IMI1 Final Project Report Public Summary

Project Acronym: IPIE

Project Title: Intelligent Assessment of Pharmaceutical in the Environment

Grant Agreement: 115735
Project Duration: 01/01/2015 - 30/06/2019

1. Executive summary

1.1 Project rationale and overall objectives of the project

The active ingredients in medicines (known as the active pharmaceutical ingredient, or API) can be released into the environment in a variety of ways. The most common route is via the sewage system, when patients excrete them. APIs can also escape into the environment when people dispose of medicines incorrectly, and during the manufacturing process. APIs are, by definition, biologically active, and although their concentration in the environment is generally extremely low, there are concerns about the effect of these chemicals on wildlife and ecosystems in general.

Since 2006, new medicines have had to undergo an environmental risk assessment before they are approved for use. However, current testing strategies need to be optimised to accurately predict harmful impacts on wildlife and screening for environmental risks at an early stage may support the development process of new pharmaceutical compounds.

Furthermore, there are over 3 000 APIs that were already in use before the new rules came into force, and only a small number of these have been subjected to environmental impact testing. As testing all of these will be a mammoth task, guidance is needed to help identify which of these 'legacy' APIs are most likely to pose a risk to the environment and so should be prioritised for testing.

The overall aim of this project was to develop predictive frameworks that utilise information from existing datasets on environmental fate and effects of APIs, toxicological studies, pharmacological mode of action and in silico models to support more intelligent environmental testing of pharmaceuticals in development and to prioritise legacy pharmaceuticals for full environmental risk assessment and/or environmental (bio) monitoring. The frameworks drew on information such as existing data on the environmental impact of APIs, toxicological studies, computer models, and studies of how medicines work.

1.2 Overall deliverables of the project

The aim of the project was delivered through the following specific objectives.

1. To review existing approaches for prioritisation and mode of action based intelligent testing of APIs to identify best practice and limitations in these approaches and to develop new and improved frameworks which are acceptable to potential end-users (WP1);

2. To establish a database, with the appropriate quality assessment /quality control (QA/QC) mechanisms, on the properties, environmental fate characteristics and ecotoxicity of APIs (and related compounds such as metabolites) and test species characteristics (e.g. presence/absence of API molecular targets, where available) and to align this database with the existing IMI eTOX database on toxicological properties of APIs (WP2);

3. To develop methods for predicting external and internal exposure to APIs and related compounds in the natural environment for different scenarios based on data compiled in the database developed in Objective 2 (WP3);

4. To develop methods and models for predicting aquatic and terrestrial ecotoxicological responses to APIs and related compounds based on existing data compiled in the database developed in Objective 2 (WP4);

5. To validate the models, concepts and frameworks developed in WPs 1, 3 and 4 using targeted experiments and develop abbreviated in vivo assays (WP5);

6. To develop a software system, that integrates data and approaches developed in WP1-5, to support intelligent testing and prioritisation of APIs in the environment. The system will be based on and be fully compatible with the IMI eTOXsys infrastructure for safety assessment of APIs (WP6);

7. To develop guidance on how the software system and associated predictive tools can be used in a) early development programmes for new compounds and b) for prioritizing legacy products for experimental testing (WP7);

8. To engage with and exchange knowledge with stakeholder groups throughout the project to achieve broad acceptability of the approaches developed by the project and to ensure the sustainability of the database and software system into the future (WP8).

1.3 Summary of progress versus plan since last period

The iPiE project has progressed in its final period as planned.

In WP2, the final release of the iPiE data base was provided in December 2018.

The iPiE database, which includes environmental fate, ecotoxicological effects and physico-chemical data, has been completed with two additional databases, one for modelling purposes, and another for the preparation of iPiE-Sum, the publicly available data base.

The iPiE sum data base contains 279 compounds with 2,185 different studies, while the full data base contains 373 compounds with 2,871 studies in all confidentiality levels.

This was a particularly large increase in data for the publicly available iPiE sum data base, which enables interested stakeholders to search for mostly otherwise unpublished environmental information.

