Photochemical water treatment: Solving or creating a problem?

The case of antipsychotic phenothiazine drugs
History of phenothiazines

Heinrich Bernthsen: phenothiazine

1876 1883 1891 1930s 1940s 1951 1990s 2010

worldwide use against helmintic infections ("worm-chocolate")

synthesis and testing of numerous new compounds

recovering of new medical indications (e.g. methylene blue against Alzheimer)

Paul Ehrlich: methylene blue as antimalarial agent

Heinrich Caro: methylene blue

Discovery of antifungal, insecticidial and anti-helmintic properties

chlorpromazine as first modern neuroleptic drug

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Christoph Trautwein
Phenothiazines as pharmaceuticals

Different modes of action

- Structural similarity with human neurotransmitters
- Use against allergies and psychoses

Promethazine, Histamine, Dopamine
Phenothiazines as pharmaceuticals

Different modes of action

Structural similarity with human neurotransmitters

Lipophilic base core provides good membrane permeability

⇒ Use against allergies and psychoses

⇒ Different core substituents allow for treatment of several medical indications (bacteria, fungi, worms, cancer, etc.)

promethazine
histamine
dopamine

phenothiazine core
Popular phenothiazine drugs

- Pharmaceuticals with phenothiazine agents
  Annual consumption in Germany > 3 t (Schwabe & Paffrath 2006)
Reviewed agents

- Eight different compounds

- chlorpromazine
- promethazine
- promazine
- trifluoperazine
- phenothiazine
- perphenazine
- fluphenazine
- triflupromazine
- thioridazine
Background: **no biodegradation**

- **Ready aerobic biodegradability**
  -> Closed Bottle test (OECD 301D)
  -> Manometric Respiratory test (OECD 301F)

- **Inherent aerobic biodegradability**
  -> Zahn-Wellens test (OECD 302B)

- **Anaerobic biodegradability**
  -> Modified Anaerobic Degradation test (ISO 11734)
Environmental fate

Degradation pathways in the aquatic environment

- Biological degradation
- Photochemical degradation

Phenothiazine
Environmental fate

Degradation pathways in the aquatic environment

- Degradation pathways in the aquatic environment
- Environmental fate
- Transformation products
- Biological degradation
- Photochemical degradation
- Persistence
- Mineralisation
Environmental fate

Degradation pathways in the aquatic environment

- Biological degradation
- Photochemical degradation
- Mineralisation
- Persistence
  - Transformation products

ground water  ➙  drinking water
Why photochemical water treatment?

- **Main objectives** *(Oppenlaender 2007)*

  - Photochemical technologies
    - pure UV treatment
    - UV treatment with auxiliary oxidants and catalysts

  - Remediation
    - Disinfection
  - Detoxification
    - Purification
    - Odor abatement
  - Mineralisation

- 3rd International Conference on Sustainable Pharmacy - Refine, Reduce, Replace -
Photochemistry of phenothiazines

- Photochemical excitation of the phenothiazine core
  (Viola & Dall’Acqua, 2006)
Photochemistry of phenothiazines

- Photoproducts and cellular oxidative stress
  (Viola & Dall’Acqua, 2006)

DNA
proteins
lipids
OH

phenothiazinyl radical

sulfoxide

polymers

Critical damage + modification of cell components

Triplett T1

ROS
reactive
oxxygen
species

- Cl

+ 3O₂

+ O₂

photoallergy

phototoxicity
Photochemical degradation

**Photoreactor batch test (OECD 316)**

- Several studies showed formation of stable photoproducts under UV-B exposure
  - Determination of carbon elimination
  - HPLC-UV/VIS-FLU-MS\textsuperscript{n} instrumental analysis

Relative xenon lamp emission intensities (UV-Consulting Peschl)

Xenon arc lamp and photoreactor
Photochemical degradation

- Colour reactions in the photoreactor

Test suspensions of eight phenothiazine drugs after 4h of irradiation
Structure elucidation

Thioridazine after 4h irradiation

Graphs showing intensity over time for different wavelengths.
Structure elucidation

Isolation and fragmentation of the target with ion trap MS
Structure elucidation

- Fragmentation in MS$^3$ mode

- Photoprodct is most probably thioridazine sulfoxide
Environmental risks

Prediction of environmental parameters using QSAR

- good water solubility
- evaporation into the atmosphere negligible
- enrichment in soils is very likely
- enrichment in biological tissues highly probable
- no biodegradation in sewage treatment plants or surface waters

EPIWEB 4.1
Case Ultra 1.4.4.6

thioridazine sulfoxide
Environmental risks

- Transformation of 8 phenothiazines to at least 216 photoproducts. QSAR results show high environmental risk.

Main pathways:

- Carboxylation
- Sulfoxidation
- Hydroxylation
- N-Oxidation
Reduction of phenothiazines by photochemical UV treatment is contraindicated:

- **Further degradation tests**
  -> of other phenothiazines (worldwide more than 4000 compounds known)
  -> advanced oxidation and filtration techniques
  -> which technique cracks phenothiazine core?

- **Toxicological assessment possible?**
  -> most phenothiazines follow „Lipinski Rule of 5“ -> pharmacoactive substances
  -> considerably formation of photoproducts makes complete testing difficult

- **Environmental sampling**
  -> use of measured concentrations for toxicity tests/QSAR
Thank you for your attention!

„Luck, ingenuity and a straightforward chemistry have made phenothiazine the most promiscuous lead structure of the 20th century – and there is more on the horizon.“

Ohl ow & Moosmann (2011)