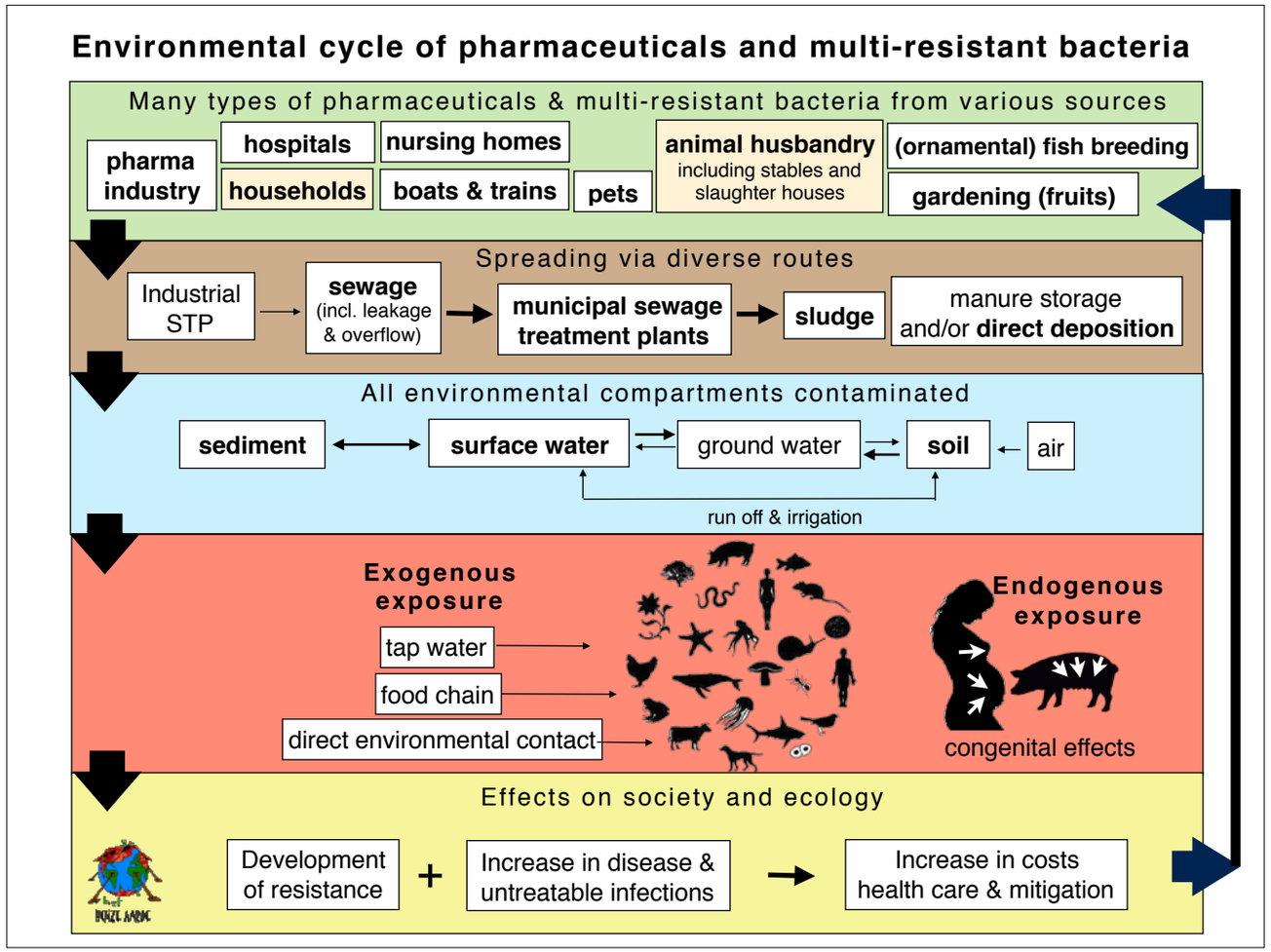


The EU INTERREG-VA project MEDUWA-Vecht(e) addresses a common challenge: the environmental cycle of human and veterinary medicines and multi-resistant bacteria that are transferred via drinking water, food and air back to humans and animals. Because of its complexity, this problem could paralyze us - as did the Greek mythological Medusa. What makes this issue so complex?

