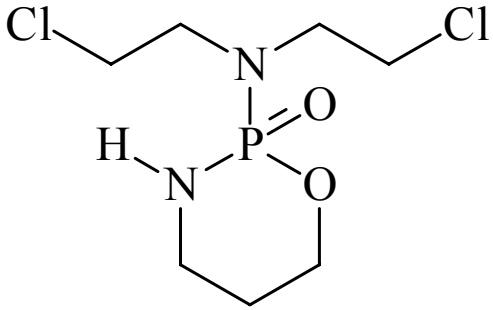


Occurrence and Fate of the Cytostatic Drugs Cyclophosphamide and Ifosfamide in Wastewater and Surface Waters

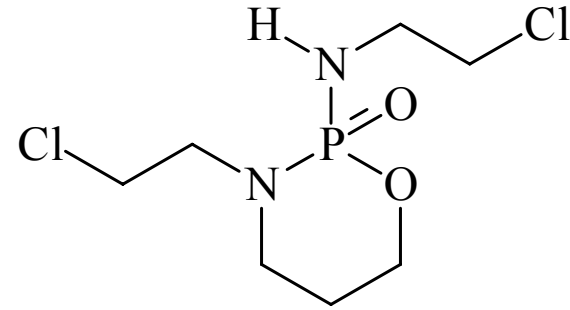
Ignaz J. Buerge, Hans-Rudolf Buser,
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Cyclophosphamide

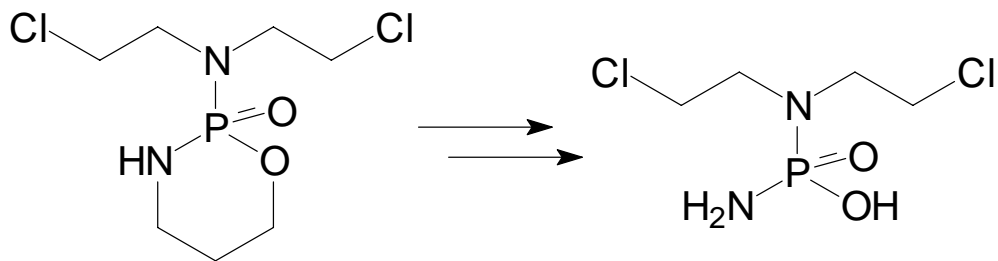


Ifosfamide

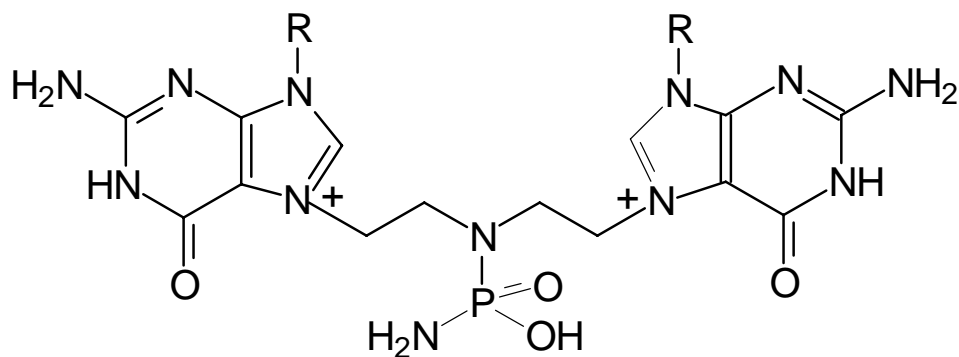
- cytostatic drugs
- chemotherapy of bronchial-, breast-, ovarian-cancer, lymphomas, leukaemias, etc.
- immunosuppression
(rheumatoid arthritis, bone marrow transplantation)



