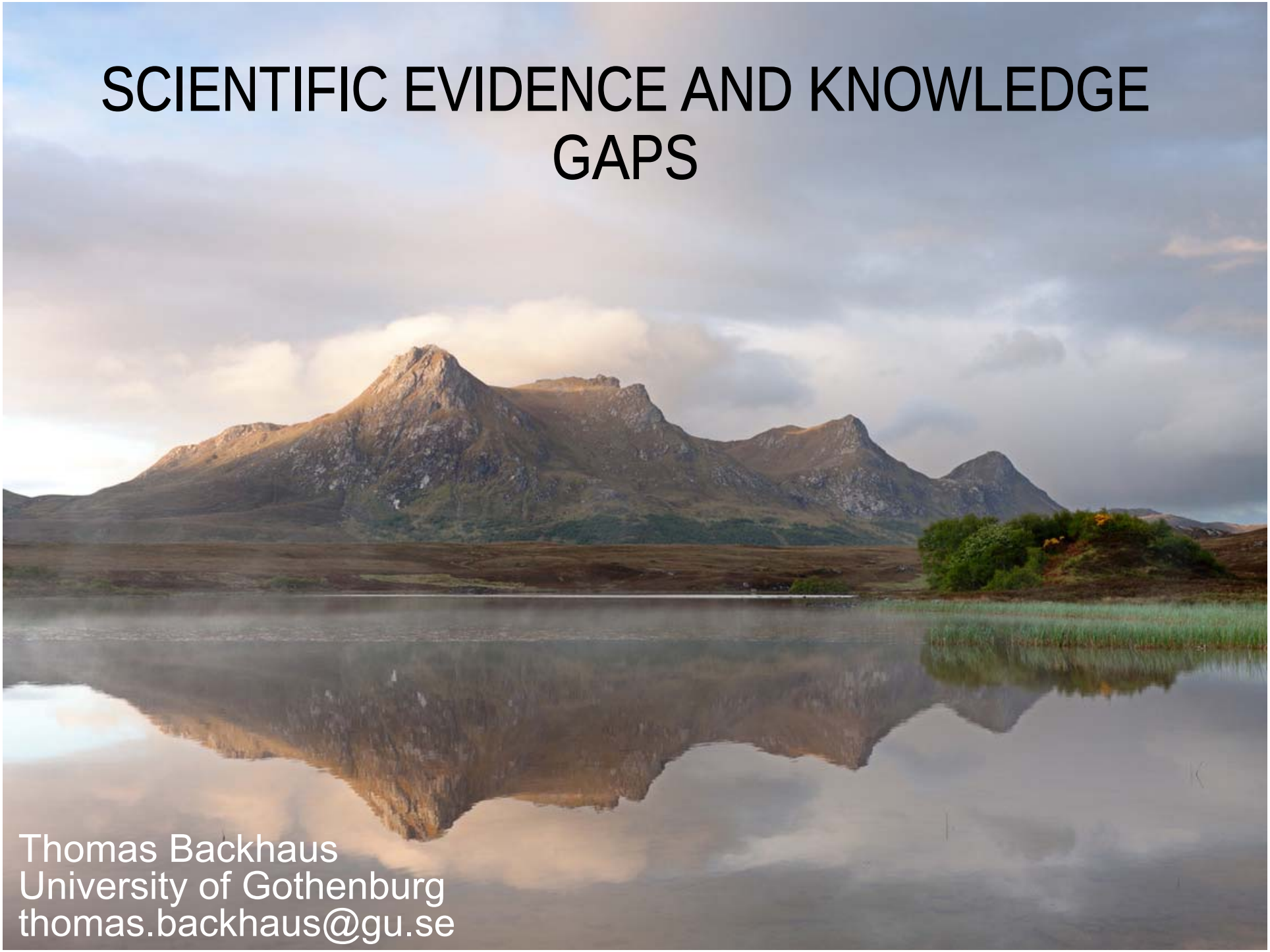
SCIENTIFIC EVIDENCE AND KNOWLEDGE GAPS



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Three postulates

- Human health is not directly impacted by pharmaceutical residues found in the environment
- The development of antimicrobial resistance is of major concern – but the issue goes beyond pharmaceuticals in the environment
- Several documented situations in which pharmaceuticals cause effects on environmental organisms at relevant concentrations

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- Human health is not directly impacted by pharmaceutical residues found in the environment
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- Several documented situations in which pharmaceuticals cause effects on environmental organisms at relevant concentrations

Impacts on human health?

The Netherlands

- 17 pharmaceuticals and 9 transformation products analyzed from surface waters, pre-treated surface waters, river bank filtrates, groundwater and drinking waters.
- 12 pharmaceuticals and 7 transformation products were detected at least once.
- No detections in final drinking water produced from surface water. Phenazone (20 ng/L) and its degradation product (10ng/L) found in drinking water from bank filtrates.

de Jongh, C.M., Kooij, P.J., de Voogt, P. and ter Laak, T.L., 2012. Screening and human health risk assessment of pharmaceuticals and their transformation products in Dutch surface waters and drinking water. *Science of the Total Environment*, *427*, pp.70-77.

Impacts on human health?

The Netherlands

- Toxicological assessment based on risk quotients: max concentration found / Provisional guideline value (pGLV), based on ADIs

Compound	Point of departure	Ref	UF	TDI or ADI (mg/kg bw/day)	pGLV (µg/L)	Group pGLV (µg/L)	Quotient DW–RBF	Quotient pre-treated SW	Quotient RBF	Quotient SW
Phenazone	Lowest daily therapeutic dose of 3.6 mg/kg bw/day for phenazone	1,2	100	0.036	125					
Dimethylaminophenazone	Pharmacological NOEL of 10 mg/kg bw/day for metamizole	3	1000	0.010	35					
Propyphenazone	Lowest daily therapeutic dose of 2.1 mg/kg bw/day for propyphenazone	4	100	0.021	75					
1-acetyl-1-methyl-2-phenylhydrazide (AMPH)	Pharmacological NOEL of 10 mg/kg bw/day for metamizole	3	1000	0.010	35	35	0.002	0.009	0.02	0.01
4-acetylaminoantipyrine (AAA)	Pharmacological NOEL of 10 mg/kg bw/day for metamizole	3	1000	0.010	35					
4-formylaminoantipyrine (FAA)	Pharmacological NOEL of 10 mg/kg bw/day for metamizole	3	1000	0.010	35					

de Jongh, C.M., Kooij, P.J., de Voogt, P. and ter Laak, T.L., 2012. Screening and human health risk assessment of pharmaceuticals and their transformation products in Dutch surface waters and drinking water. *Science of the Total Environment*, *427*, pp.70-77.