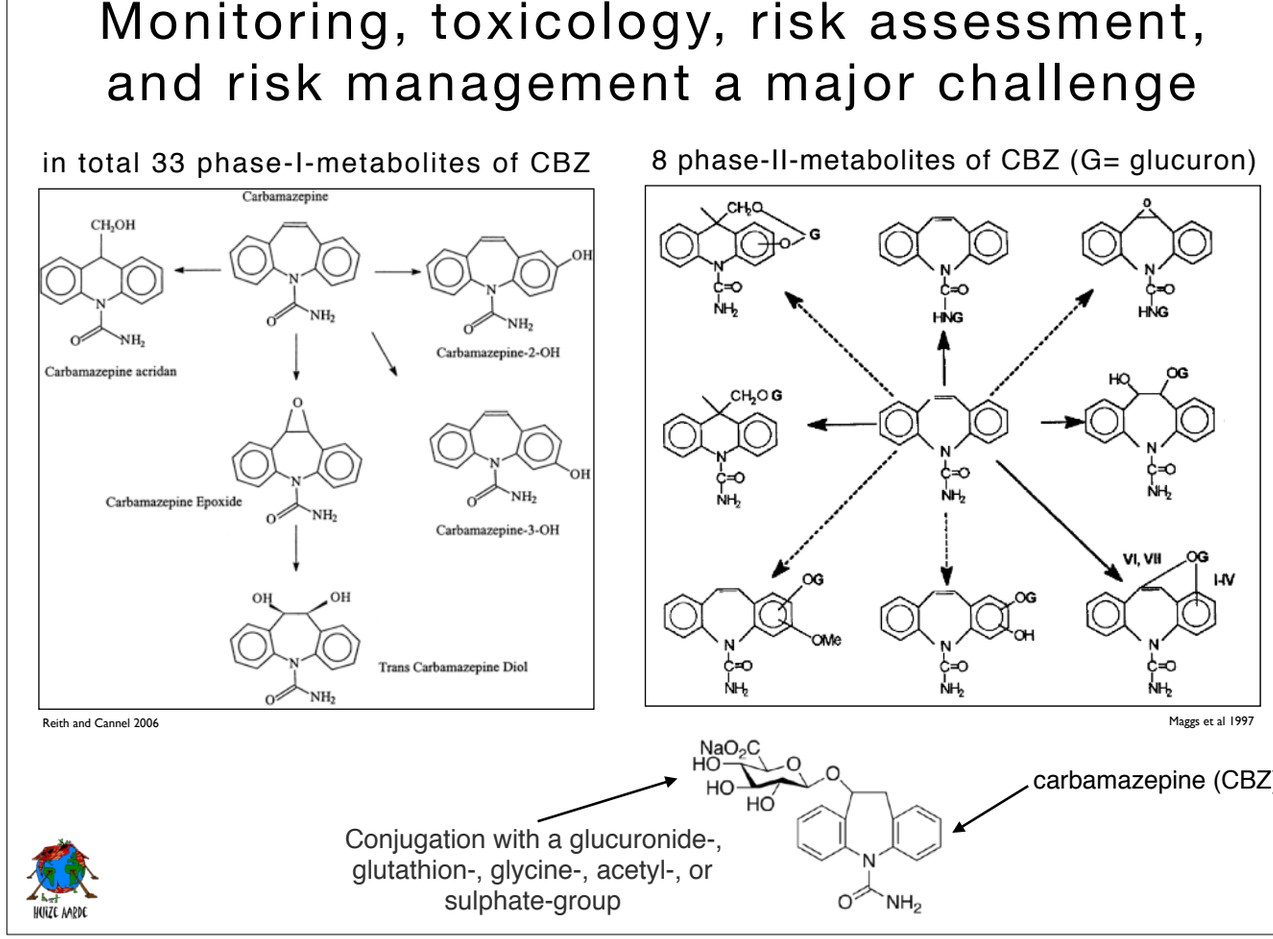
Dispersal of the problem

1. Through sewage water treatment, and manure and sludge 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.



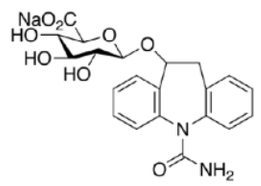
2. Medicines and multi-resistant bacteria that left the body reach the environment, and through the environment they return to us.



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)

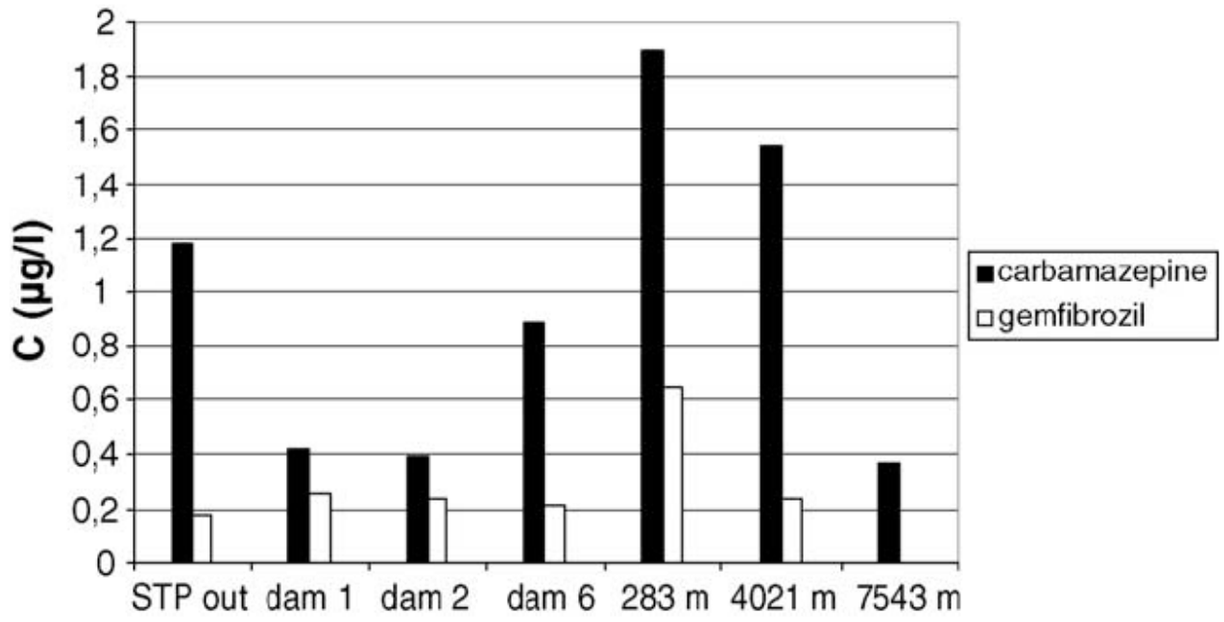
analyte	influent	effluent
CBZ	368.9 ± 5.3	426.2 ± 6.1
CBZ-EP	47.2 ± 1.8	52.3 ± 1.2
CBZ-DiOH	1571.7 ± 31.0	1325.0 ± 12.2
CBZ-2OH	121.0 ± 1.6	132.3 ± 2.1
CBZ-3OH	94.8 ± 2.2	101.5 ± 0.3
CBZ-10OH	8.5 ± 0.6	9.3 ± 0.4

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.