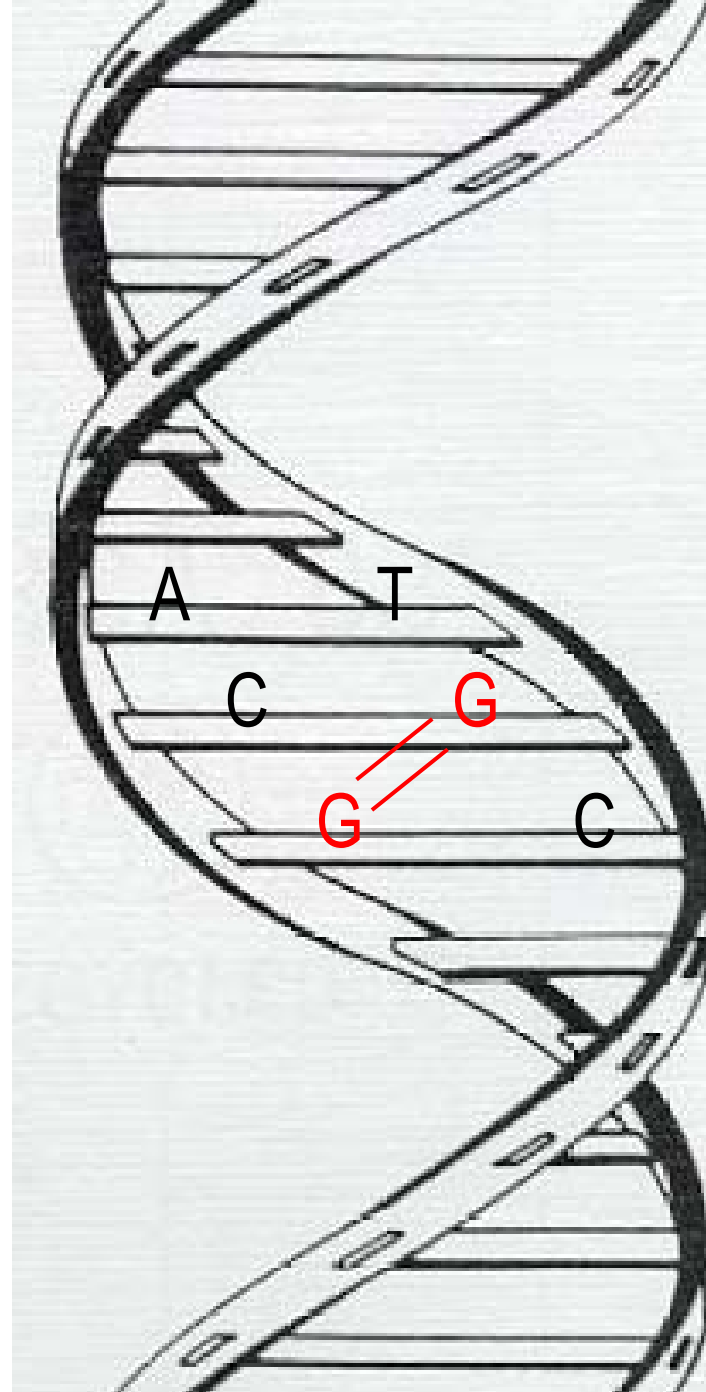
→ metabolic activation to the mustard



→ unspecific alkylation
e.g., cross-linking of guanine bases



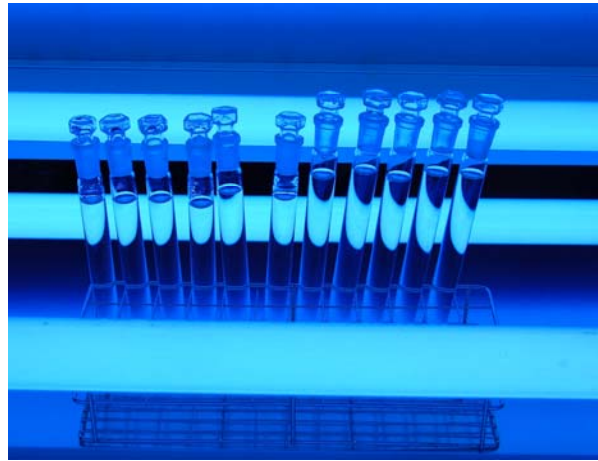
→ errors in DNA replication
→ mutagenic, carcinogenic, teratogenic,
and embryotoxic effects



