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Postlaunch Monitoring of Functional Foods
Methodology development (I)

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Abstract

Already for some years, the development of a Postlaunch Monitoring (PLM) system for functional foods is on the research agenda of several stakeholders involved, e.g. the industries, the government, and research institutes. Up till now, proposals for such a system have been highly hypothetical and only limited experience has been gained through the performance of case studies. The Dutch government is interested in the development of Postlaunch Monitoring studies in case of interference with the safety of the overall food supply. A PLM system could consist of the following phases: a) passive signalling of consumer complaints; b) active signalling of hazardous effects based on (pre- and post-market) research data; c) assessment of the relevance of the data from a and b; d) quantification of the hazardous effects on a population (group) level; e) balancing the beneficial (positive) and the hazardous (negative) effects, i.e. risk-benefit analyses, and f) regulation. Investments in the organisational structure will be necessary to establish decision-making criteria for the different phases of PLM, expert committees for assessment, and methods and frameworks for data analyses, scenario building and modelling techniques. To support our efforts in realising a feasible, cost-effective PLM system we are also extending an invitation to all those involved in the PLM field to respond with suggestions.

Het rapport in het kort

Sinds enkele jaren staat de ontwikkeling van een ‘Postlaunch Monitoring’ (PLM) systeem voor functionele voedingsmiddelen op de onderzoeksagenda van diverse betrokken partijen zoals de industrie, de overheid en onderzoeksinstellingen. Tot nu toe zijn de voorstellen voor een dergelijk systeem grotendeels hypothetisch van aard geweest en is er aan de hand van een aantal beperkte case-studies mondjesmaat ervaring opgedaan. De Nederlandse overheid heeft belangstelling voor de ontwikkeling van een dergelijk systeem in het geval de veiligheid van het totale voedselpakket voor de consument in het geding komt. Een PLM-systeem zou kunnen bestaan uit de volgende fasen: a) passieve registratie van consumentenklachten aan de hand van speciale klachtenlijnen; b) actieve registratie van ongewenste effecten aan de hand van (pré- en postmarkt) onderzoeksgegevens; c) bepaling van de relevantie van de onder a en b verzamelde gegevens; d) kwantificering van de ongewenste effecten op bevolkings(groeps)niveau; e) afweging van de gewenste (positieve) en ongewenste (negatieve) effecten; en f) regulering. Om het systeem operationeel te krijgen zijn investeringen nodig voor het opstellen van criteria en beslisbomen voor het passeren van de verschillende fasen binnen het systeem. Eveneens zullen expertcommissies in het leven geroepen moeten worden om beoordelingen uit te voeren en beslissingen te nemen. Inhoudelijk zullen er standaardmethoden ontwikkeld moeten worden voor de data-analyses waaronder het opstellen van blootstellingsscenario’s en modellering. We nodigen onze collega’s in het veld uit te reageren op dit rapport en mee te discussiëren over het onderwerp om uiteindelijk een haalbaar en betaalbaar PLM-systeem te kunnen ontwikkelen.

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Summary

Introduction
Consumption of functional foods may have beneficial health effects either on a population or individual level. However, potential disadvantages of functional foods consumption might also occur: e.g. health hazards through risks of overconsumption of specific ingredients, risks of interaction effects with other nutrients and/or active constituents in drugs, unclear long-term effects, or potential harmful effects in specific risk groups within the total population. In general, there are two aspects that play a role in the regulation of the functional foods development. First consumer safety should be warranted and second effectiveness should be proven. The demonstration of efficacy (premarket phase) and effectiveness (postmarket phase) of functional foods is regarded as a manufacturers task, provided that the final judgment about efficacy and/or effectiveness has to be made by governmental bodies through evaluation of the dossiers compiled. The warrant of the first aspect: safety, is a more delicate issue. The manufacturer is responsible for the safety of the individual marketed product. The government is responsible for the safety of the overall food supply for the whole population, including subpopulations with increased vulnerability for certain potentially adverse effects. If one or more marketed products interfere with the overall safety of the food supply for the whole population or subpopulations, the government has the responsibility to undertake appropriate action to protect public health. A Postlaunch Monitoring (PLM) system may be needed in order to carry out this task. The *objective* of a PLM system is to systematically monitor (unexpected) effects of functional foods consumption after marketing and under customary conditions of use. The task formulated by the Dutch government, that prompted the Centre for Nutrition and Health of RIVM towards the functional food topic, focused on the exploration of a system to incorporate PLM requirements into current monitoring research activities. This boiled down to three specific questions:

