TOWARDS A FOOD-ALLERGY-FREE WORLD

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TNO innovation for life

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ABSTRACT

Food allergy is one of the most common health disorders in the western world. It affects about three per cent of the total population. Food allergy is potentially lethal, and its health impact is higher than that posed by all known chemicals and microbes in food. It is also higher than that of many other disorders and diseases. Additionally, food allergy's economic impact is immense. Consider, for instance, the high number of emergency hospital visits, even hospitalisations, that are due to food-allergy reactions. And despite the food industry's huge investments in preventive measures, between 30 and nearly 50 per cent of all food recalls are allergen-related.

To reduce society's food allergy burden, three things must be done. First, we need to adequately manage existing food allergies and exposure to allergens. Second, we must prevent the emergence of allergies to new foods. And, third, cures must be found for food-allergy sufferers, and people must be protected from developing food allergies.

During the past 10 years, huge strides have been made. We have better understanding of the risks associated with allergenic foods and proteins, the effects they have on food-allergy sufferers and how we can assess and manage the risks associated with food allergy. TNO is now a world leader in this area. Today, science and technology have reached the stage in which there is a sufficient basis to develop the remaining necessary solutions. In collaboration with universities, clinical centres, patient organisations, authorities and the food industry, the multidisciplinary and non-profit TNO Shared Research Program Food Allergy is aiming high. It intends to dispel remaining existing hurdles and realise necessary innovations to keep us firmly on course **Towards a Food-Allergy-Free World**. And all by 2030.

THE PROBLEM AND CHALLENGES

Food allergy causes substantial distress. Affecting about three per cent of the total population, it is one of the most common health disorders in the western world[1,2]. It has a more detrimental effect on health than chemicals and microbes in food. Especially when one takes into account the enormous impact it has on the lives of food-allergy sufferers and their environment[3,4]. In loss of Disability Adjusted Life Years (DALYs), it is estimated that the health impact of food allergy exceeds, for example, that of skin cancer, Parkinson's disease or cardiac arrest. Loss in DALYs for food allergy is approximately the same as for prostate cancer, asthma and rheumatoid arthritis[2,4]. In a recent prospective study in the Netherlands, for every 100 people affected by food allergies, there were four emergency hospital visits and 0.6 hospitalisations per year[5]. Considering the total number of food-allergy sufferers in the Netherlands (approximately 500,000), these results suggest tens of thousands of emergency hospital visits and several thousand hospitalisations per year in the Netherlands. Compare this with the fact there are less than 100 hospitalisations per year due to food infections in the Netherlands[6]. Food companies invest heavily in preventive measures and risk management. But despite these investments, several studies have shown that between 30 and almost 50 per cent of all food recalls are allergen-related[7].

When a food-allergy sufferer eats an allergenic substance, allergy symptoms may develop within minutes and can range from mild local effects, such as lip swelling or itching in the mouth, to a variety of severe reactions. These can include gastro-intestinal complaints, skin reactions, acute respiratory or cardio-vascular effects, or even potentially fatal anaphylactic shock. There is currently no cure for food allergies. Medication merely suppresses their effects, albeit possibly saving the sufferer's life in the case of a severe allergic reaction (emergency medication). The main focus of managing food allergy is therefore to get the sufferer to avoid all contact with the allergen. This calls for *allergy management*: effective identification and diagnoses of allergy sufferers, helping them to identify unsafe foods and giving them a sufficient choice of safe food products. It also requires *allergen management*: compelling companies in the food chain to adequately manage allergen risks, make effective risk-communication decisions and provide allergy sufferers with useful allergen information.

The growing world population and the increased impact we are all having on the environment demands changes in agricultural practices and food supply. New or improved (climate-resistant) crops, currently unused by-products and alternative sources of food protein can help make our food supply much more sustainable. However, innovations in agricultural practices and food supply will only succeed if they are healthy and safe. Solving one problem must not create a new one. When it comes to products that are based on – or contain – new or modified proteins, allergenicity poses a major potential health risk. To prevent the emergence of food allergies to new foods introduced into our diet, we need adequate and accepted methods and standards for assessing consumers' expected health response to new or modified products.