Crick and Watson



consumption/dosage



dissipation behavior



occurrence in surface waters



trace analysis



occurrence in wastewater



ecotoxicity/
risk assessment

Annual Consumption/Dosage



| | Cyclophosphamide | Ifosfamide |
|-------------------|----------------------|----------------------|
| Switzerland, 2002 | 55 kg | 12 kg |
| Germany, (2000) | 200-400 kg | |
| Austria, 1997 | 39 kg | 18 kg |
| treatment | ambulant or clinical | ambulant or clinical |
| typical dosage | ≈ 1 g | ≈ 2 g |
| renal excretion | ≈ 13 % | ≈ 15 % |

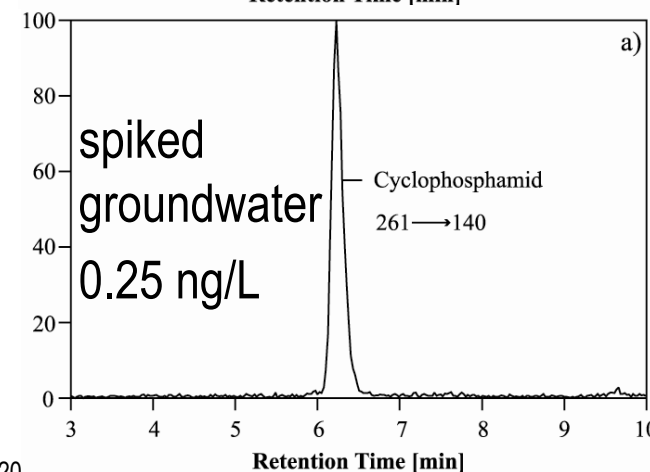
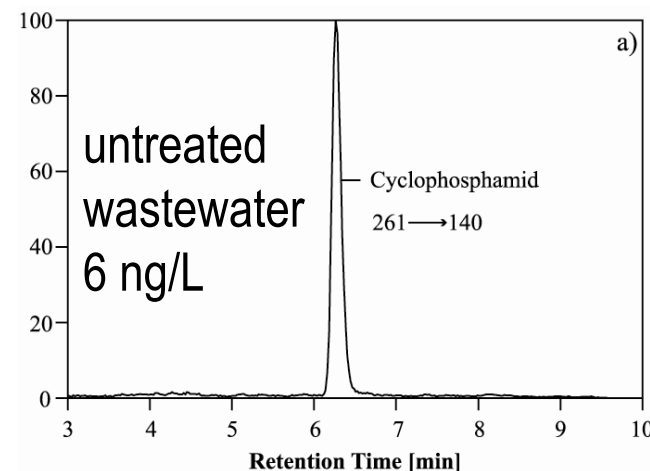
Trace Analysis



solid phase extraction
analysis by LC-MS-MS

| Matrix | Limit of Detection |
|----------------------|--------------------|
| untreated wastewater | 0.2-1 ng/L |
| treated wastewater | 0.3-0.4 ng/L |
| surface water | 0.02-0.1 ng/L |

