

## Pharmaceuticals sold in Sweden can cause serious environmental harm in India

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## India and China dominate the global generic bulk drug market

India and Chinas share:

2004: 42,4%

2006: 44,6%

2010: ~60%

Source: CPA (2006).  
*Competition in the World APIs Market. Chemical Pharmaceutical Generic Association, Milan, Italy.*



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## A common treatment plant in Patancheru (PETL) near Hyderabad receives process water from ~90 bulk drug manufacturers

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Picture: C. de Pedro

Larsson DGJ, de Pedro C, Paxeus N. 2007. Effluent from drug manufactures contains extremely high levels of pharmaceuticals. *J Haz Mat.* 148 (3), 751-755

## "Treated" effluent from PETL contains exceptionally high concentrations of different pharmaceuticals...

Active ingredient	Type of drug	Range (µg/L)
Ciprofloxacin	antibiotic-fluoroquinolone	28,000-31,000
Losartan	angiotensin II receptor antagonist	2,400-2,500
Cetirizine	H <sub>1</sub> -receptor antagonist	1,300-1,400
Metoprolol	β <sub>1</sub> -adrenoreceptor antagonist	800-950
Enrofloxacin	antibiotic-fluoroquinolone	780-900
Citalopram	serotonin reuptake inhibitor	770-840
Norfloxacin	antibiotic-fluoroquinolone	390-420
Lomefloxacin	antibiotic-fluoroquinolone	150-300
Enoxacin	antibiotic-fluoroquinolone	150-300
Ofloxacin	antibiotic-fluoroquinolone	150-160
Ranitidin	H <sub>2</sub> -receptor antagonist	90-160

*Based on LC-MS/MS, ESI+, 3-point standard addition, no preconcentration of samples*

Larsson DGJ, de Pedro C, Paxeus N. 2007. Effluent from drug manufactures contains extremely high levels of pharmaceuticals. *J Haz Mat.* 148 (3), 751-755

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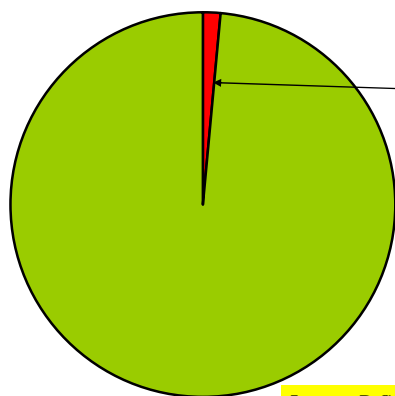
.....corresponding to large volumes and a high value for the final consumer....

Active ingredient	amount/day (g)	price for final product (SEK)
Ciprofloxacin	44 250	373 175
Losartan	3 675	408 660
Cetirizine	2 025	113 400
Metoprolol	1 313	22 838
Enrofloxacin	1 260	
Citalopram	1 208	75 167
Lomefloxacin	336	
Norfloxacin	608	5 657
Enoxacin	338	
Ofloxacin	233	13 485
Ranitidin	188	2 583
Sum:	55 431	1 014 965

Larsson DGJ, de Pedro C, Paxeus N. 2007. Effluent from drug manufactures contains extremely high levels of pharmaceuticals. *J Haz Mat.* 148 (3), 751-755

~100,000 €/day

...but the corresponding production costs are much lower !

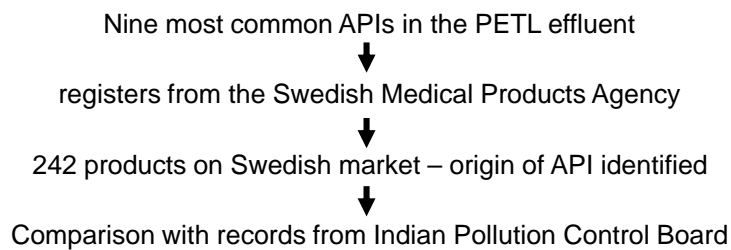


The export price for ciprofloxacin from India corresponded to ~1.5% of the final sales price of the cheapest ciprofloxacin-product in a Swedish pharmacy!

Larsson D.G.J. 2008. Drug production facilities – an overlooked discharge source for pharmaceuticals to the environment. In: Kümmerer K Ed, *Pharmaceuticals in the Environment. Sources, Fate, Effects and Risks.* Springer, Berlin, Heidelberg New York, pp 37-42.