The exposure modelling work (WP3) was further advanced by including models for adsorption and biodegradation as major parameters for estimating environmental distribution of APIs. Also, additional river basins were incorporated into the exposure model (ePIE). The progress and achievements were according to plan.

Major progress was made in terms of effects models development and evaluation (WP4). Acute and chronic baseline models were provided. Also, the refinement of the fish plasma model was completed by determining a tiered approach for estimating critical environmental concentrations based on human therapeutic plasma levels and extrapolating to modelled toxic plasma levels in fish.

The development of chronic QSARS and toxic ratio models to estimate specific (excess of baseline) toxicity of human APIs in environmental organisms could not be achieved based on the iPiE data base, because the number of usable data points for a given group of APIs, for instance based on therapeutic or toxic mechanisms, was too small a basis for QSARs and other pattern-related models. However, existing QSARs have been rescaled for ionizable APIs but could not be fully validated and implemented because there are based on limited data of IPIEs from literature. At this stage of scientific knowledge, only the fish plasma model could be recommended for estimation of chronic risks of APIs at given environmental concentrations within the applicability domain, which had been extended to ionizable APIs. Since fish are in most cases the most sensitive species for API aquatic toxicity, the risk of a lack of prediction capacity is relatively small. Further recommendations in terms of research needs are given in deliverable D4.6.

In WP5, the experimental work for validating the models and testing the underlying hypotheses were completed. For some compounds, a full study set of tests in fish, fish embryos, daphnia invertebrates, and algae are available to provide information on species sensitivity and specificity of endpoints in different species. In validating the exposure models, further monitoring campaigns were conducted. The progress and achievements were according to plan.

The software development (WP6) for integration of models and retrieval of data from the iPiE data base was completed. The implementation of models (ePIE, adsorption, baseline effect models, fish plasma models) was completed. The release of the latest version of the public iPiE sum data base was also provided. The final iPiE sys programme was delivered to the partners at the end of the project.

In a Forum meeting in October 2018, the achievements were discussed with the Scientific Advisory Board (SAB) members, who supported the project progress and provided very useful comments.

1.4 Significant achievements since last report

WP1 – Project scoping and development of conceptual frameworks for prioritisation and intelligent testing

A framework for prioritization and prediction was developed, which includes the use of iPiE output within different scenarios for prioritization and prediction of APIs for environmental risks.

- Framework for prioritization of a larger group of compounds with unknown aquatic hazards and risks
- Validation of framework by using a subset of compounds measured in monitoring programmes
- Framework for prediction of potential aquatic risks of a new API in development
- Description of examples for how to apply the framework in the R&D process

WP2 – Development and population of database

- Schema updated to remove details for quality assessment and change the Data Type column as a result of concerns within the consortium that absence of quality assessments for Good Laboratory Practice (GLP) studies might give the impression that these studies were not reliable or valid compared to the literature studies
- UBA conducted quality assessment of 30 literature studies on sorption to sludge and sediment extracted by RU for input to exposure model exercise
    - 33% (10/30) studies ranked reliability/relevance class 1 or 2
    - 66% of literature are of insufficient data quality and should not be used
- ECT conducted quality assessment of 7 literature on ecotoxicity (algae/daphnia/fish) to support WP5 ecotoxicity studies for model evaluation
    - 29 % (2/7) studies ranked as reliable with/without restriction class 1 or 2
    - 71% of literature are of insufficient data quality and should not be used
- Quality assessment sheets were uploaded to the iPiE sharepoint
- There were two database releases in year 4, the 2018.1 database release scheduled for June and an additional release 2018.2 in December. The latter was prompted by several requests to change the status of donated data and allowed more data to be released to the public iPiESum 2018.2 version of the database
- The database was supplemented with drug targets and Anatomical Therapeutic Chemical (ATC) Classification System codes, where available, using data extracted from supplementary data provided with Santos, R. et al., 2017, A comprehensive map of molecular drug targets, Nature Reviews Drug Discovery, 16, pages 19–34 doi:10.1038/nrd.2016.230
- The procedure for adding new data was documented in deliverable D2.9
- Provided extract of eTOX data to Lilly for mammalian read across
- Two quality issues were raised in year 4 relating to use of the ecotoxicity data for modelling activities. The first by ECT concerning whether results were for measured or nominal concentrations and either the salt or un-neutralised form. The second by LJMU regarding NOEC values not matching test concentrations. Data donors were alerted to these issues and asked to investigate. Where the data donor replied with corrections these were implemented in the database