Impacts on human health?

Portugal

- 31 pharmaceuticals were analyzed in water and finished water
- 16 were detected at 0.005 – 46 ng/L (source water) and 0.089 – 46 ng/L (tap water)
- Risk Assessment based on risk quotients, calculated as max concentration /age specific drinking-water equivalent levels (DWEL, estimated from ADI values)

de Jesus Gaffney, V., Almeida, C.M., Rodrigues, A., Ferreira, E., Benoliel, M.J. and Cardoso, V.V., 2015. Occurrence of pharmaceuticals in a water supply system and related human health risk assessment. *Water research*, *72*, pp.199-208.

Impacts on human health?

Compounds	Conc.Max (μg/L)	0–3 months		6–12 months	
		DWEL (μg/L)	RQ	DWEL (μg/L)	RQ
Caffeine	0.046	625	0.00007	1240	0.00004
Carbamazepine	0.014	1.52	0.01	2.48	0.01
Atenolol	0.002	11	0.0001	22	0.00007
Propranolol	0.0067	233	0.000003	463	0.000001
Sulfadiazine	0.001	83	0.00002	165	0.000009
Sulfamethazine	0.0005	6.7	0.00007	13	0.00004
Sulfapyridine	0.0019	208	0.00001	413	0.000005
Sulfamethoxazole	0.0013	542	0.000002	1075	0.000001
Erythromycin	0.005	167	0.00003	331	0.00002
Ibuprofen	0.021	458	0.00005	909	0.00002
Naproxen	0.006	192	0.00003	380	0.00002
Nimesulide	0.027	1542	0.00002	3059	0.000009
Gemfibrozil	0.018	5.4	0.003	11	0.002
Indomethacin	0.037	388	0.0001	769	0.00005
Diclofenac	0.011	6.7	0.002	13	0.0008
Acetaminophen	0.047	1417	0.00003	2811	0.00002

de Jesus Gaffney, V., Almeida, C.M., Rodrigues, A., Ferreira, E., Benoliel, M.J. and Cardoso, V.V., 2015. Occurrence of pharmaceuticals in a water supply system and related human health risk assessment. *Water research*, *72*, pp.199-208.

Impacts on human health?

Japan

- 64 pharmaceuticals and metabolites were analyzed in source water and finished water at 6 drinking water purification plants and 2 industrial water purification plants.
- 37 compounds were detected in source water (6-24 per facility).
- 8 compounds detected in the finished drinking water.

Simazaki, D., Kubota, R., Suzuki, T., Akiba, M., Nishimura, T. and Kunikane, S., 2015. Occurrence of selected pharmaceuticals at drinking water purification plants in Japan and implications for human health. *Water research*, *76*, pp.187-200.

Impacts on human health?

Japan

- Margins of exposure estimated as daily minimum therapeutic dose / maximum daily intake via drinking

Pharmaceutical	Maximum concentration in finished water samples (ng/L)	Minimum daily therapeutic dose (mg/day)	Margin of exposure (–)
Amantadine	9.0	100	5.6×10^6
Carbamazepine	25	100	2.0×10^6
Diclofenac	16	75	2.3×10^6
Epinastine	8.0	10	6.3×10^5
Fenofibrate	31	53	8.5×10^5
Ibuprofen	6.0	200	1.7×10^7
Iopamidol	2400	900[b]	1.9×10^5
Oseltamivir acid	38	137[c]	1.8×10^6

Simazaki, D., Kubota, R., Suzuki, T., Akiba, M., Nishimura, T. and Kunikane, S., 2015. Occurrence of selected pharmaceuticals at drinking water purification plants in Japan and implications for human health. *Water research*, *76*, pp.187-200.

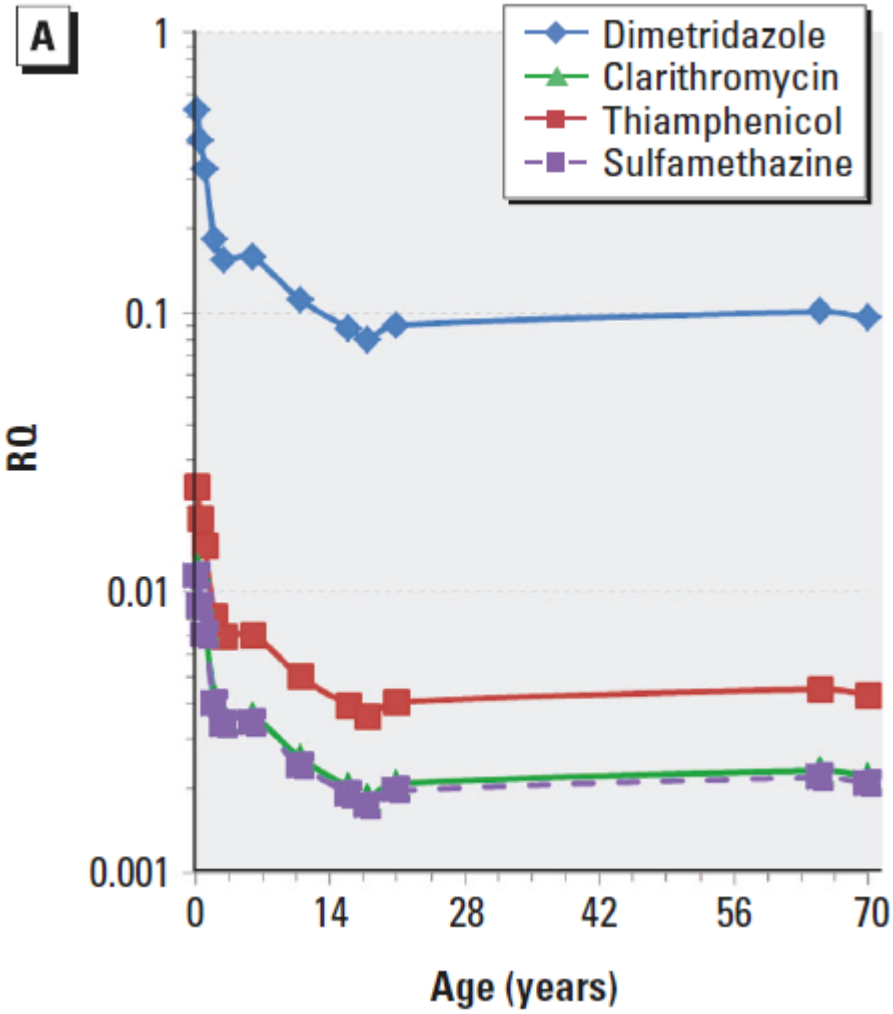
Impacts on human health?