Managing existing allergies and allergens and prevention of the emergence of new allergies due to food innovation will greatly reduce society's food-allergy burden. But, of course, we must do even more if we are to attain a food-allergy-free world. Curing food allergies or, better still, protecting susceptible individuals (particularly young children and the unborn) from developing food allergies would be the ultimate solution. This would require immune function interventions. A well-balanced immune system is key to overall health and well-being. Disturbances in this balance can cause immune-mediated inflammatory diseases, such as autoimmune, allergic and other chronic inflammatory diseases. Disturbances can also impair immunity, resulting in immunodeficiency, infectious diseases or cancer. Moreover, immunity and inflammatory mechanisms contribute to many diseases and disorders not typically considered to be immunity-related conditions. These include obesity, diabetes, ageing, mental disorders and toxicity in general. Therapeutic or prophylactic food-allergy interventions must therefore not adversely impact immune functions and balances. Currently, we lack the methods and tools to carefully assess and monitor the risks and benefits of immune interventions. We need these methods and tools to develop and apply safe approaches to curing or preventing food allergies.

TOWARDS A FOOD-ALLERGY-FREE WORLD

Today, fundamental science and technology provide sufficient starting points to realise the ambition of a food-allergy-free world. But it will take at least another 10 to 15 years of research to develop the necessary safe therapeutic and prophylactic approaches. Therefore, in addition to this, we'll also need to protect existing food-allergy sufferers and prevent the emergence of allergies to new foods or ingredients introduced into our diet. Reducing society's food-allergy burden therefore relies on three main pillars:

PROTECTION OF EXISTING FOOD-ALLERGY SUFFERERS

PREVENTION OF ALLERGIES TO NEW FOOD PRODUCTS

CURE AND PREVENTION OF ALL FOOD ALLERGIES

PROTECTION OF EXISTING FOOD-ALLERGY SUFFERERS

To optimally protect existing food-allergy sufferers, we must fully understand the health risks of allergens. We must also have adequate risk-management procedures in place. TNO was the first to propose[8] and develop[9,10] a modelling approach to examine and quantify the risks of allergens, based on probabilistic techniques. This approach is now generally, and internationally, recognised as the best way to assess a population's risks[11]. It is an extremely effective way of quantifying allergen risks in food[12]. Since TNO introduced probabilistic modelling in food allergy, other groups in the world have also started to apply it in food-allergy risk assessment. The TNO model also formed the basis for further developing risk-assessment and risk-management approaches in the EU project, *Integrated Approaches to Food Allergen and Allergy Risk Management* (iFAAM), in which TNO is a leading player. Probabilistic risk assessment relies on three key input parameters:

- the sensitivity of food-allergy sufferers
- the consumers' intake of food products
- allergen levels in food products

SENSITIVITY OF FOOD-ALLERGY SUFFERERS

Information on the sensitivities of food-allergy sufferers barely existed in 2002, when we first proposed probabilistic modelling in food allergy. TNO was the first to start systematically collating such information from Double-Blind, Placebo-Controlled Food Challenge (DBPCFC) studies available in literature and clinical centres. In addition, we established a partnership for it with the Food Allergy Research and Resources Program (FARRP) at the University of Nebraska in the US. Today, TNO and FARRP jointly own the world's largest and most complete threshold database. The database is continuously maintained, regularly updated and registered in an e-depot. It allows the production of allergy threshold distributions for allergenic foods.