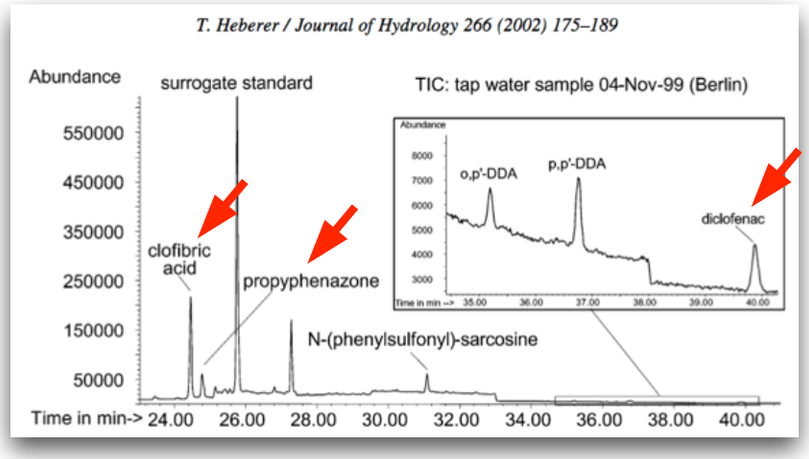
Deconjugation continues after emission



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)

6. Despite high-tech water treatment, via tap water also people are being exposed massively to medicines and multi-resistant bacteria. Therefor the interests of drinking water producers are also relevant.

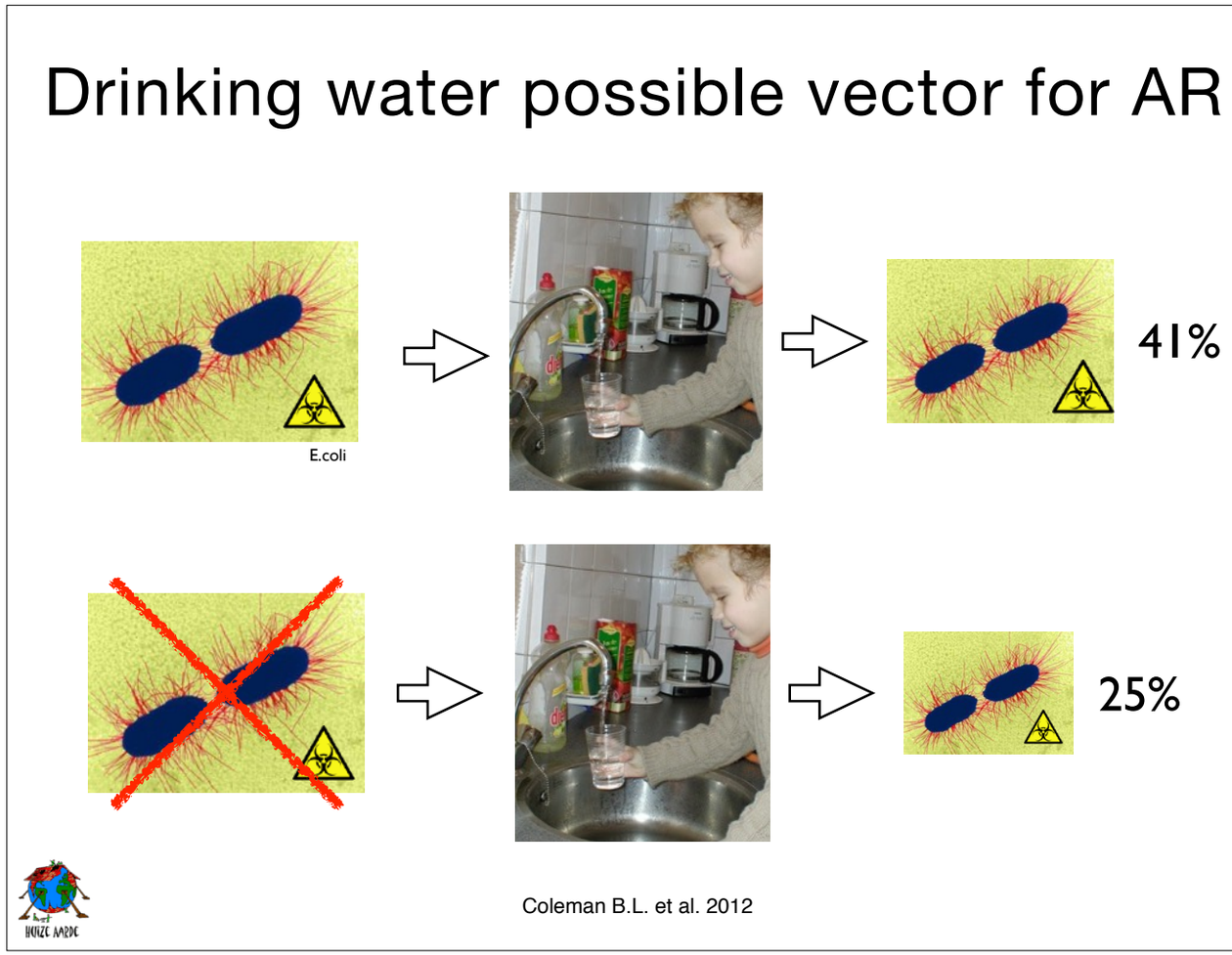
AR genes move through whole water chain

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

Different types of bacteria with identical VanA* and AmpC gene patterns found in whole chain.