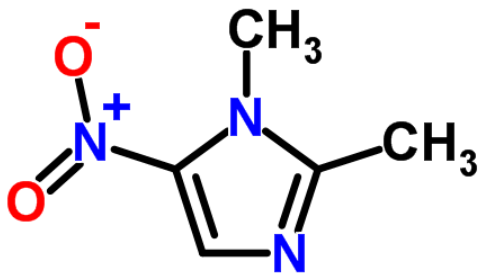
China

- 32 pharmaceuticals were analyzed in 113 tap water samples from 13 cities
- 17 compounds detected
- Risk quotients based on age-specific drinking-water equivalent levels and measured concentrations

Leung, H.W., Jin, L., Wei, S., Tsui, M.M.P., Zhou, B., Jiao, L., Cheung, P.C., Chun, Y.K., Murphy, M.B. and Lam, P.K.S., 2013. Pharmaceuticals in tap water: human health risk assessment and proposed monitoring framework in China. *Environmental health perspectives*, *121*(7), p.839.

Impacts on human health?



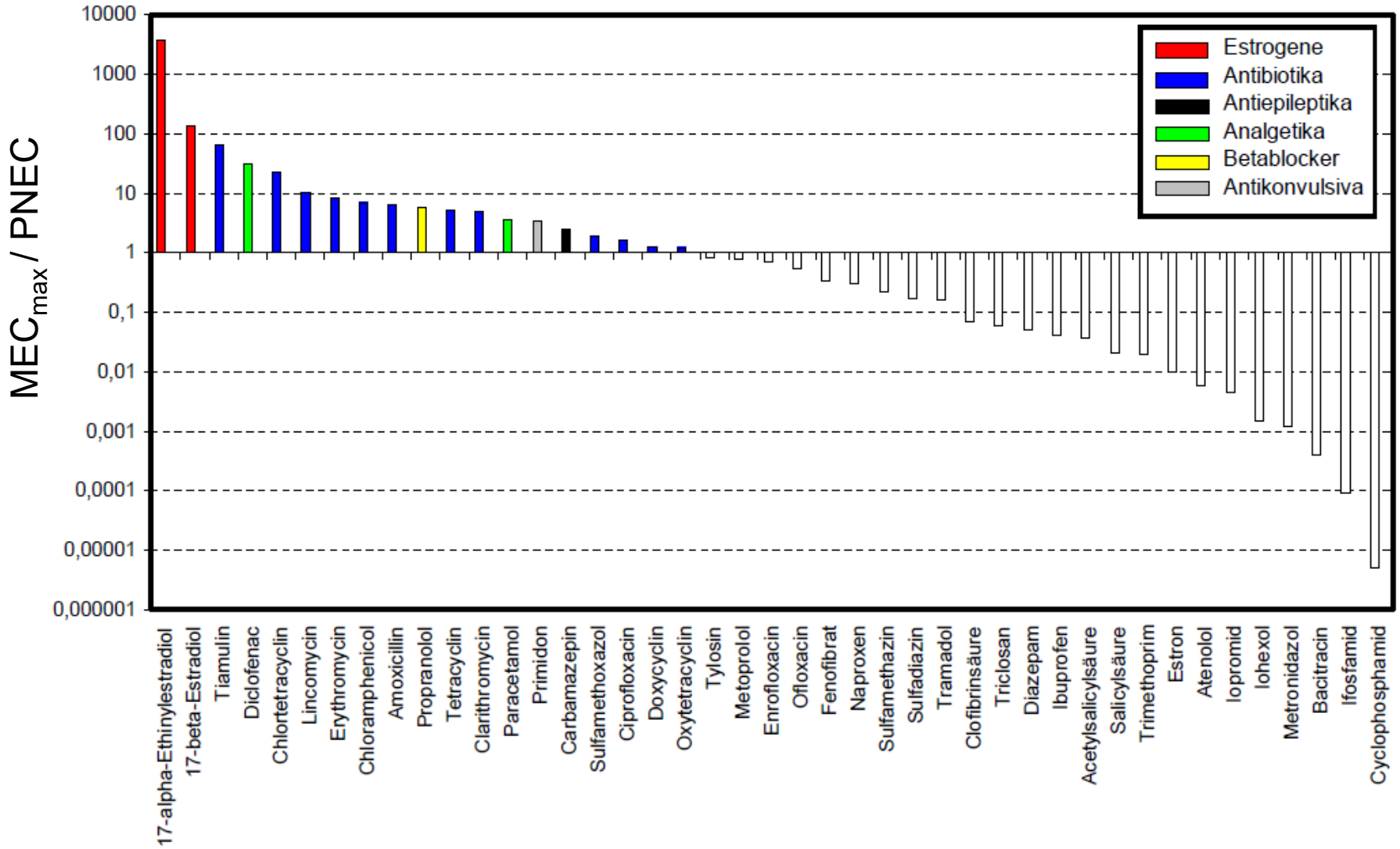