1. what is a useful methodology to assess the intake and the possible associated risks of intake of functional foods in the population given the already existing research activities and the necessities of PLM?
2. for what aspects are investments necessary in order to have meaningful data to monitor any risks in the future?
3. what considerations should be taken into account to decide on necessary investments given the requested input and the anticipated population risks?

Results

A PLM system assessing safety aspects might look as presented below. The term ‘smoke’ refers to any ‘suspicion to some degree’ with respect to potential health hazards due to consumption of functional foods.

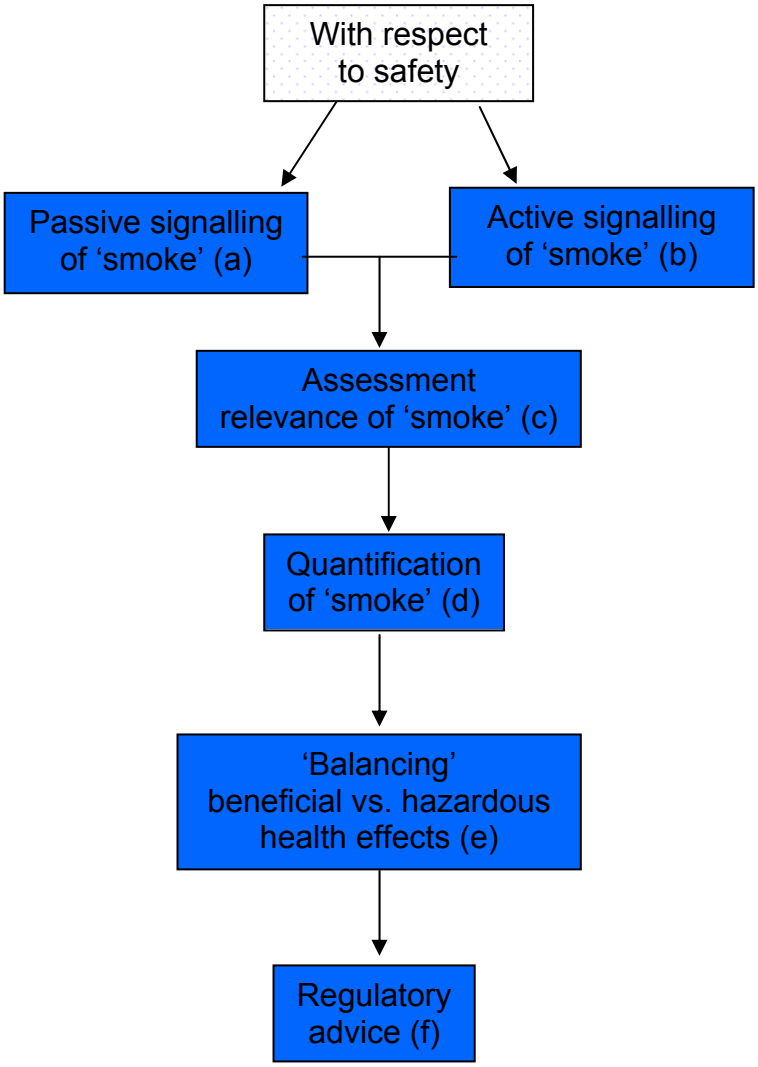

Figure 1: Presentation of a theoretical PLM model focused on safety issues

Below we will shortly discuss the different phases of the PLM system.

a) The main objective of a system that registers the passive signaling of ‘smoke’ or in other words the consumer complaint regarding particular functional foods, is hypothesis generation and should therefore always be operational. A drawback of a passive signaling system is the difficulty of getting the overall picture of the problem. Furthermore, it requires input of specialists to be able to assess causality between the reported problem and the consumption of a particular food.