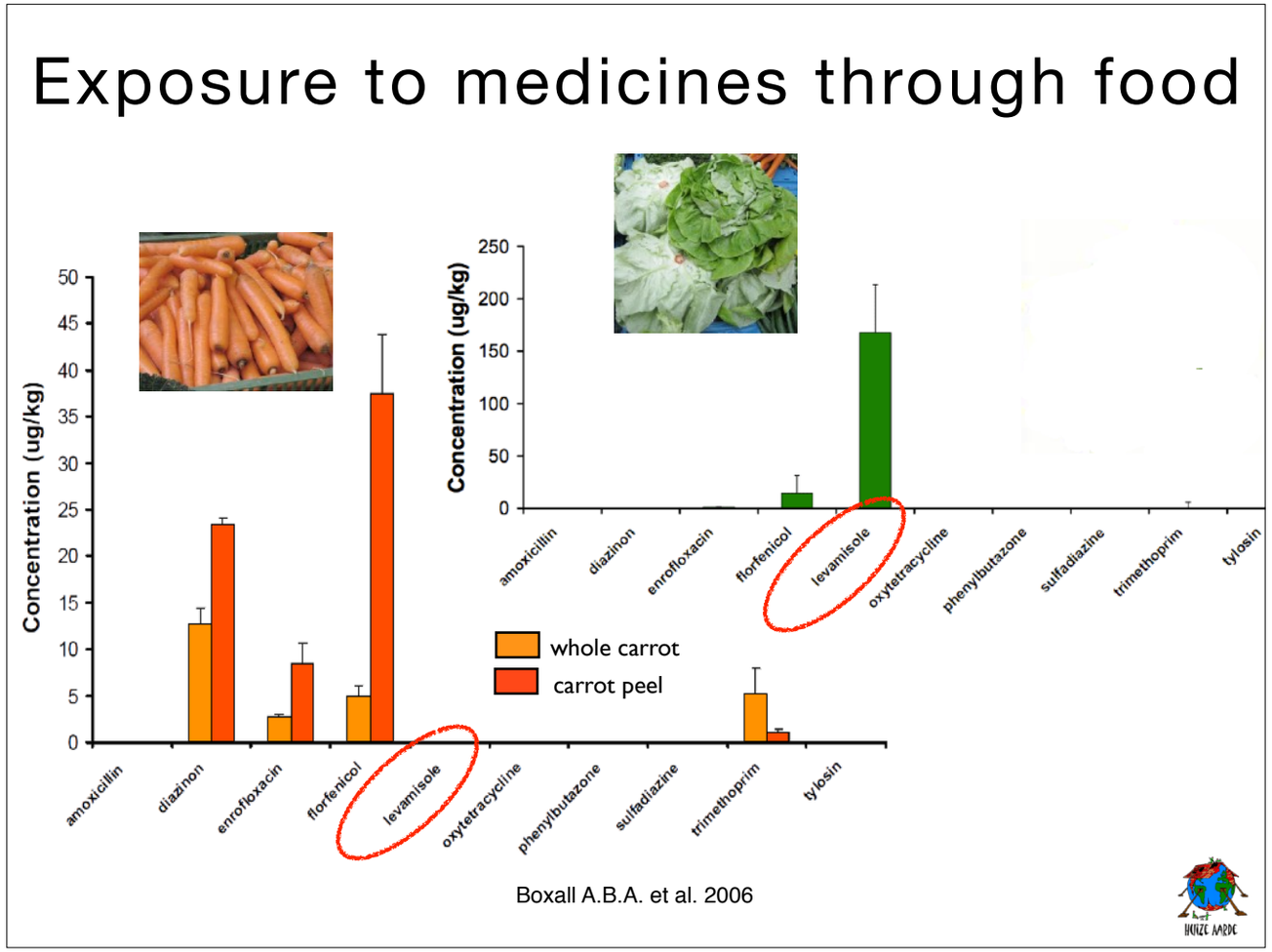
Schwartz T et al, 2003

7. Also multi-resistant bacteria in the environmental cycle 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

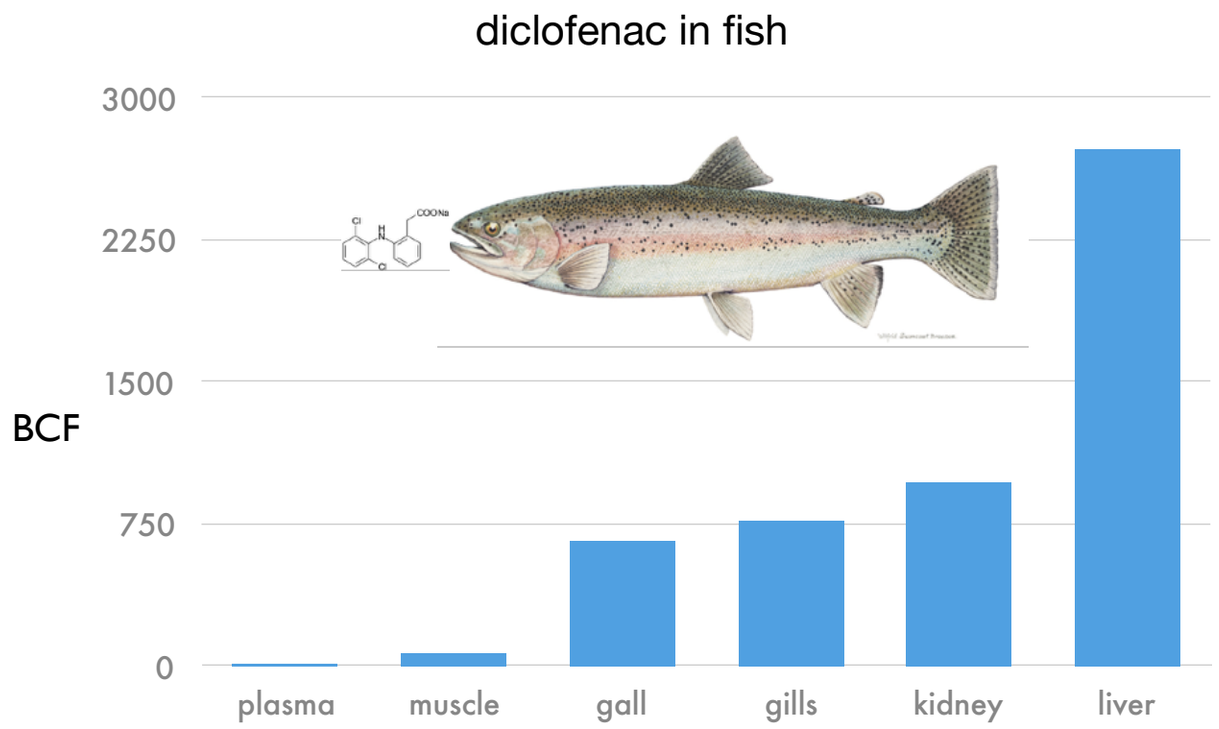
A Canadian study showed that 41% of healthy people exposed to low concentrations of resistant E. coli bacteria via contaminated drinking water carry resistant bacteria in their guts, compared to 25% who did not acquire resistance bacteria due to pre-treatment of their drinking water.