# Where do these drugs end up, and where are the drugs produced that you and I use?

- Origin of active substance often very difficult to track



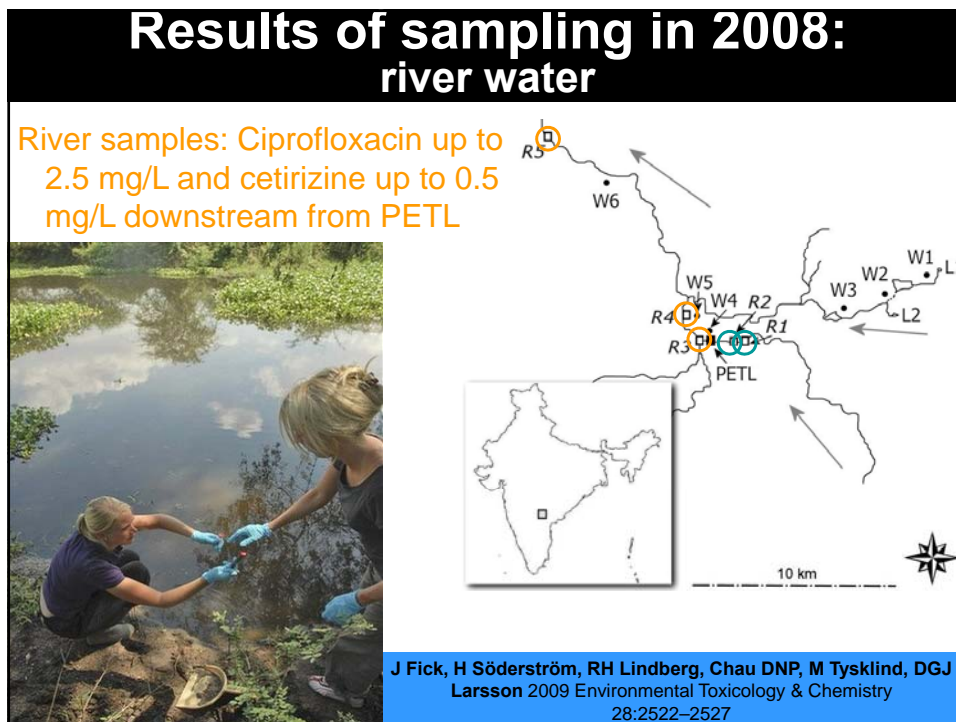
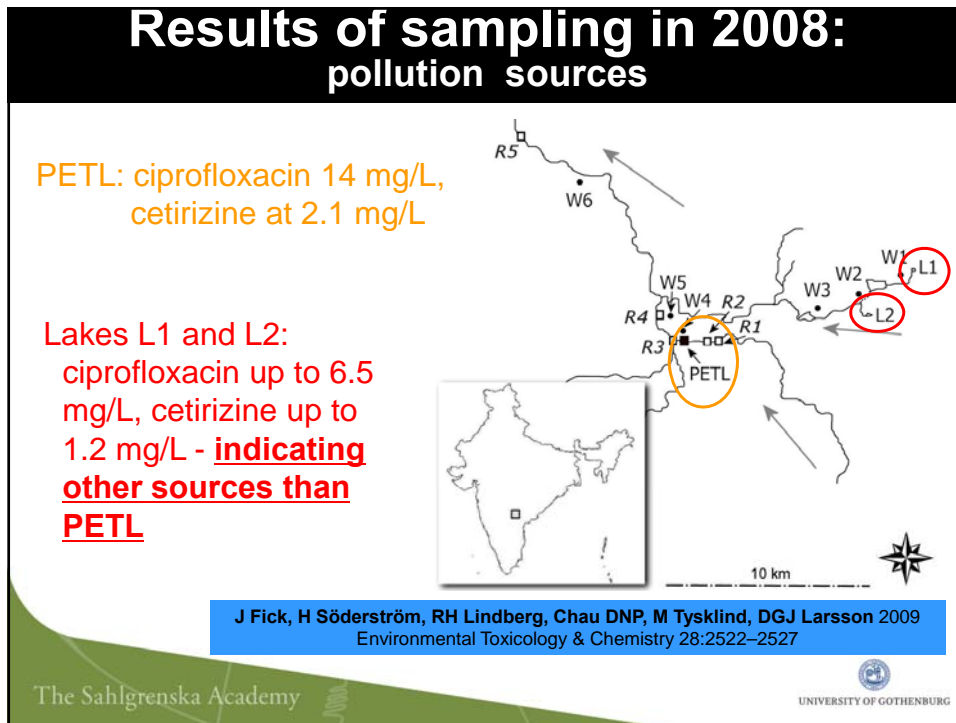
Larsson DGJ and Fick J. 2009. Transparency throughout the production chain – a way to reduce pollution from the manufacturing of pharmaceuticals. *Regul Tox Pharm.* 53:161-163.