b) The topic of active research on smoke, is to evaluate whether there is evidence of any potential health hazard that can be related to functional food exposure that might need further research and follow-up. It is not feasible to focus on each and every functional food or ingredient immediately. Criteria should therefore be developed to prioritize the focus of the active signaling. The signals may come from either in vivo or in vitro premarket (exposure) research or in vivo or in vitro postmarket (exposure) research.

c) In case it has been decided that a further safety evaluation might be necessary, it is important to assess the relevance of the smoke, i.e. to assess the potential health hazards for the population or specific subpopulation caused by the consumption of the functional food. For this assessment data are needed with respect to the identification and description of users and their lifestyle, the prevalence and type of functional food and drug usage (intake database), and clinical effects in humans, such as (long-term) health and nutritional status characteristics and/or biomarkers per individual. In this phase, a 'quick and dirty' method has to be applied in order to maintain a speedy process. Either the manufacturer will be informed and has to study the specific problem, or an independent research institute will be assigned to follow the topic either by analyzing existing (epidemiological) backing databases, by defining relevant scenarios followed by modeling exercises, or by performing new focused research.

d) Quantification of the effect is a delicate step because for a *valid* estimate of the risk for the population large datasets are necessary. The penetration rates of newly launched products are usually low, and only slowly increase on an annual basis. In order to have enough power to classify consumers into certain population risk groups, either a combined (EU/global) study-force approach or a realistic scenario building and modeling approach will be necessary in order to estimate and quantify risk on a population or population group level.

e) Risk assessment and the assessment of beneficial health effects have followed different tracks, up till now. The outcome measures of both tracks have been quite different and as a consequence difficult to compare or to balance to each other. So far, therefore, a risk/benefit assessment has been performed on a qualitative (subjective) basis. Quantitative methods (and thus more objective methods) to simultaneously assess both risks and benefits of a given food or compound should be constructed in this PLM phase in order to express the net effect of use of the functional product through the application of a uniform outcome measure such as a composite public health measure.

f) The outcomes of the risk-benefit analyses should form the ultimate basis for the policy decisions regarding the functional food(s) under study. A policy decision tool should be developed in order to end with the functional outcome of the whole process: advice on the particular functional food. This advice may vary from changing the label up to complete market withdrawal.

Below the specific PLM actions involved in the different phases are presented schematically:

PLM phase	PLM actions involved
passive signaling of 'smoke' (a)	- structuralization and evaluation of spontaneous reports of consumer complaints
active signaling of 'smoke' (b)	- prioritizing topics of interest - job assignment to study topics of interest - evaluation of study reports
assessment relevance of 'smoke' (c)	- 'quick and dirty' study track assignment to available research institutes - gathering of 'quick and dirty' data by assigned research institute - evaluation of study reports
quantification of 'smoke' (d)	- study assignment to available research institutes - gathering of data by assigned research institute - evaluation of study reports
risk / benefit analyses (e)	- study assignment to available research institutes - gathering of data by assigned research institute - evaluation of study reports (weighing of pro's and cons)
regulatory action (f)	- construction of summarizing overall report

Figure 2: Overview of the different organisational actions involved with the six phases of PLM

Concluding remarks

Once a theoretical PLM framework has been established a case-by-case approach is advised in order to learn and evaluate the suitability of the whole system. Specific actions for the future may be:

- Formalization of several procedures and defining decision criteria. This could for example be the mandate of a task force representing the institutes involved in PLM activities;
- Installation of a broadly oriented but independent PLM committee: a fair chance for research institutes to collaborate with each other on this topic;
- Investments in optimizing meta-analyses techniques, scenario building techniques, the modeling process, and the development of a risk/benefit equation to reliably complete the evaluative phases of the PLM model;
- Close association with the development of a new National Food Consumption Survey in order to have also data suitable for PLM purposes (intake figures plus at least detailed demographics);

- Pay attention to the accessibility of the existing different backing datasets for PLM purposes;
- Association with the development of modern linking techniques and investments in order to link intake data with registries of morbidity and mortality through different channels.