WP3 – Development of methods for estimating exposure to APIs

- Development of a QSPR for sorption of APIs to activated sludge of WWTPs
- Development of a QSPR for biodegradation of APIs in activated sludge of WWTPs
- Description of the simplified realistic worst-case exposure model (D.3.4)
- Application of the ePiE model to predict surface water concentrations of APIs in several European river basins (collaboration with WP5)
- Update of the technical description of ePiE (D.3.1)
- Extension of the number of river basins included in ePiE, now covering all European river basins with the exception of the 4 largest basins because of technical limitations
- Two scientific publications, i.e. one on the ePiE model and one on degradation of APIs in surface water

WP 4 - Development of methods for predicting effects of APIs and related compounds

- Development of updated and robust baseline acute and chronic toxicity QSARs for fish, Daphnia and algae derived from the extracted iPiE data
- Toxic ratio (TR) analysis for acute, chronic (LOEC survival) and fish embryo toxicity data
- Grouping analysis according to ATC
- Identification of structural features associated with toxicity in excess of the baseline toxicity with a toxic ratio TR exceeding ten
- Critical membrane concentration concept for analysis of excess toxicity
- Development of gene ortholog predictions of specific drug targets in wildlife species associated with classes of active pharmaceutical ingredients to identify and prioritize taxa most and least likely to be sensitive to API exposures. ECOdrug linked into iPiEsys
- Development of refined fish plasma model based on a tiered approach, implemented in iPiE sys. Level 0: Screening for drug conservation in humans and fish. Level 1: Prediction of $K_{plasma/water}$. Level 2: internal fish plasma steady state concentrations based on $K_{plasma/water}$. Level 3: calculation of CEC for fish based in human therapeutic data. Level 4: calculation of CEC for fish based on mammalian tox data
- *In-vitro* to *in-vivo* extrapolation (IVIVE Model) based on Tox21 *in vitro* data and baseline toxicity QSARs
- Completion of Deliverable 4.7 Effect assessment framework with a comprehensive data collection in the appendix

WP5 – Experimental validation of developed models

- Toxicity testing of the selected APIs in invertebrates, primary producers, and fish embryos was finalised
- The extended experimental work regarding validation of the fish plasma model was finalised (i.e., with salbutamol, naproxen, vardenafil, olmesartan, and amitriptyline)
- Testing of biodegradation, sorption and uptake into invertebrates was conducted and finalised
- Monitoring of API in selected wastewater treatment plants and surface water sites was continued and finalised. Both the number of sites and the number of analytes was extended considerably for this second year of monitoring (six sampling campaigns and 40 APIs respectively)

- Task 5.5 (validation of predictive frameworks) has been conducted, comparing extensive monitoring data to spatially-explicit environmental concentrations predicted by ePiE and by comparing observed to predicted effects. The limitations imposed by the non-availability of models for chronic aquatic toxicity were balanced by extended analyses of generated data that is expected to support respective model development in the future

WP6 – Integrated software system for database search and retrieval and decision support for the identification of the potential environmental risk of APIs and related substances