Dimetridazole

- ❑ Veterinary drug
- ❑ Anti-infective (protozoan)
- ❑ Suspected carcinogen

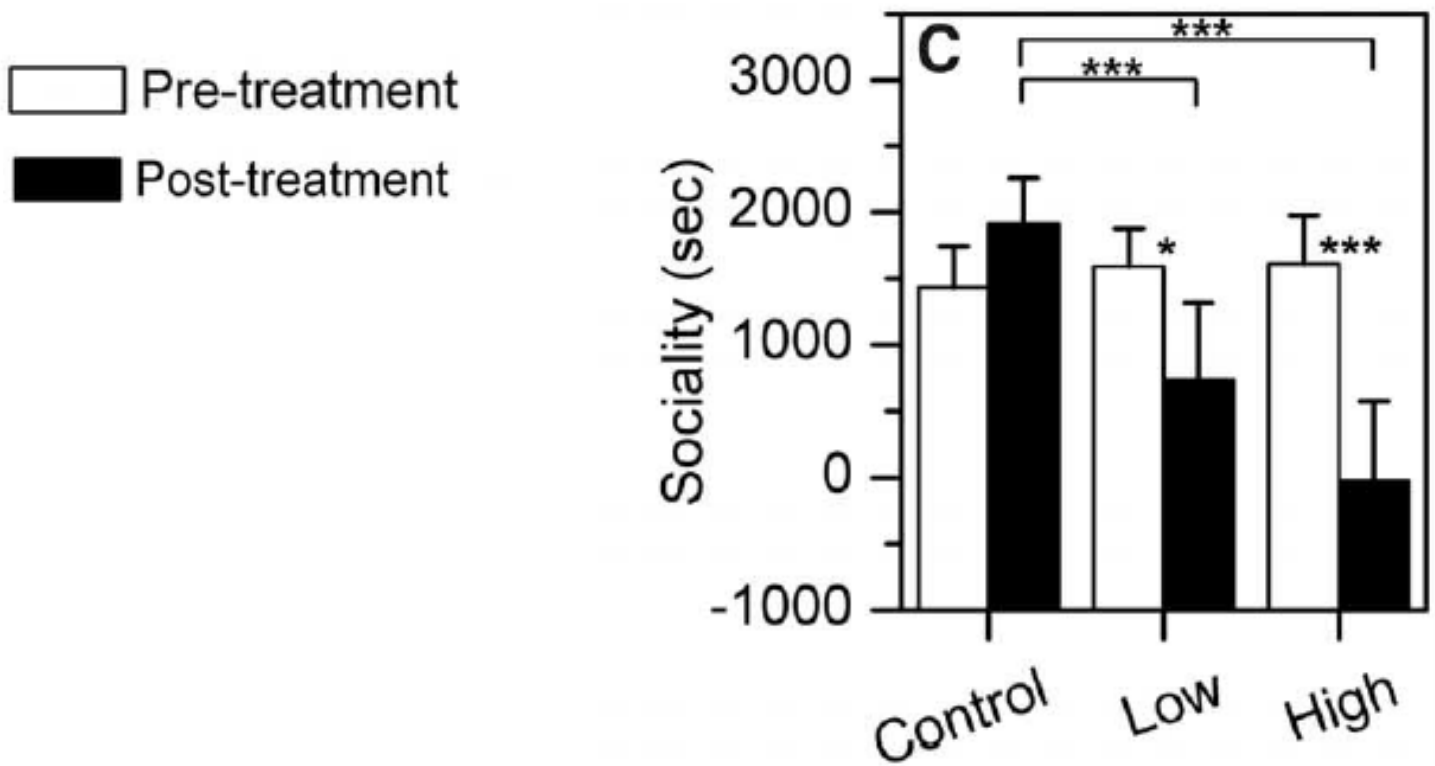
Leung, H.W., Jin, L., Wei, S., Tsui, M.M.P., Zhou, B., Jiao, L., Cheung, P.C., Chun, Y.K., Murphy, M.B. and Lam, P.K.S., 2013. Pharmaceuticals in tap water: human health risk assessment and proposed monitoring framework in China. *Environmental health perspectives*, *121*(7), p.839.

Impacts on environmental organisms?



Bergmann, Compilation of monitoringdata on pharmaceuticals, Report to the German Environment Agency, 2010