Information on the sensitivities of food-allergy sufferers does not yet cover all relevant allergenic foods. Data may be generated for some of them through DBPCFC studies, but it's unlikely that sufficient DBPCFC data will become available for all allergenic foods within an acceptable timeframe, or even at all. To expand the threshold database, TNO and FARRP are therefore exploring ways to use other types of data, such as open challenge data. TNO and FARRP are also improving the methods for statistical analysis of threshold data. These activities will provide the needed insight into allergic individuals' sensitivity to most major allergenic foods by 2020.

INTAKE OF FOOD PRODUCTS

Most available, published food-intake data is derived from food-consumption surveys that were initially conducted for nutritional and toxicological purposes. For these, average food intake figures over longer periods of time are usually the appropriate parameter. In food-allergy risk assessment, however, food intake at a single eating occasion is the crucial parameter. TNO therefore developed a database and food-intake distributions specifically attuned to the needs of food-allergy risk assessment.

Given the international nature of food supply and trade, the harmonisation of food-intake figures used in such risk assessment is desirable. TNO and its iFAAM-project partners are collating food-intake data from various European countries in order to harmonise food-allergy risk assessment. The collated data should be available in 2017. TNO will expand its analysis to also include US data by 2018. The data is based on the general population or specific age groups thereof, and not on food-allergy sufferers. It is unlikely that food intake at a population level differs too much between allergic and non-allergic populations. It should not make a significant difference in risk-assessment outcomes. But this still needs validation and confirmation. On TNO's initiative, a study for this validation and confirmation, in collaboration with the Netherlands National Institute Public Health and the Environment (RIVM) and the University Medical Centre Utrecht (UMCU), will be completed by 2019.

ALLERGEN LEVELS

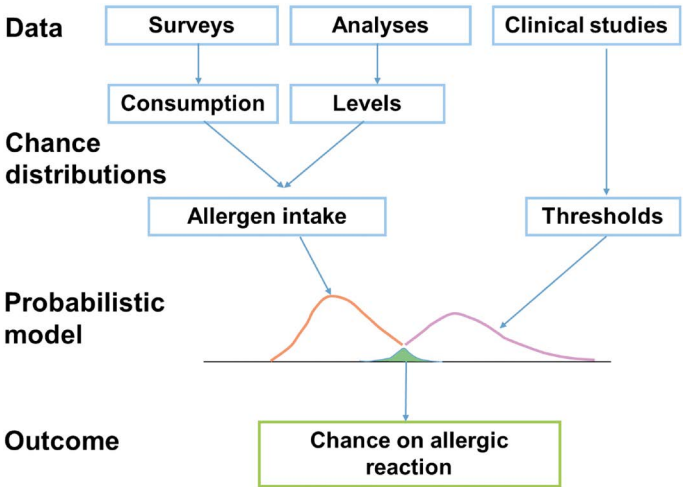
Establishing the presence of an allergen in a food product is one of the main reasons for performing a risk assessment. Information on allergen levels in food products is generally derived from analytical tests. However, this often requires extensive analytical monitoring, which is very ineffective and inefficient for collating information on allergen presence and concentrations in case of incidental traces of allergens. Therefore, TNO is developing modelling approaches for predicting the likelihood and levels of allergen contamination in food products. This will help food producers analyse the risks and develop more effective, efficient and targeted sampling and analysis protocols by 2021. Subsequently, food companies' ability to assess and manage allergen risks will be significantly improved, as will their risk-communication decisions. Ultimately, they will thus be able to give allergy sufferers more useful allergen information.

QUANTITATIVE GUIDANCE FOR PRECAUTIONARY LABELLING

For many years, legislation in most regions of the world has insisted that food manufacturers declare the use of major allergenic foods and ingredients on their product labels. However, allergenic substances may also be inadvertently present in food products, due to cross-contact during transport, storage or in production facilities, for example. Food producers often alert consumers to this risk by using precautionary warnings, such as 'this product may contain peanuts' or 'produced in a factory that also processes milk'. Various studies[12,13,14] have demonstrated that there is limited or no correlation between such warnings and the actual risks. Many products with zero or negligible risk carry warnings, and products without warnings sometimes contain high levels of allergens. The precautionary warnings system has therefore lost its credibility. Consequently, when food allergy sufferers eat, it is often compared to a form of Russian roulette. Whether a food carries a precautionary warning or not. Many of these individuals suffer from one or more unexpected allergic reactions every year, most of which are moderate to severe. Many require emergency medical intervention or hospitalisation[5,15,16]. Clearly, quantitative guidance for precautionary labelling is urgently needed.