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.

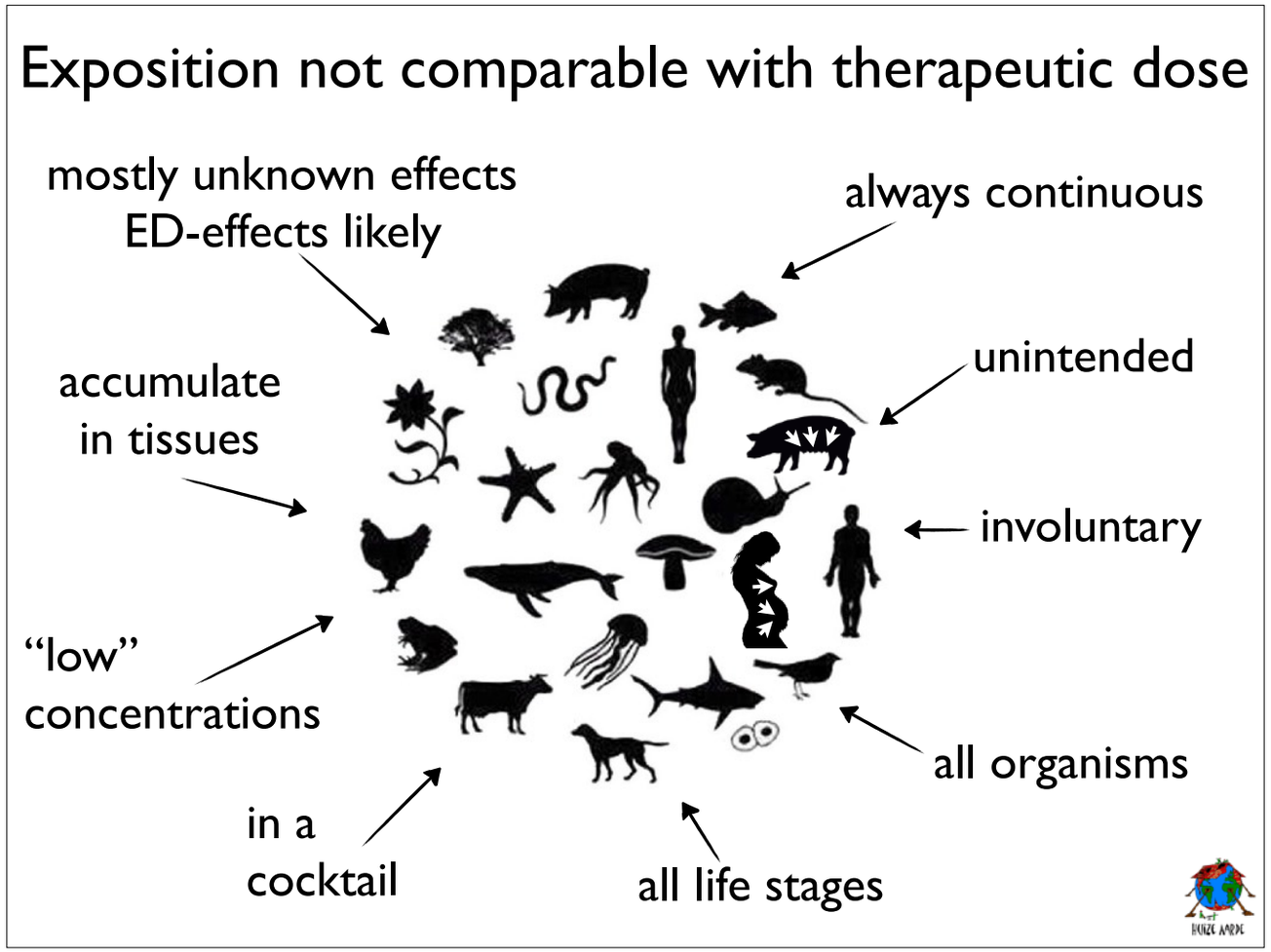
Tissue-dependent accumulation in organisms



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.

In this case of fish exposed to diclofenac in environmental concentrations: under a microscope cell damage can be detected in gills, kidney and liver, while no external damage is visible.

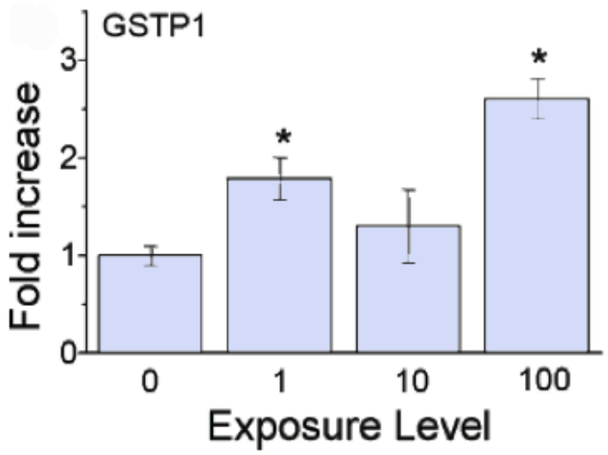


11. Environmental exposure to medicines is not comparable with a therapeutic dose

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. Because a) there is a continuous unintentional and involuntary exposure of all organisms at all stages of life to a cocktail of medicines and other substances, that accumulate in tissues, with mainly unknown effects; and b) in the case of endocrine disrupting effects and DNA damage there is no minimal effect concentration.

