EU Projects

The EU-project ERAPharm

Incentives for the further development of guidance documents?

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Abstract

Triggered by the detection of a large variety of pharmaceuticals in surface waters, soils and groundwaters across the world (e.g. Halling-Sørensen et al. 1998, Daughton & Ternes 1999, Jones et al. 2001, Heberer 2002) and the widespread occurrence of endocrine active compounds and related effects in the environment (e.g. Purdom et al. 1994, Tyler et al. 1998, Vethaak et al. 2002), pharmaceuticals in the environment have become an issue for both the scientific and the public community. During the last few years, our understanding of the fate and effects of pharmaceuticals in the environment has progressed significantly. However, there are still a number of uncertainties concerning the effects of pharmaceuticals on the environment and the assessment of potential exposure (e.g. Hanisch et al. 2004, Salomon 2005). These uncertainties will be addressed by the EU-project 'Environmental risk assessment of pharmaceuticals' (ERAPharm). This project, a specific targeted research project, is carried out within the priority 'Global change and ecosystems' of the 6th framework programme of the European Union. ERAPharm has started on 1st October 2004; the project duration is three years.

Keywords: ERAPharm (environmental risk assessment of pharmaceuticals); EU projects; exposure; global change; human and veterinary pharmaceuticals; persistence of chemicals; pharmaceuticals in surface waters, soils and groundwaters; risk assessment

1 The ERAPharm Consortium

The ERAPharm consortium consists of 14 partners from eight different countries (seven European countries and Canada; **Table 1**). It comprises representatives from the interest groups involved in the registration of pharmaceuticals (i.e. competent authorities, pharmaceutical industry), scientists from universities and research institutes and two SMEs (small to medium-sized enterprises). The project is co-ordinated by ECT Oekotoxikologie GmbH.

2 Project Objectives

The overall objective of ERAPharm is to improve and complement existing knowledge and procedures for the environmental risk assessment of human and veterinary pharmaceuticals. ERAPharm will cover

- fate and exposure assessment,
- effects assessment and
- environmental risk assessment.

An overview of the structure and the work packages of the project is given in **Fig. 1** and **Table 2**, respectively.

Table 1: The ERAPharm consortium

Project partner	Short name	Country
ECT Oekotoxikologie GmbH	ECT	Germany
AstraZeneca UK Ltd.	AstraZeneca	United Kingdom
Brunel University	UBRUN	United Kingdom
Federal Institute of Hydrology	BfG	Germany
Centre National du Machinisme Agricole du Genie Rural des Eaux et des Forets	Cemagref	France
University of York	UoY	United Kingdom
The Danish University of Pharmaceutical Sciences	DFU	Denmark
Eidgenössische Anstalt für Wasserversorgung, Abwasserreinigung und Gewässerschutz	EAWAG	Switzerland
Geotechnisches Institut AG	GI AG	Switzerland
Utrecht University	UU	The Netherlands
Instituto Nacional de Investigación y Tecnologia Agraria y Alimentaria	INIA	Spain
National Environmental Research Institute	NERI	Denmark
Umweltbundesamt	UBA	Germany
Canadian Water Network	CWN	Canada

Table 2: Work packages and responsible leaders of work packages within ERAPharm

Environmental fate processes	Thomas Ternes	BfG
Modelling fate and exposure	Kathrin Fenner	EAWAG
Bioanalytical assays for an initial hazard screening and mode of action classification	Beate Escher	EAWAG
Impact of antibiotics on environmental microorganisms and development of antimicrobial resistance	Heike Schmitt	UU
Impact of pharmaceuticals on terrestrial invertebrates	Jörg Römbke	ECT
Impact of pharmaceuticals on aquatic invertebrates	Jeanne Garric	Cemagref
Impact of pharmaceuticals on fish: transfer of knowledge from toxicology to ecotoxicology	Tom Hutchinson	AstraZeneca
Environmental risk assessment	Alistair Boxall	UoY
Co-ordination and project management	Thomas Knacker	ECT

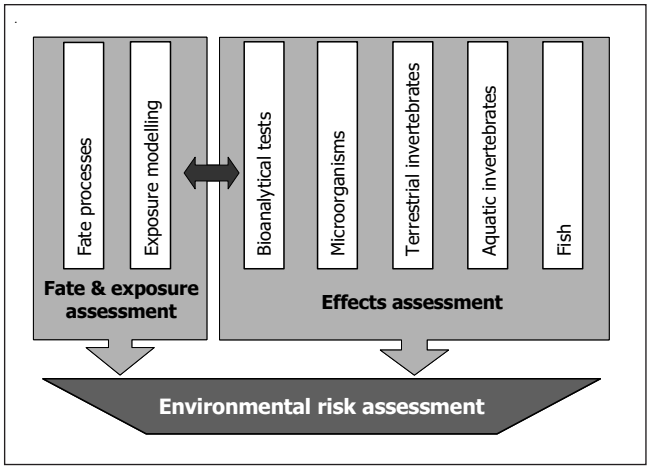

Fig. 1: Overview of the structure of the project

Based on existing regulatory frameworks on the environmental risk assessment (ERA) of pharmaceuticals and on the outcome of previous projects (e.g. the EU-projects ERAVMIS, POSEIDON and REMPHARMAWATER), ERAPharm will address the following aspects for both human and veterinary pharmaceuticals.