## About 1/3 of the 242 investigated products on the Swedish market came from producers sending waste to PETL!

API	No. of products on the Swedish market	Products with API produced in India		No. of products contracting API-producers that send waste to the investigated plant	
		#	%	#	%
Ceterizin	17	3	18	1	6
Ciprofloxacin	58	29	50	26	45
Citalopram	77	59	77	19	25
Levofloxacin	5	0	0	0	0
Losartan	22	12	55	12	55
Metoprolol	21	0	0	0	0
Norfloxacin	10	5	50	5	50
Ofloxacin	1	0	0	0	0
Ranitidine	31	15	48	11	35
Sum	242	123	51	74	31

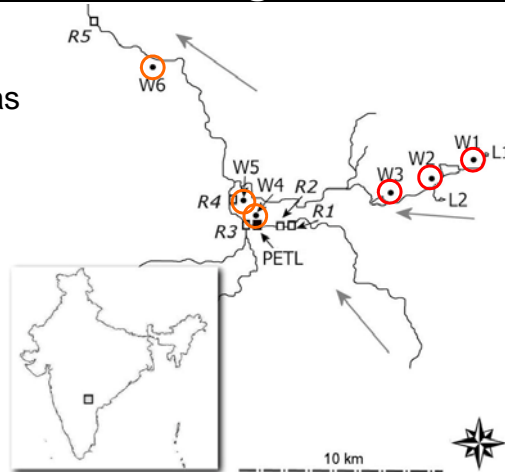
- Ethical responsibility of Western buyers
- A more transparent production chain is needed!

Larsson DGJ and Fick J. 2009. Transparency throughout the production chain – a way to reduce pollution from the manufacturing of pharmaceuticals. *Regulatory Toxicology and Pharmacology.* 53:161-163.



## Results of sampling in 2008: water wells in six villages

All but two wells are used as sources for drinking water



J Fick, H Söderström, RH Lindberg, Chau DNP, M Tysklind, DGJ Larsson 2009  
Environmental Toxicology & Chemistry 28:2522–2527

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## Results of sampling in 2008:

Microgram per liter concentrations found in drinking water

	W1 <sup>a</sup> ng L <sup>-1</sup>	W2 ng L <sup>-1</sup>	W3 ng L <sup>-1</sup>	W4 ng L <sup>-1</sup>	W5 ng L <sup>-1</sup>	W6 ng L <sup>-1</sup>
<u>Ciprofloxacin</u>	44	14000	180	390	720	1100
Enrofloxacin	30	n.d.	67	n.d.	7	23
Norfloxacin	n.d.	n.d.	31	21	n.d.	n.d.
Ofloxacin	26	n.d.	480	n.d.	n.d.	160
<u>Enoxacin</u>	80	1900	630	800	1000	n.d.
Lomefloxacin	35	n.d.	n.d.	n.d.	n.d.	15
<u>Cetirizine</u>	550	28000	2500	950	1200	1500
Trimethoprim	n.d.	27	21	21	22	17
Metoprolol	90	n.d.	n.d.	n.d.	n.d.	n.d.
<u>Terbinafine</u>	1800	1700	1000	100	250	90
Enalapril	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
<u>Citalopram</u>	n.d.	n.d.	n.d.	80	260	1400

J Fick, H Söderström, RH Lindberg, Chau DNP, M Tysklind, DGJ Larsson 2009  
Environmental Toxicology & Chemistry 28:2522–2527

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## Three risks with high concentration of antibiotics in effluents

- **Reduced treatment efficiency of other pollutants**
- **Ecological effects**
- **Resistance development**



## Potential for ecological effects:

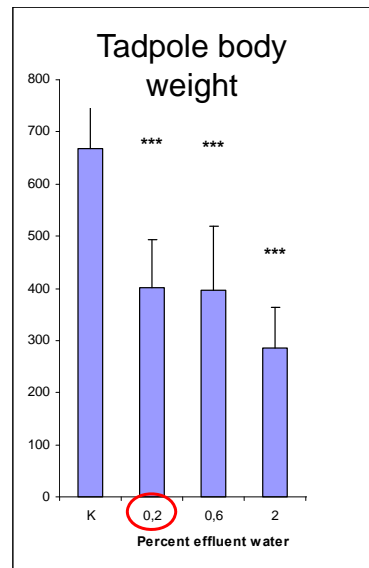
Some unpublished data on the toxicity of the effluent on natural freshwater bacterial communities has been removed from this slide

S Broshé, DGJ Larsson, T Porsbring, T Backhaus. In preparation.