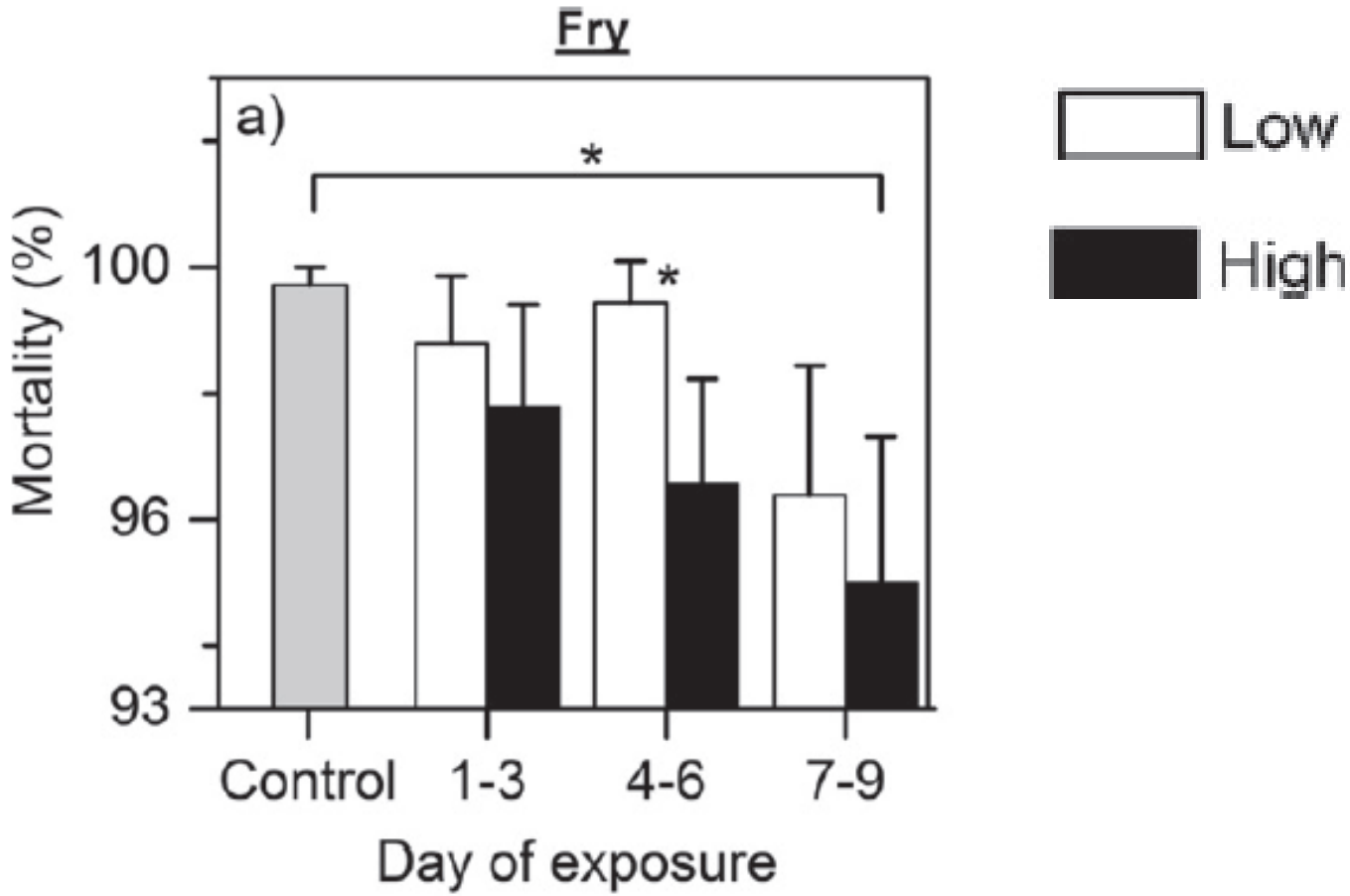
Effects of Oxazepam on fish behaviour



- Anti-anxiety drug
- Tested concentrations: 1.8 and 910 µg/L
- Surface water concentrations: max. 2.2. µg/L (Sadezky et al., 2008)

Brodin, T., Fick, J., Jonsson, M. and Klaminder, J., 2013. Dilute concentrations of a psychiatric drug alter behavior of fish from natural populations. *Science*, *339*(6121), pp.814-815.

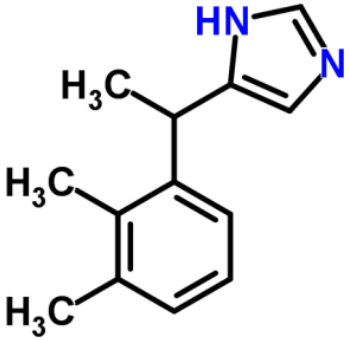
Effects of Oxazepam on fish development



- Roe exposed to 1 µg/L (low) resp. 1 mg/L (high) Oxazepam for 24 hrs

Klaminder, J., Jonsson, M., Fick, J., Sundelin, A. and Brodin, T., 2014. The conceptual imperfection of aquatic risk assessment tests: highlighting the need for tests designed to detect therapeutic effects of pharmaceutical contaminants. *Environmental Research Letters*, *9*(8), p.084003.

Ecotoxicological mode of action might be different from therapeutic or toxicological mode of action

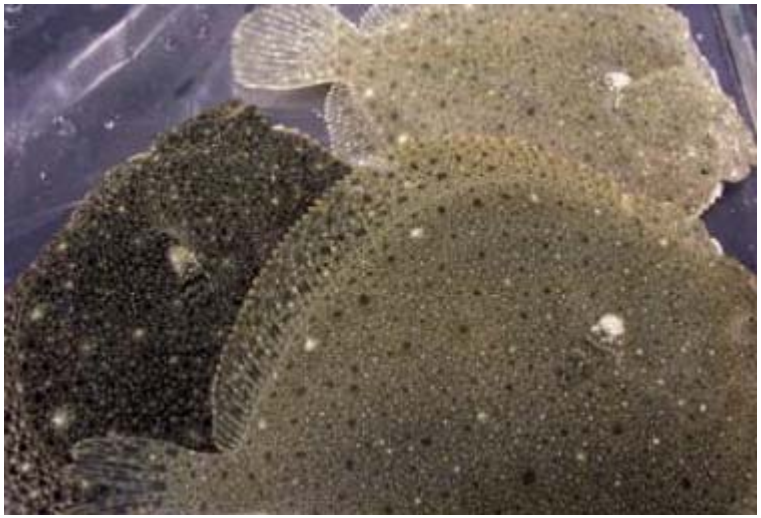


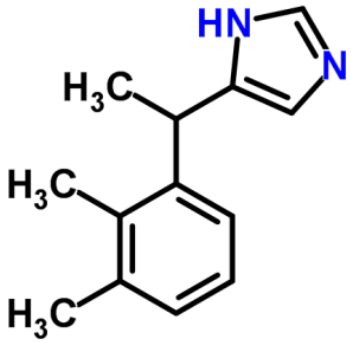
Medetomidine

- sedative for mammals
- α2-receptor agonist, octapamine receptor agonist

Dahlström et al. (2005) Evidence for different pharmacological targets for imidazoline compounds inhibiting settlement of the barnacle *Balanus improvisus*. Journal of Experimental Zoology. Part A – Comparative Experimental Biology: 303:551
Lennquist: Responses to fish exposed to medetomidine, Marine Env. Research, 2010