Given that we understand the risks of allergens in food, we can establish targets and criteria for its risk management. In 2010, TNO and FARRP developed a proposal for a quantitative guidance for precautionary labelling, based on accepted residual risk levels. Our understanding of allergen risks enabled us to calculate health-based Reference Doses for allergens. They are based on safety objectives agreed upon by key stakeholders. Such Reference Doses can be used to calculate action levels for precautionary labelling. In their Voluntary Incidental Trace Allergen Labelling (VITAL®) system, the Australian-New Zealand Allergen Bureau adopted and implemented the TNO/FARRP proposal[17,18]. Various expert groups reviewed and recognised the VITAL® system and the underlying Reference Doses in several international projects and workshops[19,20,21,22]. Today, many food companies, scientific bodies and authorities apply the VITAL® standards, or use them as a benchmark[23,24]. In 2016, an EU Joint Research Centre and EU DG Santé workshop concluded that the VITAL® approach was not only appropriate, but that such an approach should be developed into a mandatory EU or international system. Meanwhile, the industry was encouraged to apply the approach.

It thus is generally accepted that a system like VITAL® will be the best way of giving allergy sufferers the most meaningful allergy information. However, this does not mean that an internationally applied system is readily available. Before a system can be worked out and accepted, there must first be consensus on the detail, such as the desired safety level and the level of certainty. This will take until at least 2021. Together with our partners, TNO will continue to support the international processes that will provide this solution. Meanwhile, based on an expanded database (from about 1800 to more than 3000 data points) and improved statistical methods, TNO and FARRP plan to update the Reference Dose elaborations in 2017. This will confirm the validity of the previously proposed Reference Doses or propose new ones, such as for allergens for which insufficient data was previously available. We are aiming for an as complete as possible coverage of all major allergenic foods with (provisional) Reference Doses by 2020.



Our threshold database and food consumption database allow the best state-of-the-art risk assessment and development of quantitative guidance for precautionary allergen labeling.[9]