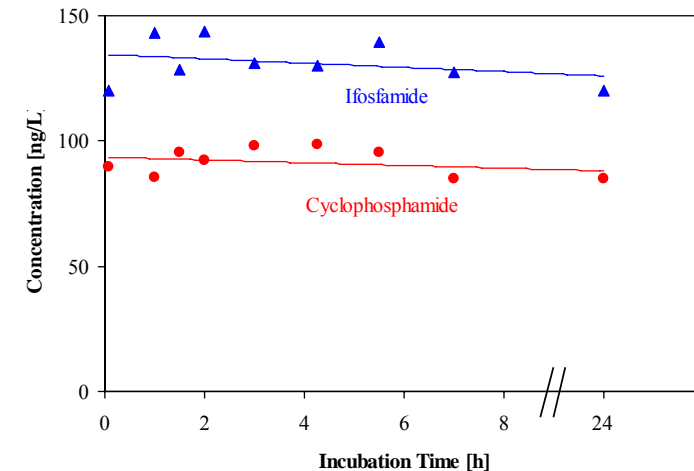
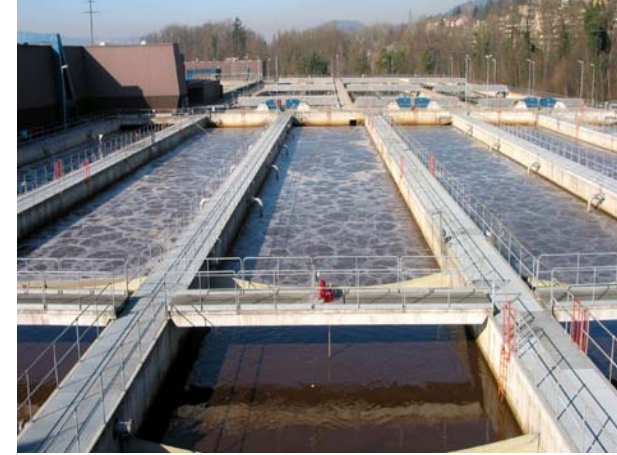
→ extremely sensitive analytical method



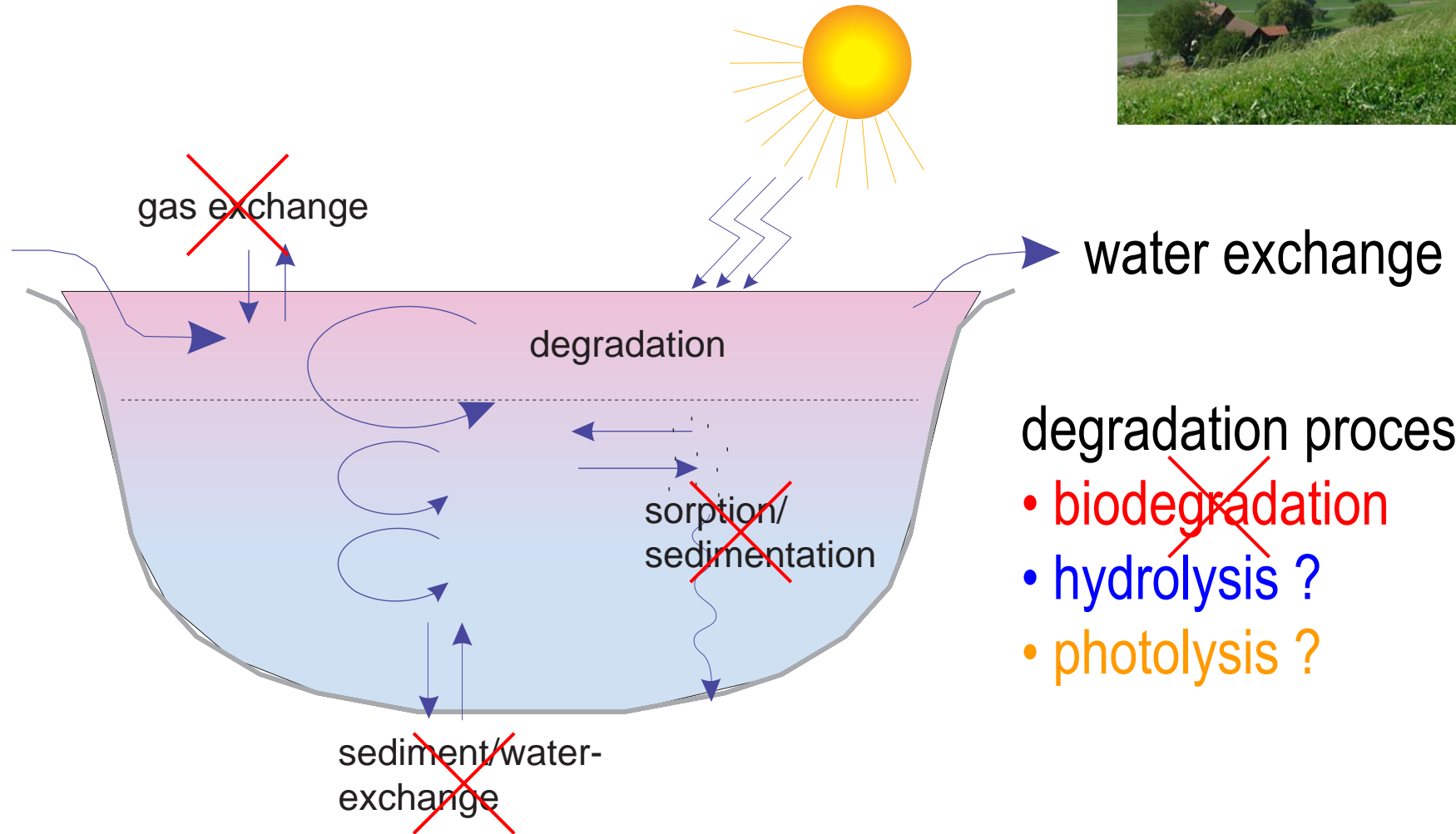
Behavior in Wastewater Treatment Plants (WWTPs)