2.1 Fate and exposure assessment

ERAPharm will focus on understanding major fate processes and exposure routes which have so far not been studied at all or only to a small extent, namely input from pasture animals and through the application of manure and sewage sludge to land.

The factors and processes affecting the behaviour of pharmaceuticals and selected transformation products in relevant environmental matrices (water, sediment, soil and manure) will be investigated in a series of laboratory, semi-field and field studies. Data will be generated on the sorption behaviour and persistence of human and veterinary pharmaceuticals for a range of environmental conditions (e.g. different soil and sediment characteristics, different microbial diversity, freshwater vs. marine conditions). The effects of the application matrix (e.g. manure, sludge) on behaviour will also be considered. Based on the results of these tests, recommendations will be provided on experimental approaches for assessing the fate of pharmaceuticals as part of the ERA process. Models for predicting key fate parameters (e.g. sorption and persistence) will be evaluated and, where possible, further developed.

A scenario-based exposure assessment system will be developed for predicting concentrations of human and veterinary pharmaceuticals in soils, surface waters and sediments as well as their leaching potential to groundwater. The FOCUS modelling tools, which are in regulatory use for pesticides, will be used as a starting point for developing a higher-tier exposure assessment system for pharmaceuticals. This system will consist of a suite of standard scenarios (for characteristically different regions of the EU member and accession states including Mediterranean and Eastern European regions) for exposure of the terrestrial and aquatic environment to pharmaceuticals and a set of adapted, process-based fate and transport models for soil, surface water and leaching/runoff. The exposure assessment system will be verified using data generated in the above-mentioned fate studies.

2.2 Effects assessment

ERAPharm will contribute to investigating whether environmentally relevant concentrations of human and veterinary pharmaceuticals pose a risk to aquatic and terrestrial organisms. The project will also improve methods and strategies for assessing the effects of pharmaceuticals. Given the fact that many pharmaceuticals contain various functional groups, multiple modes of action can be expected (Escher & Hermens 2002). Moreover, pharmaceuticals that are often designed to target specific receptor structures in mammals or in other target organisms such as pathogens and parasites, may elicit different types of effects in non-target organisms (Seiler 2002). Due to the lack of knowledge on these types of effects, test batteries covering many possible modes of action are required in order to effectively assess the potential environmental hazard caused by pharmaceuticals. A good strategy to achieve this is to include species from different taxa and with different reproduction strategies (Sanchez & Tarazona 2002). Taking this into account, ERAPharm will improve ecotoxicological test methods in order to detect the effects of pharmaceuticals from different therapeutic classes in bacteria, aquatic and terrestrial invertebrates and fish at different levels of biological organisation (individual, popula-

tion, community). The capability of single-species tests to predict effects at higher levels of biological organisation will be elucidated by micro-/mesocosm and field studies.

Emphasis will be placed on pharmaceuticals with a specific mode of action in the environment. Data generated in the effect work packages will provide the basis for improving guidance on how to address specific effects (i.e. for targeting the effects assessment), for determining relationships between acute and chronic toxicity and for evaluating the current fixed environmental concentration action limits that are used in the ERAs of pharmaceuticals.

A battery of *in vitro* and low complexity bioanalytical tests covering relevant modes of action will be used for screening the pharmaceuticals. The test battery is based on the initial interactions of the pharmaceuticals with their targets in cells and on the onset of defence and repair mechanisms in the cells. The test results will provide a first hazard characterisation and a classification according to the mode(s) of toxic action. They will be used for targeting the *in vivo* tests with invertebrates and fish. In addition, it is planned to screen degradation products, which have been identified and isolated in the fate studies and/or metabolites.

The impact of human and veterinary antibiotics on the structure and function of the microbial community will be investigated for the terrestrial and the aquatic (freshwater and marine) environment. This aspect has hardly been looked at in the context of environmental risk assessments, although the diversity of the microbial community is thought to be critical to soil health and soil quality (Garbeva 2004). Special emphasis will be placed on the potential of antibiotics to increase genetically-encoded resistance. Different microbial test systems will be evaluated with regard to their suitability for inclusion in the ERA procedure for pharmaceuticals.