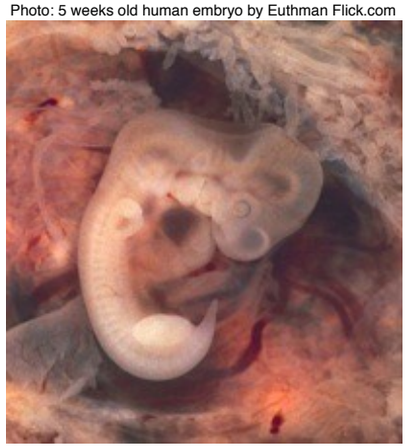
Medicine mixture disturbs cell division

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

12. 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 rate ratio.
doi:10.1371/journal.pone.0032917.t004

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

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

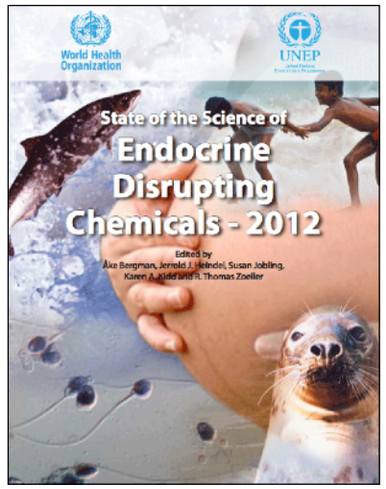
In young animals a cocktail of three neuro-pharmacological agents, in low (environmentally relevant) individual concentrations, show gene activation patterns that encodes for autism, Parkinson's and multiple sclerosis in humans.

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
from March 13 2013

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

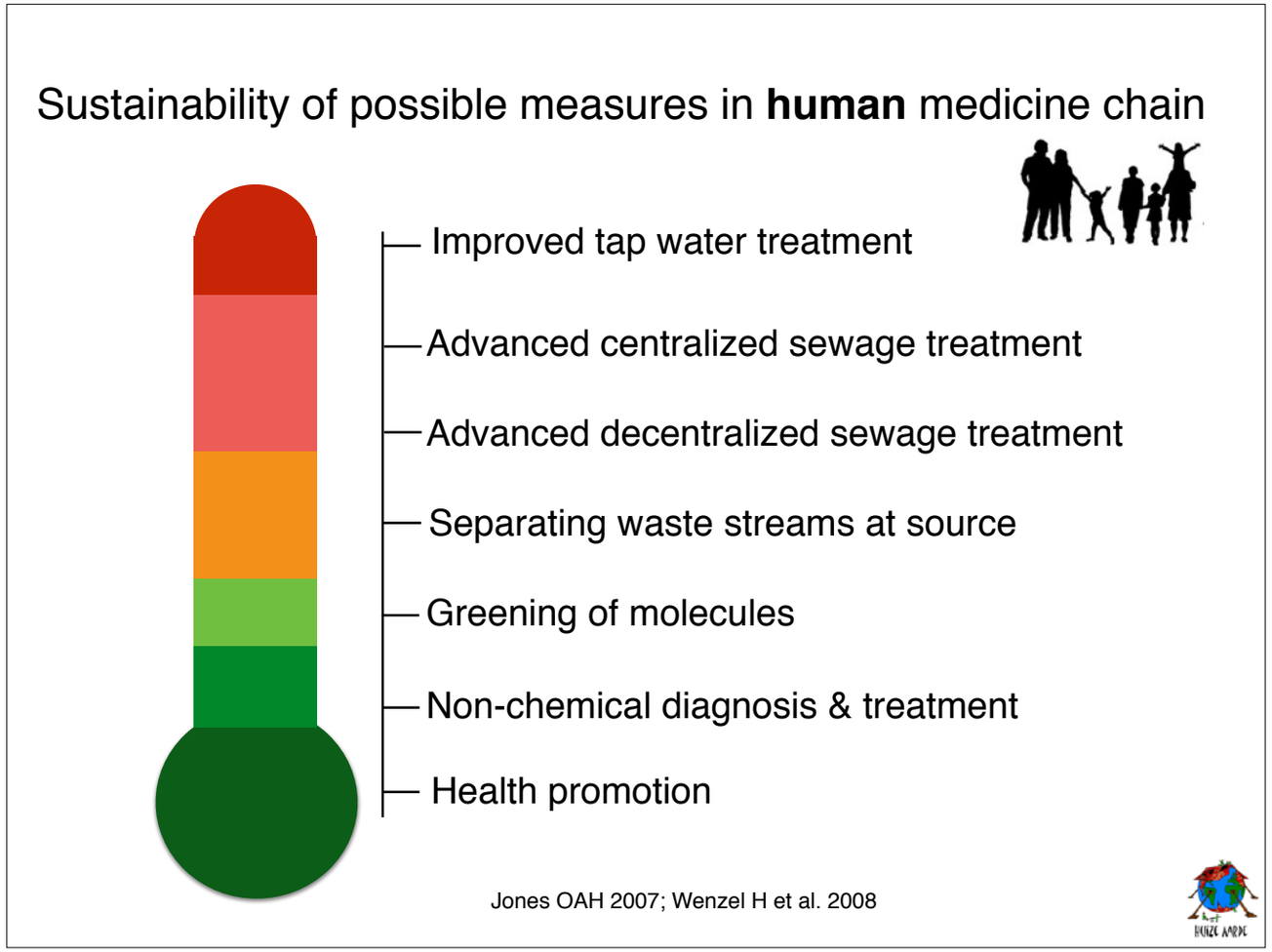
A large number of non-hormonal medicines is suspected of endocrine disrupting effects. The table, which is based on 30 papers, shows that non-hormonal medicines like analgesics and antibiotics, have possible endocrine disrupting effects. From 2012 WHO and UNEP consider medicines in the environment as 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). For the health sector it will be a major challenge when discharge of medicines no longer will be allowed.

=> 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 well being.

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.



