



PPP Project Annual Report 2018

The PPP-projects that have been established under the direction of the top sectors must submit an annual report on their technical and financial progress. This format is to be used for reporting the technical progress. A separate format ('PPP final report') is available for PPP-projects that have been completed in 2018.

The annual reports will be published in full on the websites of the TKIs/top sector, excluding the blocks 'Approval coordinator/consortium' and 'Planning and progress' . Please ensure that no confidential matters are left in the remaining blocks.

General information	
PPP number	AF-16035
Title	PhenFlex-based resilience as measure for health effects of diet
Theme	Voeding & Gezondheid
Executive knowledge institution(s)	Nederlandse organisatie voor toegepast natuurwetenschappelijk onderzoek TNO
Research project leader (name + e-mail address)	Dr. Karin Bosch (Karin.Bosch@TNO.nl)
Coordinator (on behalf of private parties)	
Government contact person	
Total project size (k€)	1550k euro
Address project website	
Start date	01-04-2017
End date	01-04-2020

Approval coordinator/consortium

The annual report should be discussed with the coordinator/the consortium. The TKIs appreciate being informed of possible feedback on the annual report.

The coordinator has assessed the annual report on behalf of the consortium:	<input checked="" type="checkbox"/> approved <input type="checkbox"/> rejected
Possible feedback on the annual report:	NA

Short content description/aim PPS

What is going on and how is this project involved?
 What will be delivered by the project and what is the effect of this?

On a daily basis, people have to cope continuously with environmental influences that affect healthy homeostasis (e.g. intake of suboptimal foods, physical exercise, etc). Such changes disrupt the physiological or psychological balance, and the individual has to respond to the new situation and regain homeostasis. The central assumption of the PhenFlex project is to define health as "the ability to optimally adapt" to continuous perturbations of the physiological homeostasis due to environmental changes. The ability to adapt or "the homeodynamic resilience of physiology" can act as indicator for maintenance of physiological function, including biomarkers for maintenance of health or prevention of (metabolic) diseases (van Ommen et al 2014, Stroeve et al, 2015).

To acknowledge the multi-target role of nutrition in the body, the objective of this project is to substantiate the concept of improvement of phenotypic flexibility by dietary intervention. Robust proof for this concept and the related emergence of new biomarkers is expected to further promote acceptance of phenotypic flexibility as health benefit in itself by regulatory authorities like the EFSA. The aim of this project is to establish proof-of-concept for the application of the challenge test concept for

the scientific substantiation of health benefits in the context of physiological resilience.

Objectives are:

1. To demonstrate that a healthy or optimal diet in an intervention study can improve “metabolic age” and “metabolic stress”, which are composite biomarkers by quantifying phenotypic flexibility, within a healthy population. These composite markers validate previous findings from other intervention studies using phenotypic flexibility and could be the next generation biomarkers.
2. To show additional advantages of personalization / tailoring of dietary recommendations over general dietary recommendations. PhenFlex-2 delivers the scientific evidence that a healthy diet is beneficial for your health specially when this is tailored to the (nutritional) needs of a person.
3. To encourage acceptance of the approach by the international scientific community by publications in peer-reviewed journals and discussions with regulatory authorities.
4. To learn more about other new biomarkers, (DIY) methods and study-designs that in the future can be used to substantiate health effects of food and nutrition.

The measurement of health effects of food and diet remains a hurdle in the innovation pipeline of many food companies in Europe. Nutrition science has difficulty to demonstrate specific health-beneficial effects related to diet or dietary ingredients such as probiotics. PhenFlex represents a new avenue of providing evidence for building health claims and strengthens the importance of resilience-thinking in health research. Being resilient is a great value for any dynamic system and a prerequisite to maintain sustainable system performance in increasingly complex, demanding and connected societies. Health is no exception to this. The Netherlands, and TNO as recognized party, is a frontrunner in resilience thinking and this project will contribute to strengthen this position.