- Design, development and final release of the iPiE SYS (version 2) application based on end user requirements with a new intuitive and state-of-the-art user interface for database search and retrieval and in silico predictions
- Interface for secure and encrypted connection and search and retrieval of the latest release 2018.02 of the iPiE database (collaboration with WP2)
- Integration of the ePIE system into iPiEsys for environmental exposure and fate modelling of pharmaceuticals in European watersheds including the display of the environmental concentrations of the APIs in an interactive geographical map of the respective river basin (collaboration with WP3)
- Integration of model for sludge sorption of APIs (collaboration with WP3)
- Integration of the predictive models into iPiEsys on concentrations of APIs in fish plasma and aquatic acute baseline and chronic toxicity of APIs (collaboration with WP4)
- Integration of model documentation and parameter description into iPiEsys
- Design, development and final release of the iPiE·Sum application for project dissemination purposes including secure and encrypted connection to the latest release 2018.02 of the iPiE·Sum database for summarization view of iPiE database content (collaboration with WP2). https://ipiesum.eu/
- Finalization of deliverables D6.3 and D6.4 including accompanying report with systems documentation
- Successful preparation of the iPiE post-project sustainability phase for iPiEsys and iPiE·Sum (collaboration with WP8)

WP7 – Development of guidance

- A project workshop was held in Schwielowsee near Berlin to develop case studies to illustrate how the tools developed during iPiE could be used for prioritisation and intelligent testing of APIs
- A Guidance Document has been developed that briefly describes the main tools developed during the iPiE project (database, in silico models, ePiE model, fish plasma model, ECODRUG and iPiEsys. The document then uses a series of case studies to illustrate how the tools can be used to address different prioritisation and intelligent testing questions. The Guidance is provided in D7.1
- A dissemination workshop was run for EFPIA members in February 2019. During this workshop, the main outcomes of the different work packages were presented and a demonstration of the iPiEsys given.
- A special session was run immediately before the SETAC Europe Annual meeting where the results of the project were presented to the wider stakeholder community and a demonstration of the iPiEsys given
- A final iPiE project conference was held in June 2019 to disseminate the findings of the project to the wider scientific community. This was attended by around 70 participants

WP8 – Scientific coordination, project management and sustainability

- Management procedures and monitoring have been applied to ensure that the project is progressing according to the work plan and to solve the day to day operational issues
- Amendment 3 and 4 were finalised, to request the extension of additional 6 months to finalise the project activities
- In terms of communication, the iPiE project website (www.i-pie.org) has been continuously updated with news and publications. New newsletters have been prepared and released, as well as News Flash, for rapid release of brief news items
- The Sustainability group has continued its activities to devise the sustainability plan (D8.7)

1.5 Scientific and technical results/foregrounds of the project

The project has produced a number of important scientific information and technical tools, which will improve scientific knowledge of environmental hazards and risks of human pharmaceuticals, will make risk assessment and prediction more powerful, and will support the prioritization of large numbers of APIs with lack of environmental data.

In terms of science, the project had developed the following foreground:

- A high quality data base on APIs, including mainly industry sponsored studies for environmental fate, effects and behaviour of APIs, which had mostly not been publicly accessible before
- A high-resolution spatial model to predict exposure to pharmaceuticals in European surface waters (ePiE)
- Quantitative Structure-Property Relationships (QSPRs) to predict sorption, biodegradation, and bioconcentration of APIs
- Data base, which reflects the presence of pharmacological targets of APIs in environmental taxa (ECOdrug)
- Acute and chronic baseline models for effects in fish, invertebrates and algae
- Improvement of the fish plasma model for estimating critical environmental concentrations

Additionally, numerous scientific papers reflect the research which was conducted to support and validate the above output.