The effects of human and veterinary pharmaceuticals on terrestrial invertebrates will be studied on the laboratory, semi-field, e.g. terrestrial model ecosystems (Knacker et al. 2004), and field scale, taking the environmental conditions in different European regions into account. Both structural and functional endpoints will be considered. A main focus will be to systematically evaluate the effects of parasiticides on dung flies and beetles since there is concern about the effects of these compounds on pasture ecology (Floate et al. 2005).

Effects of human and veterinary pharmaceuticals on aquatic invertebrates will be investigated considering both exposure via the water column and exposure via the sediment. While terrestrial organisms may be exposed locally and temporarily to higher concentrations of pharmaceuticals (e.g. when veterinary pharmaceuticals such as parasiticides are administered to grazing animals), aquatic animals are typically exposed continuously to relatively constant low levels of pharmaceuticals, especially with regard to human pharmaceuticals. Emphasis will thus be placed on life-cycle and multi-generation tests. In these tests, a broad spectrum of ecologically-relevant endpoints and indirect effects can be evaluated. Energy-based models (Péry et al. 2003) will be used to predict effects at the population level. The impact of pharmaceuticals will be investigated at the single-species and microcosm level. In addition, the project will be able to draw upon long-term mesocosm studies with aquatic invertebrates that are performed by the Canadian Water Network.

Chronic effects of human pharmaceuticals on fish will be investigated. As vertebrates with target structures that are often very similar to those in humans, fish are very likely to be affected by human pharmaceuticals as was demonstrated e.g. for ethinylestradiol (Larsson et al. 1999). Within ERAPharm, information from pharmaco- and toxicodynamic studies with mammalian species and from mechanistic (molecular biological) studies will be used to supplement fish tests with additional specific endpoints in order to detect chronic effects of human pharmaceuticals. It will be evaluated whether data on pharmaco- and toxicodynamics in mammalian species can be used to predict potentially hazardous environmental concentrations and the type of effects to be expected in fish and in other environmental organisms.

2.3 Environmental risk assessment

The information on fate and effects of pharmaceuticals in the environment and the improved techniques for determining exposure and effect concentrations, which have been generated by the above-mentioned studies, will be used to propose improvements of existing ERA procedures for human and veterinary pharmaceuticals (CVMP/VICH 2000 and 2004, EMEA/CHMP 2005). ERAPharm will develop screening approaches for identifying (1) those substances that require testing, (2) those environmental compartments and organisms that are most at risk, and (3) the potential to bioaccumulate. The results of these approaches can then be used to target testing. Moreover, PEC action limits and trigger values of the current ERA procedures will be evaluated. Pragmatic approaches will be developed for evaluating the risks of transformation products. These approaches will draw upon current research in the pesticides area, where methods for assessing fate and effects of transformation products based on the structure and physico-chemical properties of the transformation product and the parent compound are being developed (e.g. Fenner et al. 2003, Sinclair & Boxall 2003).

A web-based database with information on fate and effects of pharmaceuticals will be compiled and a web-based risk assessment system will be developed. Case studies will be carried out, i.e. both the newly developed methodologies and the current ERA approaches will be applied to two selected pharmaceuticals. Based on the results, recommendations on the environmental risk assessment of human and veterinary pharmaceuticals will be provided that will be made available to regulators, industry and the scientific community.

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References

CVMP/VICH (2000): VICH Topic GL6 (Ecotoxicity Phase I) Step 7. Guideline on environmental impact assessment (EIAS) for veterinary medicinal products – Phase I (CVMP/VICH/592/98)

CVMP/VICH (2004): VICH Topic GL 38 (Environmental impact assessments (EIAs)) for veterinary medicinal products (VMPs) – Phase II (CVMP/VICH/790/03-Final)

Daughton CD, Ternes T (1999): Pharmaceuticals and personal care products in the environment: agents of subtle change? A review. Environ Health Perspect 107, 907–938

EMEA/CHMP (2005): Note for guidance on environmental risk assessment of medicinal products for human use. Draft (CHMP/SWP/4447/00 draft)

Escher BI, Hermens JLM (2002): Modes of action in ecotoxicology: their role in body burdens, species sensitivity, QSARs, and mixture effects. Environ Sci Technol 36, 4201–4217

Fenner K, Scheringer M, Hungerbühler K (2003): Joint persistence of transformation products in chemicals assessment: case studies and uncertainty analysis. Risk Analysis 23, 35–53