Acceptance of this kind of evidence in health claim dossiers by regulatory authorities requires broader acceptance, testing and further development of the methodology by the global scientific community. This requires dissemination of results in peer reviewed papers and in major scientific conferences. Therefore, dissemination of the study results and lessons learned will be the main deliverables within this project.

Planning and progress (if there are changes to the project plan, please explain)	
Is the PPP going according to plan?	We have performed the planned intervention study. In order to measure the PhenFlex analysis, the PhenFlex shake was provided to the participants as planned. However, within the study the participants received a PhenFlex shake that contained mold, by error of the manufacturer. After an interruption in the study to solve this issue, shakes were produced that appeared later to have the wrong composition in sugar. Furthermore, again these shakes were contaminated with mold. The contamination and composition differences of the shakes will influence the challenge results and therefore our main study results.
Have there been changes in the consortium/project partners?	Yes, in 2018 an amendment on the agreement was processed to add Roquette as a partner to the consortium. This has been approved.
Is there a delay and/or deferred delivery date?	We have finalized the intervention study, but we will be unable to publish the results of this particular study. Therefore, the milestone to publish these results will not be met with using the current data set. We are discussing with the partners for next steps.
Are there any substantive bottlenecks?	Yes, see above. Due to the issue with the shakes during the intervention study, we will not be able to fully answer our research question with the obtained data. TNO is claiming NIZO, the Phenflex shake producer, for providing a drink not according to the agreed contract. The financial consequences for the PhenFlex project will heavily

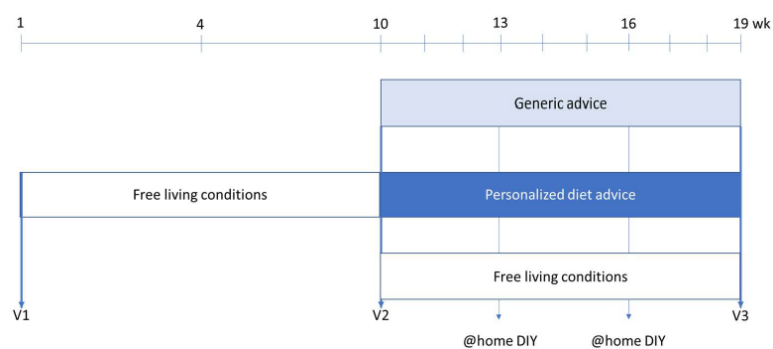
	depend upon the outcome of this legal dispute.
Are there any deviations from the projected budget?	In this stage we are investigating the options for this project. If we want to answer the full research question, we will have to perform (part of) a new study. There will not be sufficient budget and time in the current contract. Other option is to use data of other studies to answer (part of) the research question. After we have a clear view of our options, we will, in consultation with the consortium and TKI AgriFood, take a decision on how to continue with the project.

Results in 2018/ so far

Give a short description of the high-lights and (most important) project deliverable in 2018 / so far and their target group

After successful design and approval of the PhenFlex study in 2017, we have conducted the intervention study in 2018. The primary objective of the intervention study was to demonstrate that a healthy or optimal diet in an intervention study within an apparently healthy population can improve "metabolic age", which is a composite biomarker quantifying phenotypic flexibility. This composite biomarker validates previous findings from other intervention studies using phenotypic flexibility and could be the next generation biomarker. We want to confirm that 'metabolic age composite biomarker' has an added value as compared to evaluation by the single biomarkers the composite biomarker contains.

Participants were randomized to the control group (no change in dietary habits), the general advice intervention or the personalized advice intervention after stratification on PhenFlex response (= metabolic age), age, BMI and gender.



V1, V2 and V3 represent the visit day numbers the subjects will have their challenge test day in the metabolic ward. Between visit 1 and 2, the free living period, will be at least nine weeks.

All subjects started their treatment after visit 2 for at least nine weeks. Visit 3 was the last test day and with this visit the study is closed for each subject.