Ecotoxicological mode of action might be different from therapeutic or toxicological mode of action





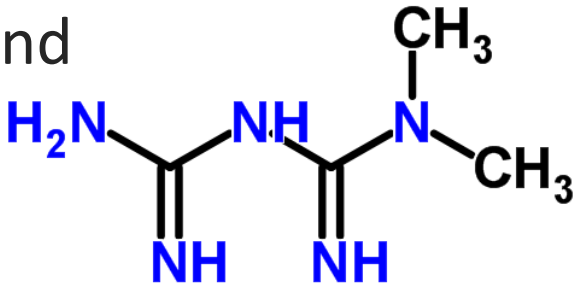
Medetomidine

- ❑ sedative for mammals
- ❑ α2-receptor agonist, octapamine receptor agonist
- ❑ Use as a biocide

Dahlström et al. (2005) Evidence for different pharmacological targets for imidazoline compounds inhibiting settlement of the barnacle *Balanus improvisus*. Journal of Experimental Zoology. Part A – Comparative Experimental Biology: 303:551
Lennquist: Responses to fish exposed to medetomidine, Marine Env. Research, 2010

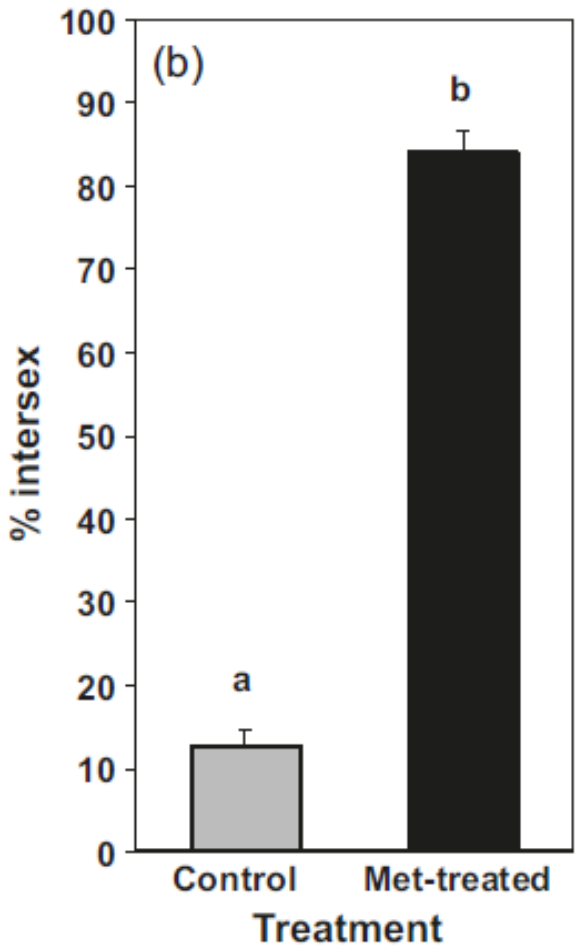
Effects of metformin on fish development and fecundity

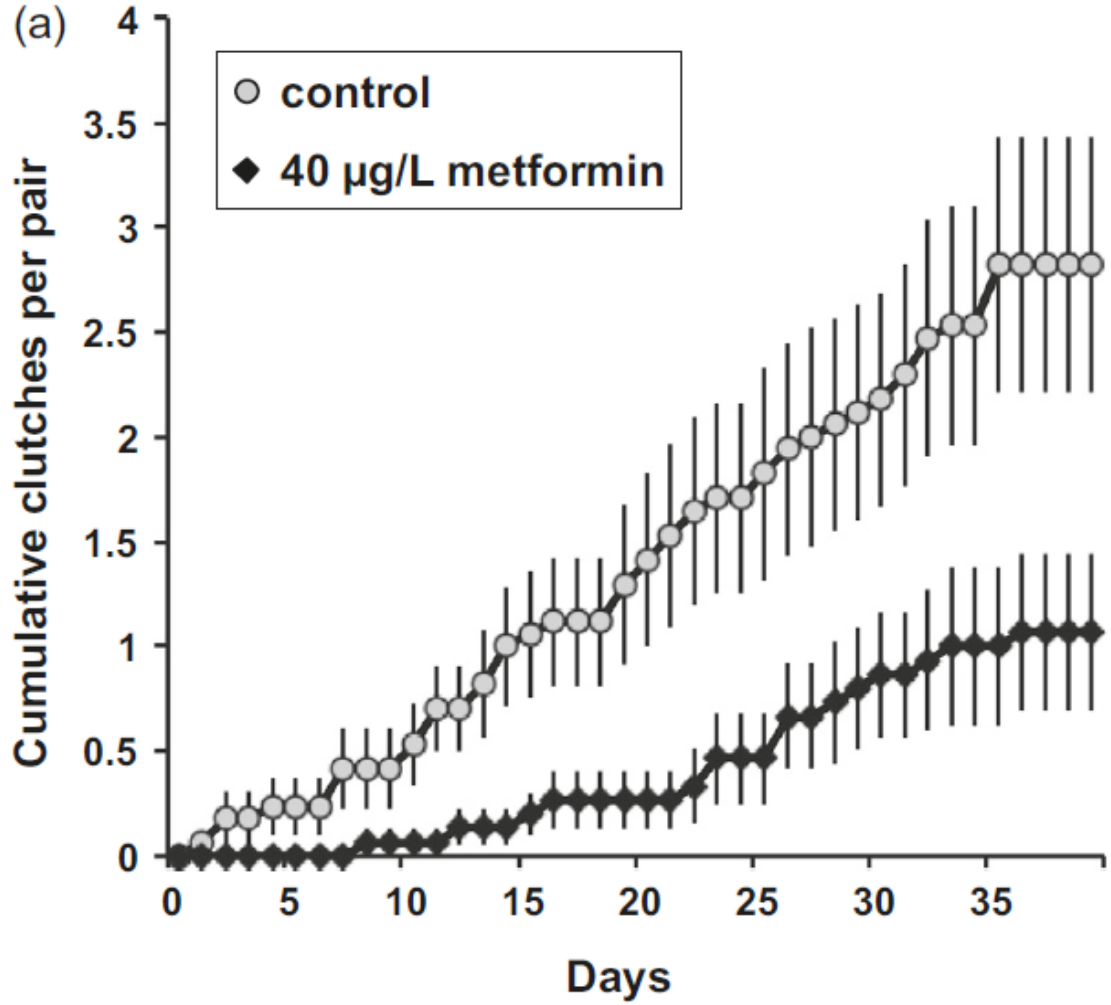
- Metformin is an anti-diabetic drug (insulin sensitizer), commonly found in the aquatic environment.
- Exposure of fathead minnow fry to 40 µg/L (wastewater concentration) over 360 days.
- Significant intersex and effects on size and reproduction



