



General information	
PPP-number	AF-18070
Title	Non-animal predictions of the behaviour of chemicals in the body
Theme	BO-46 AF-GV Gezonde en veilige producten
Implementing institute	Wageningen Food Safety Research (WFSR)
Project leader research (name + e-mail address)	Ans Punt (ans.punt@wur.nl)
Coordinator (on behalf of private partners)	Ian Sorrell, Colworth (Ian.Sorrell@unilever.com)
Project-website address	https://www.wur.nl/nl/Onderzoek-Resultaten/Onderzoeksprojecten-LNV/Expertisegebieden/kennisonline/Non-animal-predictions-of-the-behaviour-of-chemicals-in-the-body.htm
Start date	1 Jan 2019
Final date	31 Dec 2021

Approval by the coordinator of the consortium	
The annual report must be discussed with the coordinator of the consortium. The "TKI's" appreciate additional comments concerning the annual report.	
Assessment of the report by the coordinator on behalf of the consortium:	<input checked="" type="checkbox"/> Approved <input type="checkbox"/> Not approved
Additional comments concerning the annual report:	The project is on track to deliver on its goals. In the first year, the planned data generation has been successful for both the in vitro and in silico components of the project. The performance of the computational models has been evaluated and this information can be used in toxicity testing.

Summary of the project	
Problem definition	Computer models that predict the bioavailability of chemicals in a body play a substantial role in the transition towards toxicity testing strategies without animal experimentation. However, the development of such computer models solely on the basis of in vitro and/or in silico input data remains a challenge. Uncertainties with respect to the impact of different strategies to parameterize the models, the quality of the input data as well as the difficulty of determining whether all relevant processes are included in the model, requires that the model predictions still need to be evaluated on a case-by-case basis against in vivo data (e.g. plasma concentrations observed in animal or humans). Key for the transition towards non-animal testing strategies is to move away from this case-by-case evaluation and optimization of the models against in vivo data and to identify other strategies for the evaluation of the adequacy of in vitro- and in silico-based computer models to estimate in vivo plasma and tissue concentrations. To enable this, it would be of help to gather knowledge on the predictive value of different in vitro and/or in silico input methods that can be used for the development of the computer models. In addition, insight in chemical characteristics is needed that would indicate whether a chemical is outside the applicability domain of the model performance.
Project goals	The goal of the first year of the project was to evaluate the performance of computer models that are build based on in vitro and in silico input data to predict plasma concentrations in rats and

	humans. In the second part of the of the project (year 2 and 3), possibilities to improve the model predictions based on in vitro input data for transporter kinetics or extrahepatic metabolic processes will be evaluated.
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Results	
Planned results 2019	<ul style="list-style-type: none"> - Selection of the model compounds and gathering of the in vitro and in silico input data (both literature available and newly generated) to develop the computer models for these compounds. - Building of a workflow to generate model predictions based the gather in vitro and in silico input data. - Evaluation of the performance of the model predictions against (existing in-house and literature available) plasma concentrations of the chemicals in rats and humans. - Draft manuscript on the predictive value of the rat computer model to predict peak plasma concentrations in rats (followed-up by a second manuscript in 2020 on the predictive value of the models for humans).
Achieved results 2019	<ul style="list-style-type: none"> - In vitro and in silico data have been gathered for 44 compounds to evaluate the performance of the rat model predictions, and for 48 compounds to evaluate the performance of the human model predictions. - In vitro liver metabolism measurements (part of the model input) were generated at WFSR for 16 chemicals with rat liver fractions and for 10 chemicals with human liver fractions. - A workflow has been developed in R to generate predictions of the peak plasma concentrations of the chemicals in rats and humans based on in vitro/in silico input data and to evaluate the performance of the computer models against existing in vivo data - A draft manuscript has been prepared that contains the introduction and results obtained with the rat computer model.
Planned results 2020	<ul style="list-style-type: none"> - Completion of the in vitro liver metabolism measurements and generation of in vitro measurements for intestinal uptake. - Submission of the manuscript on the predictive value of the computer models that predict plasma concentrations of chemicals in rats. - Draft manuscript on the predictive value of the computer models that predict plasma concentrations of chemicals in humans. - Method development to extent the computer models to include transporter mediated processes <p>(Poster) presentations at workshops, seminars, or symposia:</p> <ul style="list-style-type: none"> - Oral presentation at the 11th World Congress on Alternatives and Animal Use in the Life Sciences 2020 (23-27 Aug). Symposium: Building confidence in NexGen Risk Assessment - Oral presentation at Eurotox 2020 (6-9 Sept). Symposium: Building confidence in the use of New Approach Methodologies for safety decision-making

Deliverables/products in 2019 (provide the titles and /or a brief description of the products/deliverables or a link to a website.
<u>Scientific articles:</u> Draft manuscript, provisional title " Predictive value of NAM PBPK models in rat" (introduction and results obtained with the PBPK model in rat).
<u>External reports:</u>
<u>Articles in professional journals/magazines:</u>

(Poster) presentations at workshops, seminars, or symposia.

- Oral presentation at the "Coumarin next generation risk assessment (NGRA) case study workshop" at Unilever Colworth, 15-17 Oct 2019.

TV/ radio / social media / newspaper:

Remaining deliverables (techniques, devices, methods, etc.):

- Excel files that contain the collected in vitro and in silico input data for the model development and evaluation (stored at GitLab Wageningen UR)
- R scripts of the workflow to generate model predictions based on the in vitro/in silico input data and to evaluate the performance of these models against existing in vivo data (stored at GitLab Wageningen UR)