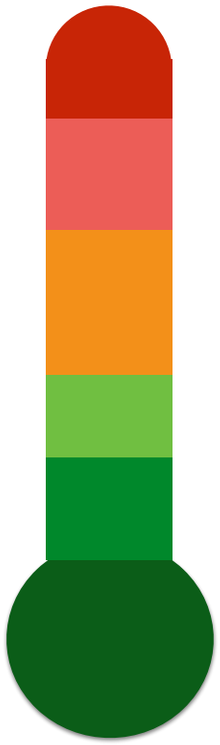
For this complex issue partial solutions aren't fruitful. An integrated approach is needed to avoid ecological and social damage in the whole product chain. Here a "Sustainability Thermómeter" is shown for measures that lower/reduce pollution by pharmaceuticals. Presumably, the lower in the thermometer the more sustainable (more effective, less costly, less side effects) measures would be.

For example, high-tech filters would create false safety: they do not work 100%; they are quickly outdated because they are fast behind developments in pharmacy and chemistry; they aren't sustainable due to high energy and purchase and maintenance costs, and the generation of new toxic waste streams; and they help only partially as there are too many sources and too many emission routes.

NB the introduction of green molecules does't mean responsible use of medicines either.

Therefor, to solve this complex contamination the development of a package of complementary source oriented measures by the whole product chain is needed.

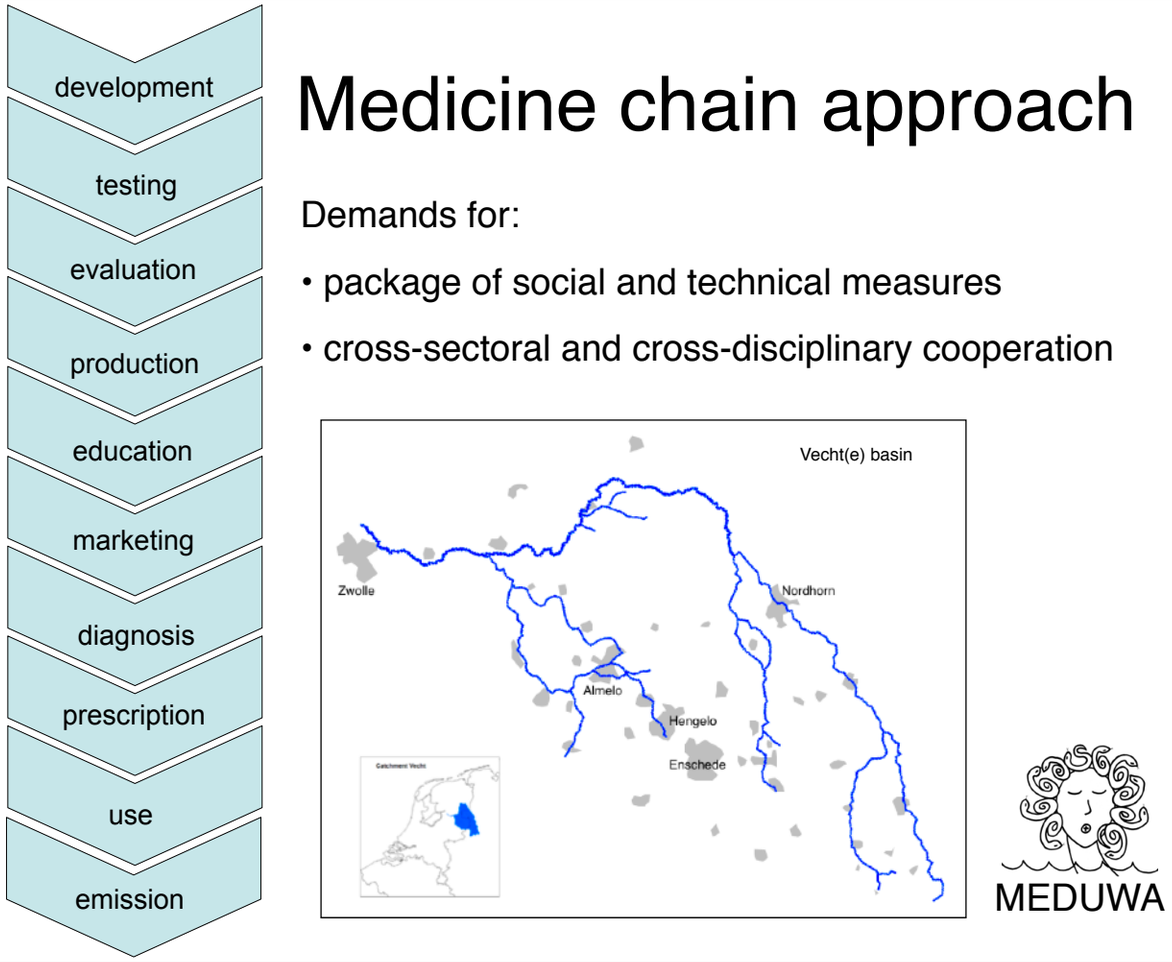
Sustainability of possible measures in **veterinary** medicine chain



- Fermentation, incineration of dung; oxidation of urine
- Recollection of unused medicine
- Biodegradation in manure
- Smart fertilizing
- Admission on basis of environmental impact assessment
- Non-chemical diagnosis & treatment
- Vaccination
- Animal health & hygiene promotion
- Moderate meat consumption & food waste reduction

Jibichibi B et al. 2007; Eikelenboom D et al. 2012

see former slide



Medicine chain approach

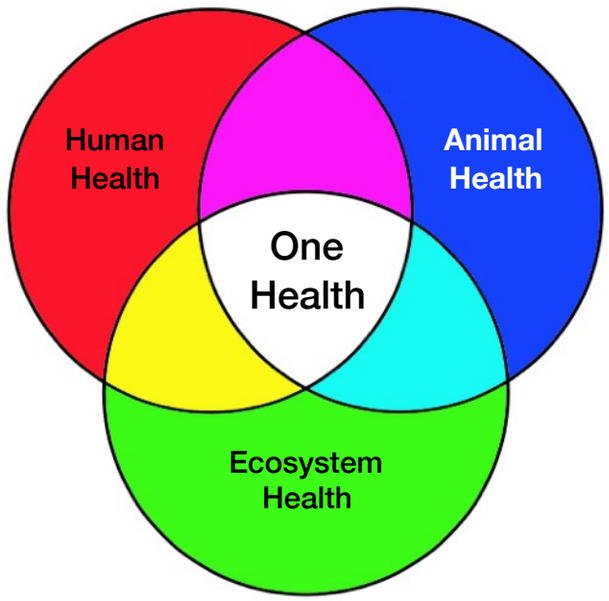
Demands for:

- package of social and technical measures
- cross-sectoral and cross-disciplinary cooperation

MEDUWA

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

Human and veterinary health linked



One-Health strives for animal health, human health and environmental health together.