Niemuth, N.J. and Klaper, R.D., 2015. Emerging wastewater contaminant metformin causes intersex and reduced fecundity in fish. *Chemosphere*, *135*, pp.38-45.

Effects of metformin on fish development and fecundity





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Effects of metformin on fish development and fecundity

- Exposure was to 40 µg/L, resembling wastewater concentrations (1- 50 µg/L).
- Concentrations in surface waters: 3 – 0.02 µg/L (UBA monitoring database)
- Concentration in drinking water: 0.75 µg/L (Vulliet & Cren-Olivé, 2011)
- ***Conclusion?***

Niemuth, N.J. and Klaper, R.D., 2015. Emerging wastewater contaminant metformin causes intersex and reduced fecundity in fish. *Chemosphere*, *135*, pp.38-45.

Summary and conclusions

Human health is not directly impacted by pharmaceutical residues found in the environment

- Concentrations in surface waters might approach levels of concern. Increased dependence on water purification technologies and demands for continuous monitoring.
- Pharmaceuticals contribute to the development of antimicrobial resistance, with massive consequences for public health.
  Cross-cutting issue!

Summary and conclusions

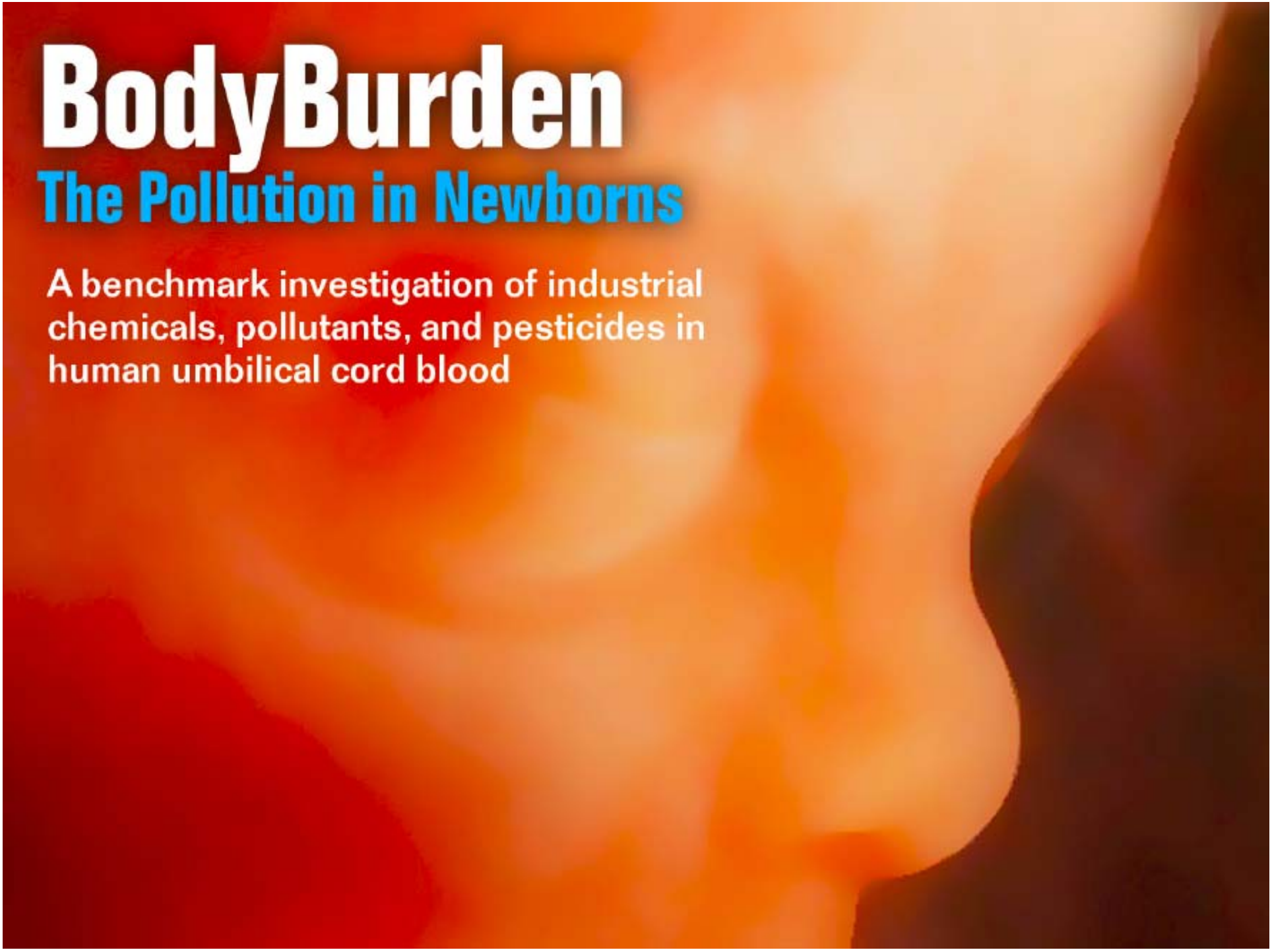
Human health is not directly impacted by pharmaceutical residues found in the environment

- Pharmaceuticals in drinking water contribute to endpoints also triggered by other environmental chemicals.