Floate KD, Wardhaugh KG, Boxall ABA, Sherratt TN (2005): Fecal residues of veterinary parasiticides: nontarget effects in the pasture environment. Annu Rev Entomol 50, 153–179

Garbeva P, van Veen JA, van Elsas JD (2004): Microbial diversity in soil: selection microbial populations by plant and soil type and implications for disease suppressiveness. Annu Rev Phytopathol 42, 243–270

Halling-Sørensen B, Nielsen SN, Lanzky PF, Ingerslev F, Holten-Lützhoft HC, Joergensen SE (1998): Occurrence, fate and effects of pharmaceutical substances in the environment. A review. Chemosphere 36, 357–393

Hanisch B, Abbas B, Kratz W, Schüürmann G (2004): Humanarzneimittel im aquatischen Ökosystem – Bewertungsansatz zur Abschätzung des ökotoxikologischen Risikos von Arzneimittelrückständen. UWSF – Z Umweltchem Ökotox 16, 223–238

Heberer T (2002): Occurrence, fate, and removal of pharmaceutical residues in the aquatic environment: a review of recent research data. Toxicol Letters 131, 5–17

Jones OAH, Voulvoulis N, Lester JN (2001): Human pharmaceuticals in the aquatic environment: a review. Environ Technol 22, 1383–1394

Knacker T, van Gestel CAM, Jones SE, Soares AMVM, Schallnaß H-J, Förster B, Edwards CA (2004): Ring-testing and field validation of a terrestrial model ecosystem (TME) – An instrument for testing potentially harmful substances: conceptual approach and study design. Ecotoxicology 13, 9–27

Larsson DGJ, Adolfsson-Erici M, Parkkonen J, Pettersson M, Berg AH, Olsson E, Förlin L (1999): Ethinyloestradiol – An undesired fish contraceptive. Aquat Toxicol 45, 91–97

Péry ARR, Ducrot V, Mons R, Garric J (2003): Modelling toxicity and mode of action of chemicals to analyse growth and emergence tests with the midge *Chironomus riparius*. Aquat Toxicol 65, 281–292

Purdom CE, Hardiman PA, Bye VJ, Eno NC, Tyler CR, Sumpter JP (1994): Estrogenic effects of effluents from sewage treatment works. Chem Ecol 8, 275–285

Salomon M (2005) Arzneimittel in der aquatischen Umwelt – Der Rat von Sachverständigen für Umweltfragen: Handlungsbedarf. UWSF – Z Umweltchem Ökotox 17, 50–53

Sanchez P, Tarazona JV (2002): Development of a multispecies system for testing reproductive effects on aquatic invertebrates. Experience with *Daphnia magna*, *Chironomus prasinus* and *Lymnaea peregra*. Aquat Toxicol 60, 249–256

Seiler JP (2002): Pharmacodynamic activity of drugs and ecotoxicology – Can the two be connected? Toxicol Letters 131, 105–115

Sinclair CJ, Boxall ABA (2003): Assessing the ecotoxicity of pesticide transformation products. Environ Sci Technol 37, 4617–4625

Tyler CR, Jobling S, Sumpter JP (1998): Endocrine disruption in wildlife, a critical review of the evidence. Crit Rev Toxicol 28, 319–361

Vethaak AD, Rijs GBS, Schrap SM, Ruiter H, Gerritsen A, Lahr J, Belfroid AC, de Boer J, Bulder AS, Kuiper RV, Legler J, Murk AJ, de Voogt P, van der Velde EG, Verhaar HJM (2002): Estrogens and xeno-estrogens in the aquatic environment of the Netherlands. Occurrence, potency and biological effects. RIZA/RIKZ-Report Nr. 2002.001

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Related projects of the 6th EU framework programme

Project title	Acronym	Objective	Co-ordinator	Further information
Novel methods for integrated risk assessment of cumulative stressors in Europe	NoMiracle	Development of methods for assessing the cumulative risks from combined exposures to multiple stressors	Hans Løkke, National Environmental Research Institute, Silkeborg, Denmark	http://viso.jrc.it/nomiracle
Models for assessing and forecasting the impact of environmental key pollutants on marine and freshwater ecosystems and biodiversity	MODELKEY	Development of predictive modelling tools, effect-assessment and analytical methods applicable to European freshwater and marine ecosystems	Werner Brack, Environmental Research Centre (UFZ), Leipzig, Germany	http://www.modelkey.org
Integrated modelling of the river-sediment-soil-groundwater system; advanced tools for the management of catchment areas and river basins in the context of global change	Aquaterra	Improvement of the scientific basis for river basin management through a better understanding of the river-sediment-soil-groundwater system	Peter Grathwohl, Eberhard-Karls-University Tübingen, Germany	http://www.eu-aquaterra.de