One-Health includes the avoidance of environmental & health effects of human and veterinary medicine use.

In MEDUWA besides the life cycle approach also the One-Health approach is being applied.
One-Health strives for animal health, human health and environmental health together.
By that, One-Health includes the avoidance of environmental & health effects of human and veterinary pharmaceutical use.

Inter-sectoral cross-border MEDUWA-Vecht(e) coalition

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.

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.

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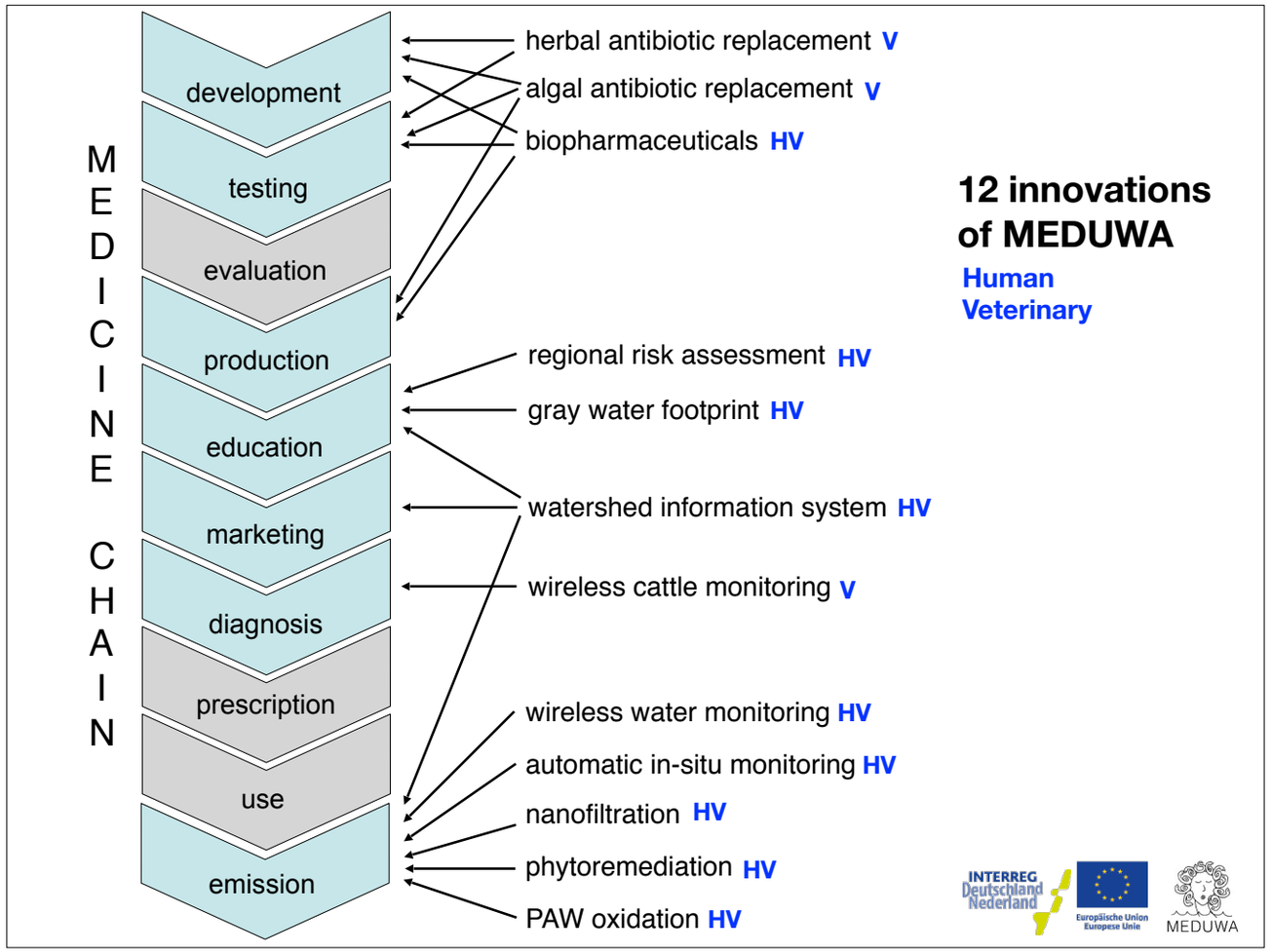
MEDUWA costs 8,5 million Euro. The project is for 50% subsidized by the EU Regional Development Fund (ERDF); for 20% by the regional INTERREG-VA Program Partners, and for 30% co-financed by the project partners themselves.



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. Research institutions and companies 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	■				

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MEDUWA

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

Roles of MEDUWA Stakeholders

1. Co-creation

- Advising on intermediate & finished products
- Bringing and retrieving information
- Cooperating with test sites, sampling etc.

MEDUWA Stakeholder & Partner Meeting 2018

2. Embedding

- Putting theme on the agenda and linking solutions to current and new programmes
- Wide dissemination of innovations within existing networks

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In order for the innovations to be useful and applied, cooperation is necessary with the sectors that have to put solutions into practice. That is why we try to involve all types of stakeholders in the project.

Thank you!

For more info, see meduwa.eu