PREVENTION OF ALLERGIES TO NEW FOOD PRODUCTS

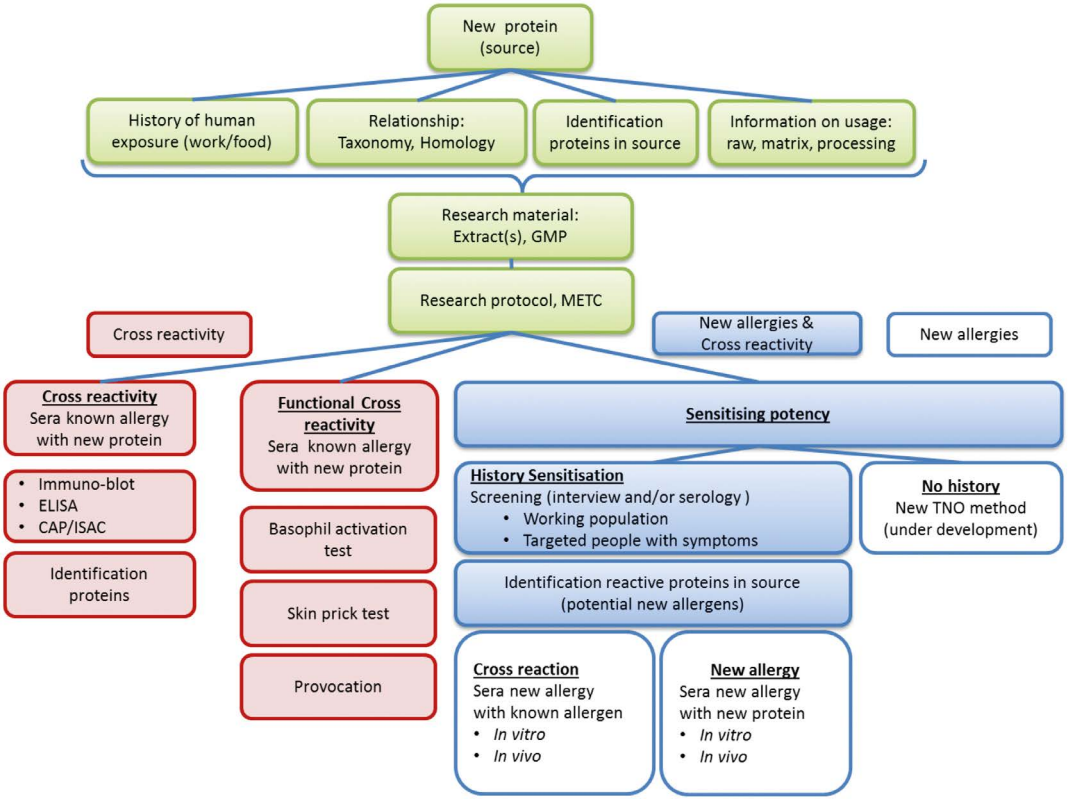
Allergies to new food products can result from cross-reactivity in existing sensitised or allergic individuals or from *de novo* sensitisation of – and development of new allergies in – susceptible individuals. Sometimes, *de novo* sensitisation may manifest itself prior to introduction of a new product in the food chain. This can, for example, be through the development of allergies in production workers, as has been observed for insect proteins. When a history of human sensitisation and potential cross-reactivity are known, methods for assessing such cross-reactivity and *de novo* sensitisation are available. Such methods formed the basis for guidelines to assess the allergenicity of Genetically Modified Organisms (GMO). The EFSA's Genetically Modified Organisms Panel drafted them in 2010[25], and updated them in 2011 (weight-of-evidence approach)[26]. These guidelines, however, are not always directly applicable for new or modified food proteins or protein sources.

ALLERGENICITY ASSESSMENT FOR NEW OR MODIFIED FOOD PROTEINS OR PROTEIN SOURCES

Immunological and clinical methods for investigating cross-reactivity have been available already for many decades. They are constantly being expanded and improved. However, a systematic approach for applying such methods to assess the allergenic cross-reactivity of novel or modified food proteins or protein sources in existing sensitised or allergic populations was not previously available. That is, until TNO, in collaboration with UMCU, developed and published a strategy for it[27]. This strategy was successfully applied to assess the allergenic cross-reactivity of mealworm proteins in an existing food-allergic population. It demonstrated that mealworm proteins cause food-allergic reactions in most shrimp-allergic patients[28,29,30]. The strategy also provides guidance for assessing allergenicity in situations in which a history of human sensitisation to a protein source can be established. TNO and UMCU successfully applied it this way and demonstrated the occurrence of primary food allergy to mealworm in individuals with a history of exposure to mealworms[31]. This proved that *de novo* sensitisation to mealworm proteins can occur and that exposure to mealworm can induce new food allergies.