BodyBurden

The Pollution in Newborns

A benchmark investigation of industrial chemicals, pollutants, and pesticides in human umbilical cord blood



UNIVERSITY OF GOTHENBURG

…found an average of 200 industrial chemicals and pollutants in umbilical cord blood from 10 babies born in August and September of 2004 in U.S. hospitals. Tests revealed a total of 287 chemicals in the group.

Jane Houlihan, et al. (2005): Body Burden, the pollution in newborns, The Environmental Group,

Summary and conclusions

Human health is not directly impacted by pharmaceutical residues found in the environment

- Critical issues:
  - Methodologies for deriving points of departure differ widely. Does it make sense to use the minimum therapeutic dose?
  - Data on relevant (subtle) toxicological endpoints often absent (effects on behavior, neural development, immune system, learning disorders).
  - Data on the consequences of exposure during critical time windows are also often lacking.

Summary and conclusions

Several documented situations in which pharmaceuticals cause effects on environmental organisms

- The question is not *whether* pharmaceuticals in the environment cause relevant effects, but *which compounds under which circumstances*

- Three main study types:
  1. Using standardized bioassays
  2. Assuming the mode(s) of action described in humans is relevant also for environmental organisms
  3. Tests with micro- and mesocosms, field derived communities, field observations, etc.

Summary and conclusions

Several documented situations in which pharmaceuticals cause effects on environmental organisms

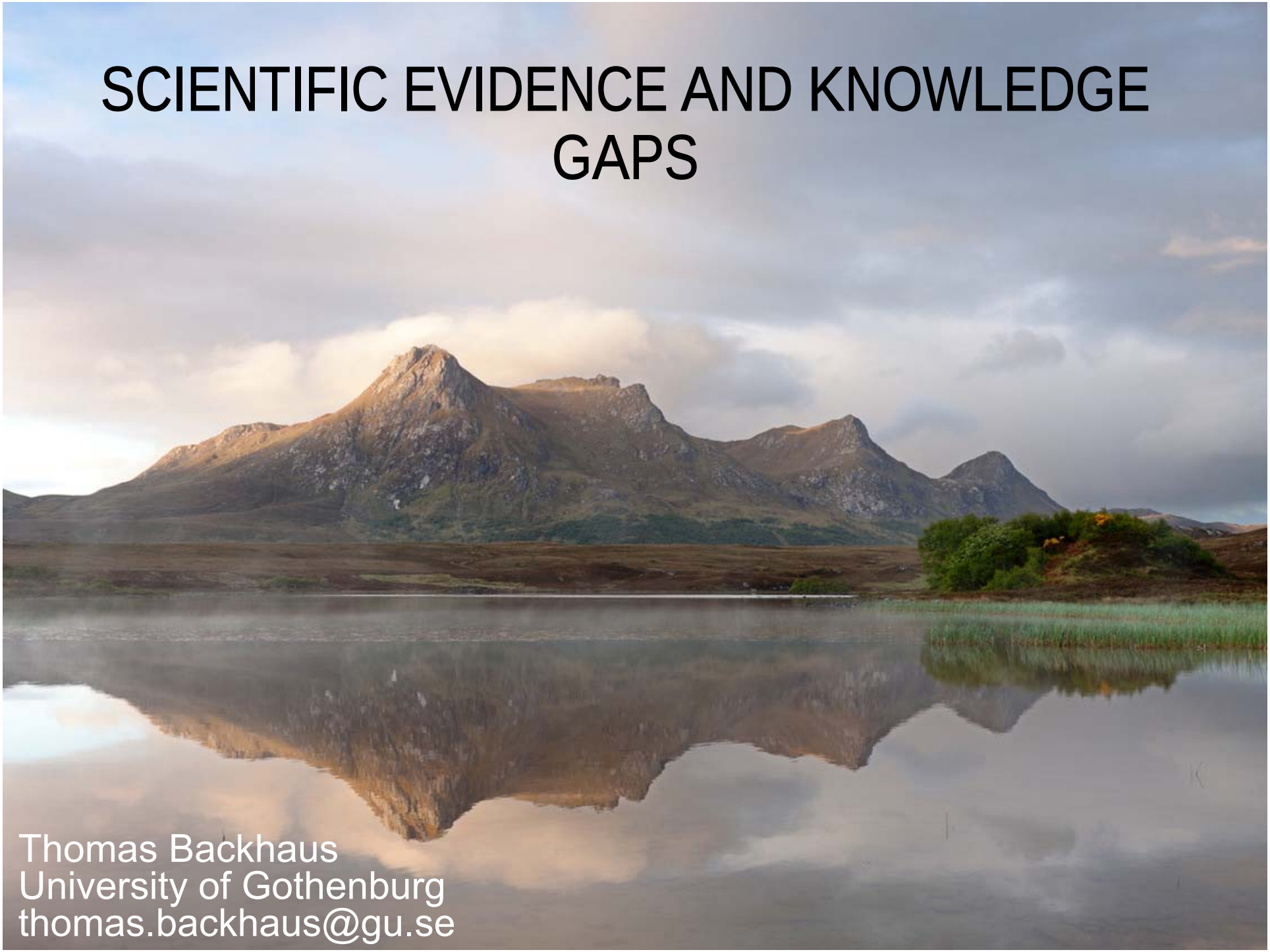
- ❑ Studies often use too few test concentrations. Studies should include at least one concentration directly relevant for surface waters.
- ❑ Missing data for the coastal & estuarine environment

Summary and conclusions

Several documented situations in which pharmaceuticals cause effects on environmental organisms

- Better endpoints needed: More ecologically relevant, better coupled to the modes of action.
- Pharmaceuticals will act in concert with other environmental chemicals…

SCIENTIFIC EVIDENCE AND KNOWLEDGE GAPS



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