- non biodegraded in activated sludge
- no sorption to sewage sludge ($\log K_{OW} = 0.97$)
- no volatilization ($K_H = 7 \cdot 10^{-11}$ atm L/mol)

→ high persistence in WWTPs



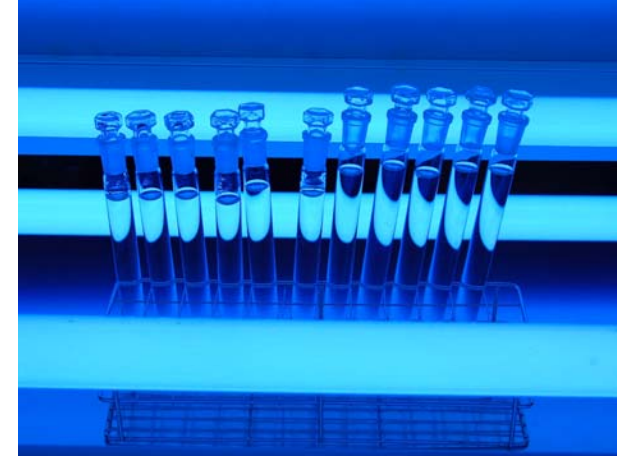
Behavior in Surface Waters



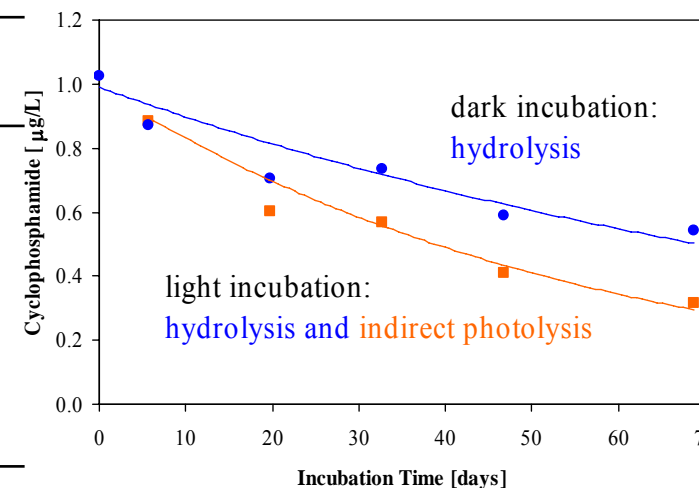
degradation processes

- ~~biodegradation~~
- hydrolysis ?
- photolysis ?