The effluent is also very potent to aquatic vertebrates



Pollution of at least 750,000 m<sup>3</sup> water per day to a degree that strongly affects aquatic life!



Carlsson G, Örn S and Larsson DGJ. 2009. Effluent from bulk drug production is toxic to aquatic vertebrates. *Environmental Toxicology and Chemistry* 28:2656–2662

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Effluent diluted 1:500 affects the expression and activity of detoxification enzymes and increase blood plasma phosphate in fish



[www.febit.com](http://www.febit.com)



Gunnarsson L, Kristiansson E, Rutgersson C, Sturve J, Fick J, Förlin L and Larsson DGJ. 2009. Pharmaceutical industry effluent diluted 1:500 affects global gene expression, CYP1A activity and plasma phosphate in fish. *Environmental Toxicology and Chemistry* 28:2639–2647

Unpublished data on the character and frequency of multiresistant bacteria at PETL has been removed from this slide

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Schouche et al, in preparation

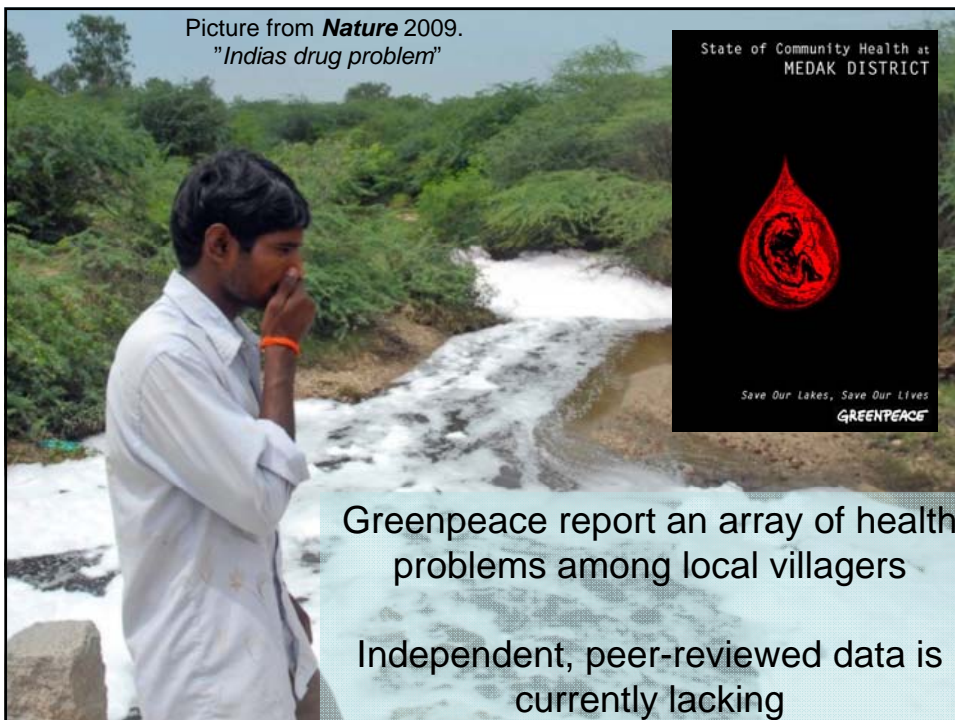
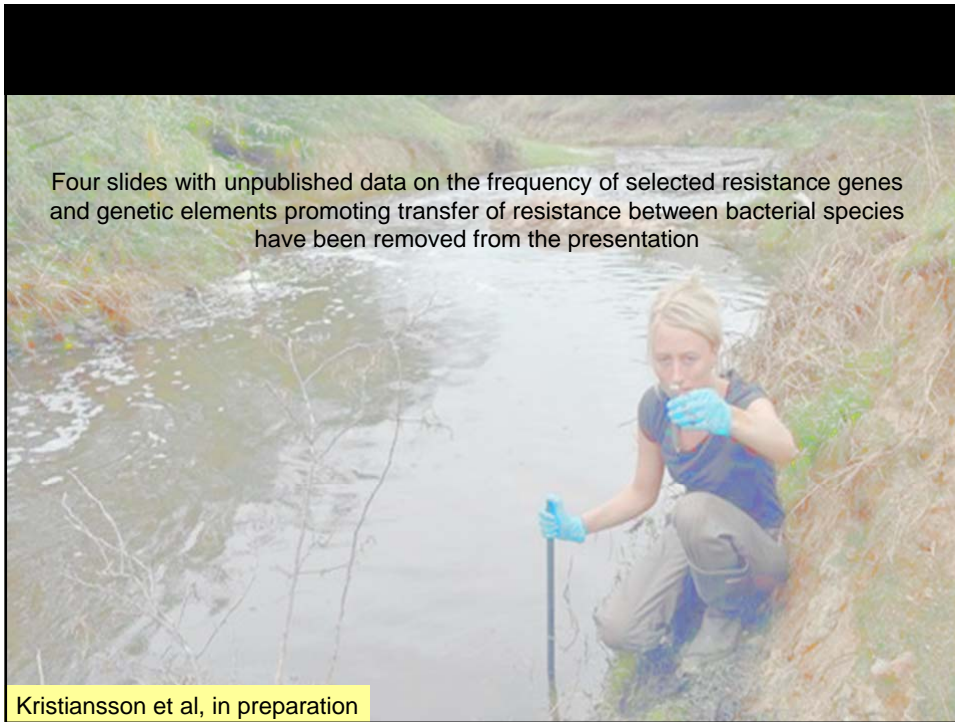


