# Environmental fate of estetrol (E4), a native estrogen used in oral contraception

Erick Nfon[1], Patrick Kestemont[2], Glwadys Rausin[3], Celine Gerard[3], Jean Michel Foidart[3,4]

[1] Smithers, Harrogate, United Kingdom; [2] Institute of Life, Earth & Environment, University of Namur, Namur, Belgium; [3] Mithra Pharmaceuticals, Liège, Belgium; [4] University of Liège, Liège, Belgium

## Background

Estetrol (E4) is a unique native estrogen produced by the human fetus during pregnancy. E4 formulated as monohydrate is a new active substance that received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) for use in a combined oral contraceptive (COC). Through its use in the COC, E4 may be released into the environment. This presentation is assessing the mobility, bioaccumulation and persistence of E4 using data generated as part of the environmental risk assessment of E4.

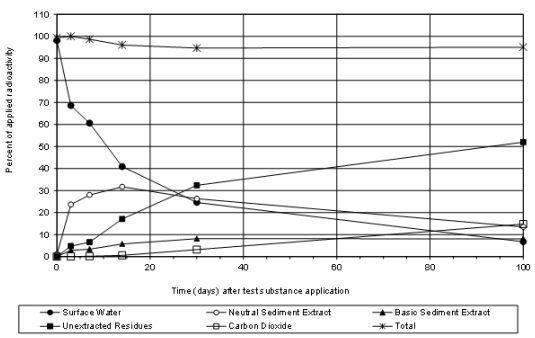
**The results presented illustrate the transient nature of E4 in the aquatic environment and indicate that bioaccumulation of E4 is not expected**

## Environmental Tests, Endpoints, and Results

| Tests | Endpoints and Results |
|---|---|
| **Partition Coefficient Test (OECD 107)**<br>▪ Double distilled water saturated with n-octanol and n-octanol saturated with double distilled water. | **Results**<br>▪ Partition coefficient (log $K_{OW}$) = 1.65 |
| **Ready Biodegradability Test (OECD 301B)**<br>▪ Inocula - activated sludge from Burley Menston sewage treatment works, North Yorkshire UK | **Results**<br>▪ % of theoretical $CO_2$ yield = 3% over 28 days |
| **Adsorption-Desorption in Soils and Sludges (OECD 106)**<br>▪ Three soils (0.7 to 3.6% organic carbon).<br>▪ Two sludges (36.9 to 38.0% organic carbon) | **Results**<br>▪ Adsorption $K_{FOC}$: 88 to 147 L/kg (Soils); 35 to 36 L/kg (Sludges)<br>▪ Desorption $K_{FOC}$: 176 to 227 L/kg (soils) |
| **Fate in Water-Sediment Systems Test (OECD 308)**<br>▪ Two aerobic systems – sandy silt loam (4.9% organic carbon) and loamy sand (0.6% organic carbon) | **Results**<br>▪ Rapid dissipation in both systems<br>▪ Two major transformation products (TP) (>10% AR).<br>▪ $DT_{50}$ (20ºC): 3.81 to 12.08 days (water); 4.09 to 6.71 days (sediment)<br>▪ Mineralization to $^{14}CO_2$ : 8 to 15% AR |

$K_{FOC}$: Freundlich coefficient; TP Transformation product; AR Applied radioactivity; PBT Persistent, Bioaccumulative and Toxic

**Fate of E4 in Sandy silt loam water-sediment system**




## Conclusions

- The log $K_{OW}$ < 3, low potential for bioaccumulation in aquatic species
- E4 is classified as high mobility in soil (McCall) and is not expected to bind to sludge in a wastewater treatment plant.
- E4 is transformed extensively under aerobic conditions in water-sediment systems.
- $DT_{50}$ normalised to 12ºC (range 8.1 to 25.7 days) is below regulatory thresholds for classification for Persistence.
- E4 is not considered a PBT

Poster presented at the SETAC Europe 32nd Annual Meeting May 15-19, 2022, in Copenhagen, Denmark

Acknowledgments: The authors would like to thank Jo Gilbert, Study Director of the environmental fate studies for E4, and Hope Aubin for contributing to the format of this presentation.

Contact Dr. Erick Nfon, Regulatory Affairs Scientist, at infoERS@smithers.com for more information.