Half-Lives under Laboratory Conditions



| | CP | IF |
|--|-------|----------|
| hydrolysis | 80 d | > 1 year |
| indirect photolysis by HO• radicals | 100 d | 140 d |



Extrapolation to Surface Waters



| | CP | IF |
|--|---------------|---------------|
| hydrolysis | 1-2 years | several years |
| indirect photolysis by HO• radicals | several years | several years |

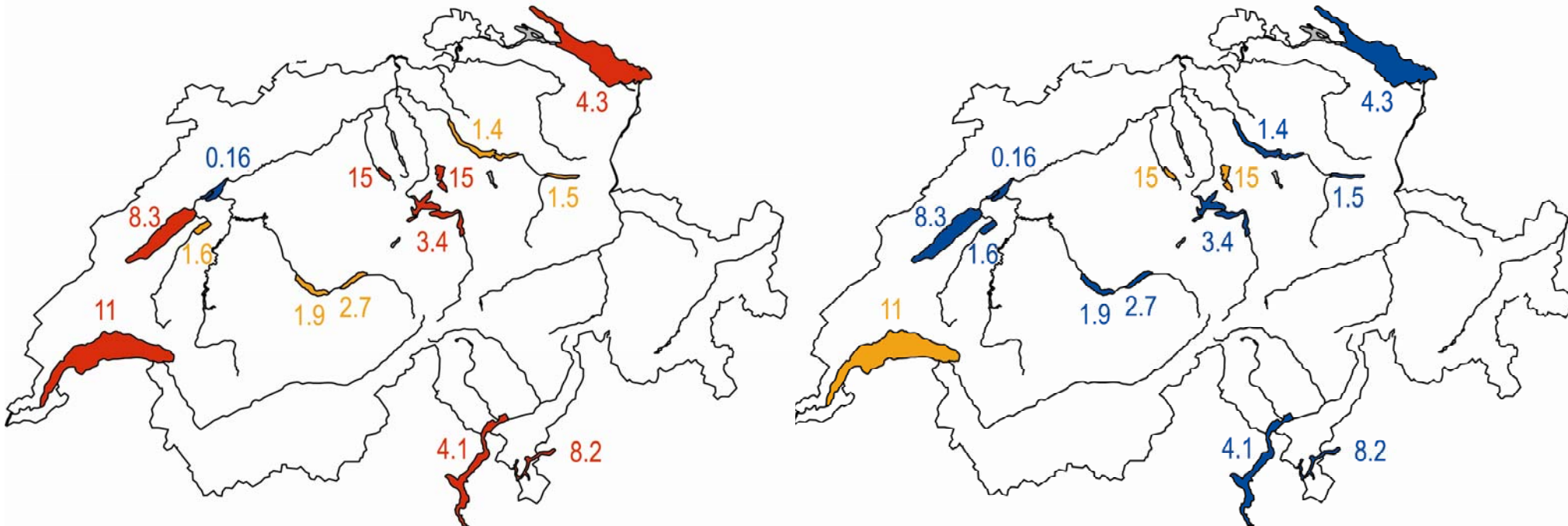
→ slow degradation in surface waters primarily by hydrolysis

Comparison of Dissipation by Water Exchange and Hydrolysis



CP

IF

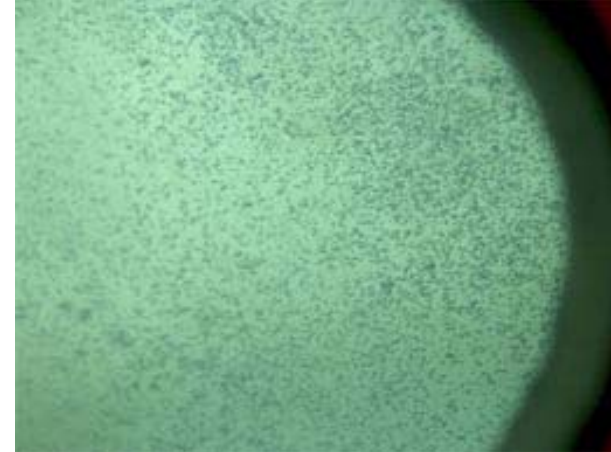


water exchange

water exchange, hydrolysis

hydrolysis

Degradation by Photochemically Formed HO· Radicals



- diffusion controlled reaction
- may be relevant only in shallow, clear, and nitrate-rich waterbodies
- could be further exploited for elimination of CP and IF by **advanced oxidation processes**, e.g., in a treatment of hospital wastewater