In terms of technical results, the project has developed the following foreground:

- Data base template for input of detailed study information for environmental studies of API (iPiE data base)
- Software to search and retrieve the information from the data base (iPiE sys)
- Software to extract high level study information of the data base for public access (iPiE sum)
- Software to integrate the developed models and to execute calculation operations with these models (iPiE sys)

1.6 Potential impact and main dissemination activities and exploitation of results

The output of the project was already discussed broadly in the scientific and regulatory community. A lot of attention was gained by the European Commission in context with the development of the “Strategic Approach to Pharmaceuticals in the Environment” which was published in March 2019 as Communication (COM(2019) 128 final). In this published strategy paper, the output of iPiE was referenced as a valuable information source on API environmental properties. In the upcoming

discussions on the implementation of the strategy, members of the iPiE consortium will propose to use iPiE tools as a contribution to the aims of the strategy in reducing the efforts of industry and society to assess the environmental risk of widely used pharmaceuticals. This will reduce costs of industry, regulators, water managers and communities to invest in testing, chemical analysis, treatment of waste, etc.
It will also help to reduce the use of animals in testing, if appropriate prioritization schemes for potentially harmful pharmaceuticals are in place.

Similarly as on the EU level, in many European Member states and regions there are discussions on the appropriate management of pharmaceutical residues in surface waters.
The output of iPiE can significantly contribute to the knowledge on environmental risks of APIs down to a local level, and help to design adequate strategies for reducing those risks, if needed.

For industry in particular, the data base provides information on environmental data for hundreds of (legacy) APIs, which helps to identify the availability of data for generic drug applications, which were otherwise not known, and hence, this will help to reduce testing of compounds, for which data are already available. iPiE tools will further help the investigative pharmaceutical companies to estimate the potential environmental risks of new drug development candidates, in order to consider the mitigation of those risks at an early stage. This will help to minimize the environmental impact and hence, the environmental health of pharmaceuticals coming to the market.

In conclusion, the availability of the results of iPiE comes at an important time, when policy decisions on the EU level and in many EU Member States and regions are focussing on adequate strategies for estimating and, where necessary, managing environmental risks of pharmaceutical residues in surface waters. The tools developed in iPiE help to analyze the potential risks, to prioritize potentially harmful APIs for further testing and to implement strategies for reducing environmental risks if necessary. This will contribute to economic savings in testing and reduction in animal use, waste of resources in treatment techniques, and support scientifically based decisions on the management of pharmaceuticals in the environment.
For industry, the output of iPiE helps to avoid unnecessary testing for environmental risks and to consider the mitigation of potential environmental risks at an early stage of development.

1.7 Lessons learned and further opportunities for research

The iPiE project was based on a collaborative approach of scientists and specialists from universities and research organizations, regulatory bodies, industry and SMEs. This was extremely successful in bringing together in-house knowledge of the pharma industry ecotoxicologists and toxicologists, academic research skills, a regulatory view on the developed tools, and technical excellence of specialists e.g. in the IT field. This collaboration was appreciated by all partners.
The results could never have been produced individually by either of these groups of experts, since the information on environmental data, as provided by industry, was not accessible through public sources, and the experience in modelling and the conduct of a tremendous amount of practical work such as monitoring, exposure and effect modelling, experimental lab studies, as done by the academic partners and one SME, could never been performed in industry laboratories.
The representation by regulators as partners and in the Scientific Advisory Board, where also different organizations of water management bodies were present, provided an excellent view on the needs for the practical applications of the project outcome to be applied in regulation and management of pharmaceuticals in the environment. These partners and advisors were also very helpful in disseminating the information of iPiE in the various member states of the EU and amongst regional and local regulating bodies.

In summary, iPiE was a very good example for the successful collaboration of various organizations and expertise, which showed that openness from all sides to environmental concerns and issues can be managed in a spirit of collaboration by different groups of stakeholders with their particular expertise and roles.

Further research on the environmental issues of pharmaceuticals in the environment should include the following aspects:

- Transparency of environmental information of pharmaceutical compounds for stakeholders by developing a broadly agreed data base platform
- Further look into the environmental fate and effects of mode-of-action groups of human drugs, which haven't been studied yet, for better prediction and modelling opportunities
- Analysis, whether knowledge on environmental properties of human drugs can help to design more environmentally friendly molecules
- Develop guidance on how drug related effects in environmental organisms need specific endpoints in testing protocols
- Develop guidance, how screening tools can help to save animal testing (particularly fish) for environmental risk assessment of human medicines