The following markers were evaluated on the full dataset in overnight fasting conditions:

Anthropometrics	BMI, body weight, hip circumference, waist circumference
Stress	C-reactive protein, GGT, SGOT (ASpartate Amino Transferase), SGPT (ALanine Amino Transferase)
Metabolic health	Total Cholesterol, HDL cholesterol, LDL cholesterol, glucose, insulin, Non esterified fatty acids (NEFA), Triglycerides
Other	diastolic blood pressure (DBP), systolic blood pressure (SBP), heart rate(HR), haemoglobin 1AC (HbA1C)

On the challenge test days the participants at V3 were provided with the PhenFlex shakes, shakes with mold and lumps found in two bottles in the batch of Phenflex drink. The new batch produced, turned out to have been prepared with wrong components. The sugar content in the drink is similar, but the composition of the chain lengths is different. 57 participants were provided with the original PhenFlex batch, whereas 105 participants received the PhenFlex batch with the wrong sugar component. First statistical analysis of glucose response showed a significant different response between subjects on the original PhenFlex batch and the batch with the wrong sugar component. The scientific advisory board of the PhenFlex2 project concluded that the challenge data of n=105 participants that received the batch with the wrong sugar component could not be

used for further analysis of the intervention effect.

We are currently preparing a data analysis plan for interpreting the current limited data set. Based on a decision with the consortium, we will assess how much of the data will be analyzed, or to shift our effort to a new study. We are in ongoing discussion to have the well-informed decision on how to move forward. The lessons learned of this study will improve the design of a future study considerably.

Number of delivered products in 2018 / so far (in an appendix, please provide the titles and/or description of the products or a link to the products on public websites)

Publications 2018:

- Plasma metabolome analysis identifies distinct human metabolotypes in the postprandial state with different susceptibility to weight loss-mediated metabolic improvements. Fiamoncini J, Rundle M, Gibbons H, Thomas EL, Geillinger-Kästle K, Bunzel D, Trezzi JP, Kiselova-Kaneva Y, Wopereis S, Wahrheit J, Kulling SE, Hiller K, Sonntag D, Ivanova D, van Ommen B, Frost G, Brennan L, Bell J, Daniel H. FASEB J. 2018 doi: 10.1096/fj.201800330R. [Epub ahead of print] PubMed PMID: 29718708. <https://www.ncbi.nlm.nih.gov/pubmed/29718708>
- A 12-wk whole-grain wheat intervention protects against hepatic fat: the Graandioos study, a randomized trial in overweight subjects. Schutte S, Esser D, Hoevenaars FPM, Hooiveld GJEJ, Priebe MG, Vonk RJ, Wopereis S, Afman LA. Am J Clin Nutr. 2018 Dec 1;108(6):1264-1274. <https://www.ncbi.nlm.nih.gov/pubmed/30541093>
- Whole grain wheat consumption affects resilience in a randomized controlled trial in overweight and obese adults with mild hypercholesterolemia: the Graandioos study. Femke P.M. Hoevenaars, Diederik Esser, Sophie Schutte, Marion G. Priebe, Roel J. Vonk, Willem J. van den Brink, Jan-Willem van der Kamp, Johanna H.M. Stroeve, Lydia A. Afman and Suzan Wopereis. Submitted to Journal of Nutrition

Publications 2017:

- The impact of micronutrient status on health: correlation network analysis to understand the role of micronutrients in metabolic-inflammatory processes regulating homeostasis and phenotypic flexibility. Tim J. van den Broek, Bas H. A. Kremer, Marisa Marcondes Rezende, Femke P. M. Hoevenaars, Peter Weber, Ulrich Hoeller, Ben van Ommen, and Suzan Wopereis. Genes Nutr. 2017; 12: 5. Published online 2017 Feb 8. doi: 10.1186/s12263-017-0553-7 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5299688/>
- Multi-parameter comparison of a standardized mixed meal tolerance test in healthy and type 2 diabetic subjects: the PhenFlex challenge. Suzan Wopereis, Johanna H. M. Stroeve, Annette Stafleu, Gertruud C. M. Bakker, Jacobus Burggraaf, Marjan J. van Erk, Linette Pellis, Ruud Boessen, Alwine A. F. Kardinaal, and Ben van Ommen. Genes Nutr. 2017; 12: 21. Published online 2017 Aug 29. doi: 10.1186/s12263-017-0570-6. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5576306/>
- Ranges of phenotypic flexibility in healthy subjects. van den Broek TJ1, Bakker GCM1, Rubingh CM1, Bijlsma S1, Stroeve JHM1, van Ommen B1, van Erk MJ1, Wopereis S1. Genes Nutr. 2017 Dec 6;12:32. doi: 10.1186/s12263-017-0589-8. eCollection 2017. <https://www.ncbi.nlm.nih.gov/pubmed/29225708>

Conferences / presentations on PhenFlex-2 in 2018:

- Personalised Nutrition Europe Conference, Quantifying Personalised Nutrition, London, 6th of December 2018, <https://personalisednutrition-europe.com/events/personalised-nutrition-europe-2018-0>
- Precision nutrition from the perspective of phenotypic flexibility. The 3rd China Special Food International Conference, 30 October – 1st November 2018, Beijing, China, www.sfic.net.cn/index.php/Home/Index/index.html
- Nutrition strategies to maintain optimal health The 5th DHU 2020 Autumn School « New

approaches in precision medicine : state of the art and practice », Nantes Thursday 18 ~ 19 october, Nantes, France <http://www.dhu2020.org/index.php/en/training/autumn-school-2018>

- Precision Nutrition from the Perspective of Phenotypic Flexibility. Korean Nutrition Society Annual Conference, Roadmap to Precision Nutrition, October 18~19, 2018, Pyeongchang, South Korea, <http://kns.or.kr/English/index.asp>
- Personalised nutrition from perspective of phenotypic flexibility, 4th nutrition-alimentation-metabolisme-sante, 4th October 2018, Rennes, France, <https://www.rennes-congres.fr/fr/votre-evenement/l-agenda-des-evenements/4emes-rencontres-nutrition-alimentation-metabolisme-sante>
- Phenotypic Flexibility as a Measure of Health Through the Life Cycle, 117th Abbott Nutrition Research Conference, Carbohydrates Through the Life Cycle and Across Tissues, June 20 2018, Columbus, Ohio, USA, <https://anhi.org/conferences/117-anrc-carbohydrates>
- Personalised nutrition from the perspective of phenotypic flexibility, Experimental biology April 2018, San Diego, USA, <https://experimentalbiology.org/2018/Home.aspx>
- Showcasing the possibilities of phenotypic flexibility (PhenFlex) testing as a new measure for health status and indicator for personalised dietary advice, Vitafoods educational programme, May 2018, Geneve, Swiss, <https://ezone.vitafoods.eu.com/seminars-2018?&filters.STREAM=personalised-nutrition&searchgroup=00000001-seminars-2018>
- Personalized Nutrition from the Perspective of systems Flexibility, Personalized Nutrition Guardrails Expert Meeting, ILSI North America, 25 June 2018, Washington DC (USA)
- Personalized nutrition: what is the science? HAS hogeschool Food trend college 'Personalized nutrition: Hoe gepersonaliseerd kan het zijn? 12 June 2018, HAS hogeschool, s'Hertogenbosch, <https://has.nl/nl/event/trendcollege-personalized-nutrition>
- Meten van gezondheid, NAV (Nederlandse Academie voor Voedingwetenschappen) meeting op locatie TNO, 31 May 2018, Zeist, <https://www.voedingsacademie.nl/activities/nav-op-locatie-tno/>
- MyNewGut Workshop: MyNewGut's perspectives for innovations, health claims and impact on public health policies Impact of whole grain wheat on the gut microbiome, resilience and health June 4, 2018
- <https://www.efsa.europa.eu/en/consultations/call/170306>