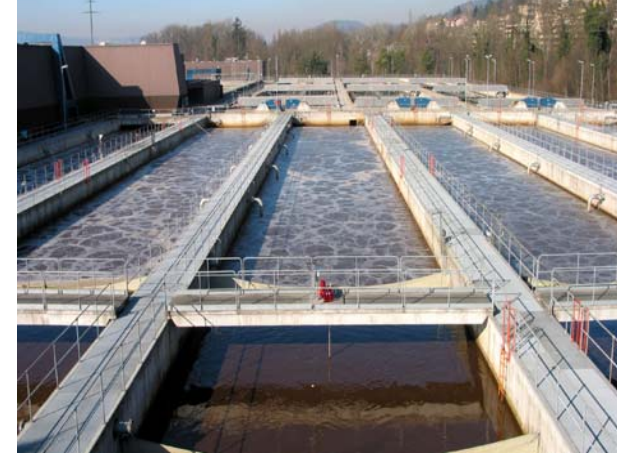
Predicted Concentrations (PEC) of Cyclophosphamide in WWTPs



| | |
|-----------------------------|--------------------|
| consumption in CH | 55 kg |
| renal excretion | 13 % |
| water consumption CH | 500 L/(person day) |
| degradation in sewer system | not considered |
| degradation in WWTPs | none |

| | |
|---|--|
| PEC untreated and treated wastewater CH | 5.4 ng/L |
| "realistic worst case" | up to \approx 100 ng/L |

Selection of WWTPs



WWTP Männedorf

- hospital with a relatively large oncology division
 - little dilution by domestic wastewater of 9000 inhabitants
- "realistic worst case" situation

WWTP Zürich

- several hospitals, surgeries, where cytostatic drugs are administered
 - high dilution by domestic wastewater of 370000 inhabitants
- typical situation for urban areas

Measured Concentrations (MEC) in WWTPs



| WWTP | Influent [ng/L] | Effluent [ng/L] |
|---|-----------------|-----------------|
| Zürich | 2-5 | 2-4 |
| Männedorf (no treatment in hospital) | ≈ 4 | ≈ 2 |
| Männedorf (with treatments in hospital) | 11 * | 10 * |
| PEC CH | 5.4 | 5.4 |
| PEC "realistic worst case" | up to 100 | up to 100 |

→ persistent in WWTPs

→ * under dry weather conditions ≈ 40 ng/L

→ PEC ≈ MEC

Measured Concentrations in Surface Waters



PEC treated wastewater
degradation in lakes

5.4 ng/L
hydrolysis considered

PEC lake Zurich

0.07-0.08 ng/L

PEC "realistic worst case" surface water

a few ng/L

MEC lake Zurich

≈ 0.05-0.07 ng/L

MEC river Limmat below WWTP Zürich

0.15-0.17 ng/L

→ PEC ≈ MEC

Ecotoxicological Data: Mutagenicity to Fish



-
- micronucleus test with erythrocytes of *Anguilla anguilla*:
3 d exposition, highest effects at 25 mg/L
 - sister chromatide exchange with *Anguilla anguilla*:
3 d exposition, effects in the mg/L range
-

Pacheco and Santos, 1996

Santos and Pacheco, 1995

- toxicity-exposure ratio $TER \gg 1$, no acute ecotoxicological risk
- no ecotoxicological studies on chronic effects to aquatic organisms

Summary

- consumption CH: 55 kg CP, 12 kg IF
- extremely sensitive analytical method: LODs down to 0.02 ng/L
- persistent in WWTPs with activated sludge treatment
- elimination in lakes by water exchange and slow hydrolysis
- degradation by HO· radicals: AOP treatment of hospital wastewater
- MEC wastewater: 2-11 ng/L CP, < 0.3-6 ng/L IF
"realistic worst case": up to 100 ng/L
- MEC surface waters: up to 0.17 ng/L CP, 0.14 ng/L IF
"realistic worst case": a few ng/L
- no acute ecotoxicological risk, but no ecotoxicological studies on chronic effects to aquatic organisms

Buerge et al., Environ. Sci. Technol., in prep.



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