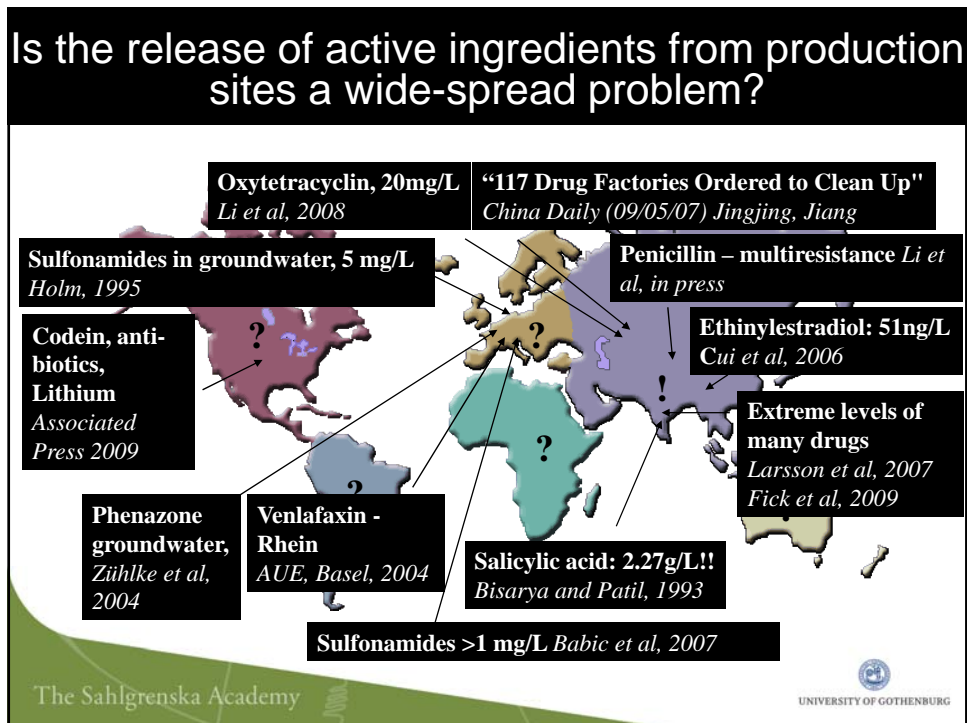
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### Ongoing studies of resistance genes and genetic elements supporting transfer of resistance in DNA of river sediments in India and Sweden



Kristiansson et al, in preparation Picture from Washington post, Jan 2009





## Some challenges

- How widespread are these problems?
- At most sites, release of APIs is not regulated!
- Under what conditions are the drugs produced that you and I use?
- To what extent does this contribute to the accelerating resistance of human pathogens?
- Antibiotic resistance – a global issue!
- Who has the responsibility for a polluted environment when the third world produces drugs for our well-being?

Larsson DGJ. 2010. Release of active pharmaceutical ingredients from manufacturing sites – need for new management strategies.  
*Integrated Environmental Assessment and Management. In press.*

# Thank you for your attention!

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[www.neurophys.gu.se/sektioner/fysiologi/endo/](http://www.neurophys.gu.se/sektioner/fysiologi/endo/)



Vetenskapsrådet

MISTRA

STIFTELSEN FÖR MILJÖSTRATEGISK FORSKNING



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