If no history of human sensitisation to a protein source is known, this does not imply that *de novo* sensitisation cannot occur. However, methods for assessing the risk of *de novo* sensitisation in such a situation are lacking. To develop such methods, we must understand why susceptible individuals become allergic to specific products, and are less likely to become allergic to other products. We must also understand why allergic individuals develop symptoms to very small amounts of certain allergens, while they tolerate larger amounts of other allergens. TNO, in collaboration with The International Life Sciences Institute (ILSI) Europe, has developed an approach for scaling and comparing the population's allergies to different foods. This approach is based on the prevalence of allergy for foods and the sensitivity of allergy sufferers to the foods[32]. It was developed through the application of the generic food safety risk analysis cycle to food allergy. It can be used to prioritise risk management of allergenic foods according to public health relevance. TNO further developed this into a proposal for an approach to express the health impact of a population's exposure to (novel or modified) foods and proteins[33,34]. These developments formed the basis for the EU COST Action Project, *Improving Allergy Risk Assessment Strategy for New Food Proteins* (ImpARAS), initiated and coordinated by TNO. One goal of this project is to further develop parameters for expressing and comparing the allergenic health risks of novel or modified foods and proteins for consumers.

Our vision is that *all proteins are allergenic, but some proteins are more allergenic than others* (derived from George Orwell in *Animal Farm*, 1945). The distinction is made by the response of the susceptible individual. It is therefore key to understand why susceptible individuals become allergic to specific food products and proteins, why they are less likely to become allergic to other products and proteins, and which combinations of factors determine the health response of consumer populations to proteins in food. We investigate this by characterising possible correlations between (combinations of) factors that may play a role, and the allergenic health impact of known, existing food proteins. Factors that are incorporated include digestion in – and absorption from – the gastro-intestinal tract, distribution through tissues, and uptake, processing and presentation by and to cells involved in immune responses. Based on correlations to be established, we aim to develop assays and a multi-parameter model for predicting the health impact of (novel or modified) food protein products in consumer populations by 2023. This will allow the industry and authorities to assess the health risks of possible new products, and thereby informs risk-management decision-making. This will ultimately support the prevention of the emergence of allergies to new food products.



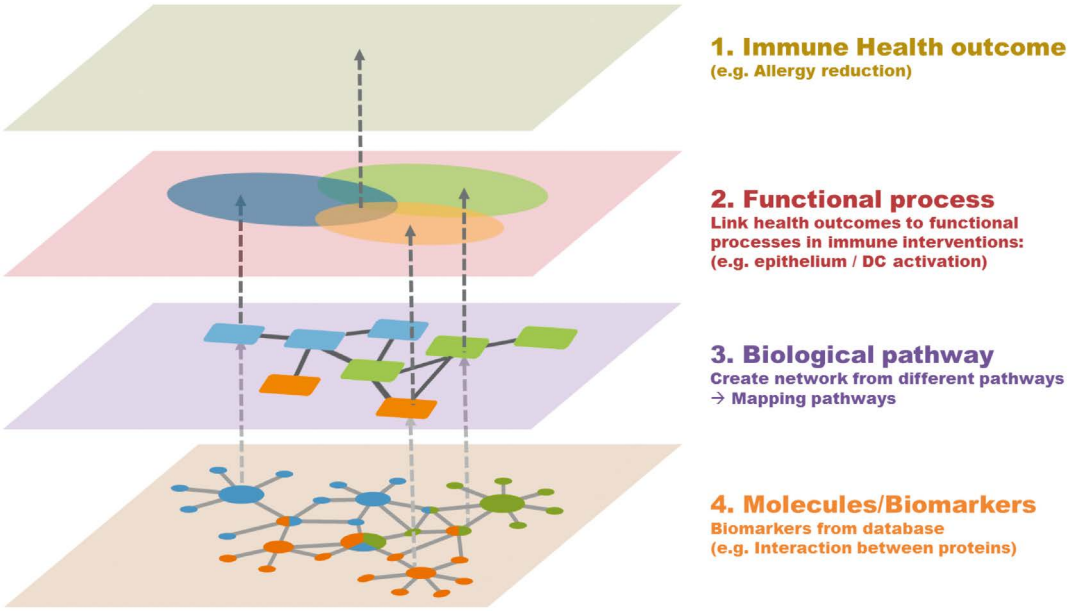
Our systematic approach to assess the allergenicity for new or modified food proteins or protein sources.[27]

CURE AND PREVENTION OF ALL FOOD ALLERGIES

To cure food-allergy patients and protect susceptible individuals from developing food allergies, we must make interventions that influence immune functions and balances. Several starting points for immune-health interventions have been identified. Possible applications are being investigated, particularly for early-life interventions[35]. However, there is a risk that therapeutic or prophylactic food-allergy interventions also adversely impact immune functions and balances. To develop effective and safe therapeutic and prophylactic interventions, we must be able to assess and monitor each intervention's effects and risk-benefit balance. Currently, methods, markers and guidance for this are largely lacking. Given that the repercussions of disturbed immune functionality could be immense, this lack is jeopardising the development of therapeutic and prophylactic interventions. A safe, general cure for – or prevention of – food allergies will certainly not be available anytime soon. TNO's study *Feasibility Early Life Immune Nutrition* (FELINI)[35] investigated the feasibility of developing a generic approach for risk-benefit balance assessment of immune interventions. It concluded that it is indeed feasible to develop guidance on how to identify crucial biomarkers for assessing and monitoring (early-life) immune nutritional interventions and to develop a generic risk-benefit assessment approach. An important role for systems biology was identified. Knowledge of the immune system and its mechanisms has increased considerably during the past 50 years. And during the past 10 years, the application of systems biology has increased our opportunities to study immune pathways and interactions. Today, however, much of the acquired knowledge is still fragmented. Understanding the network of interacting pathways in immune health will be key to developing methods and markers for the effect assessment, monitoring and risk-benefit assessment of immune-health interventions.

TOWARDS RISK-BENEFIT ASSESSMENT IN IMMUNE HEALTH INTERVENTIONS

Before the 1950s, our knowledge of biochemical pathways in living organisms was rather fragmented. Since then, our efforts to systematically identify and analyse interacting pathways have helped us take a huge step forward in understanding the relevant biochemistry. When it comes to pathways in the immune system, we find ourselves at a stage similar to that of biochemical pathways in the 1950s. The challenge for the next decade is to integrate pathway information from many different studies, so that we can develop a map of pathways in immune-health homeostasis and intervention. This will facilitate the development of generic methods and markers for effect assessment, monitoring and risk-benefit assessment of immune-health interventions. In collaboration with clinical research centres, we will help food and pharmaceutical companies to develop therapeutic and prophylactic interventions for cure and prevention of all food allergies.



Our systems-biology approach will support effect assessment, monitoring and risk-benefit assessment of immune-health interventions.

TNO'S SHARED RESEARCH PROGRAM FOOD ALLERGY

The food-allergy challenges we all face are too substantial to be addressed by individual companies or in individual projects. Together, we are stronger. Therefore, TNO has initiated a non-profit Shared Research Program Food Allergy, which is financially supported by Dutch-governmental funding through the TNO Research Cooperation Funds. In collaboration with industry, universities, clinical centres, patient organisations and other bodies, this multidisciplinary program aims to remove existing hurdles and attain the level of innovation needed to reduce society's food allergy burden. The program focuses on the challenges and needs identified in the Dutch Top Sector Agri&Food's Innovation Contract, the European Technology Platform (ETP) *Food for Life* and the Food Safety Vision of the SAFE Consortium. The program will make a significant contribution towards achieving the EU's Horizon 2020 Research & Innovation Program goals. We aim to provide optimum protection for existing food-allergy sufferers by 2021. We plan to make methods and criteria available by 2023 that will help prevent the emergence of allergies to new food products. And we intend to provide methods and markers for effect assessment, monitoring and risk-benefit assessment of immune health interventions by 2030. Thanks to all these aims, TNO is helping to keep us firmly on course **Towards a Food-Allergy-Free World**. And we plan to get there by 2030.

SRP food allergy

www.srpfoodallergy.com

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