The question whether the above described investments are necessary given the requested input and the anticipated population risks is difficult to answer at this moment and might be the topic of future work. There is a continuous change in, and enlargement of the functional foods range. Also, new EU legislation is underway which will influence the functional food area and might change the functional food supply as well as the governmental functional food policy involved. In a future assignment RIVM might document risks and benefits of key functional foods. Also collection of recent intake figures should take place as input for scenario building exercises. Basic modeling applications of the available risk/benefit data might then give more insight in any anticipated population risks.

1. Introduction

1.1 Background

It is almost impossible to imagine life today without functional foods as an important topic of interest for industrial food and nutrition developments, academic nutrition research, and/or policy related activities. It is expected that the development of functional foods will continue in the (near) future, provided that the industry will succeed in developing products that meet the whishes of the consumer. Consumption of functional foods may have beneficial health effects either on a population or individual level. In case of significant beneficial effects, the government might want to incorporate promotional or educational activities in its policy. Nonetheless, attention should also be paid to potential disadvantages of consumption of functional foods: e.g. health hazards through risks of overconsumption of specific ingredients, risks of interaction effects with other nutrients and/or active constituents in drugs, unclear long-term effects, or potential harmful effects in specific risk groups within the total population.
There are two aspects that play a role in the regulation of the functional foods development. First and foremost, consumer safety should be warranted. Second, effectiveness should be proven. With respect to the latter, the Dutch Health Council recently advised on the authorization of reduction-of-disease claims in case of strong scientific evidence. As well, the Council suggested to abandon the current policy with respect to the allowance of health claims and to restrain the wild growth of claims suggesting beneficial effects on one's health without any solid scientific proof (1). The demonstration of efficacy (premarket phase) and effectiveness (postmarket phase) of functional foods should be mainly a manufacturers task, provided that the final judgment about efficacy and/or effectiveness has to be followed up by governmental bodies through evaluation of the dossiers compiled. The warrant of the first aspect: safety, is a more delicate issue. The manufacturer is responsible for the safety of the individual marketed product. The government is responsible for the safety of the overall food supply for the whole population, including subpopulations with increased vulnerability for certain potentially adverse effects. If one or more marketed products interfere with the overall safety of the food supply for the whole population or subpopulations, the government has the responsibility to undertake appropriate action to protect public health. This may occur in case of overconsumption or underconsumption of specific nutrients (e.g. due to a growing number of products containing specific active ingredients but lacking other (essential) ingredients or changing dietary habits of consumers), unforeseen adverse side-effects or interactions or unforeseen long-term effects. Not all possible adverse effects may be predictable based on the information assessed before market introduction of a new functional food, analogous to the market introduction of a new drug. To fulfill its responsibility, the government should take care of a timely detection of potential public health hazards. A well designed Postlaunch Monitoring (PLM) system may be needed in order to carry out this task.

The *objective* of a PLM system is to systematically monitor (unexpected) effects of functional foods consumption after marketing and under customary conditions of use. The specific tasks within a PLM system to meet this objective are to:

1) assess the intake of functional foods in the population or special risk groups within the population (prevalence, amounts, duration, consumption of similar foods, consumption of potential interactive substances etc.);
2) detect potential hazardous (expected or unexpected) effects of consumption of functional foods;
3) evaluate whether the potential hazardous effects are of public health significance;
4) quantify the potential hazardous effects on a population (group) level, after which a quantitative weighing of pros and cons may take place;
5) formulate regulatory actions.

The task formulated by the Dutch government, that prompted the Centre for Nutrition and Health of RIVM towards the functional food topic, focused on the exploration of a system to incorporate PLM requirements into current monitoring research activities. This boiled down to three specific questions:

1. what is a useful methodology to assess the intake and the possible associated risks of intake of functional foods in the population given the already existing research activities and the necessities of PLM?
2. for what aspects are investments necessary in order to have meaningful data to monitor any risks in the future?
3. what considerations should be taken into account to decide on necessary investments given the requested input and the anticipated population risks?

1.2 Demarcation

In the scientific as well as the political scene, several definitions of foods with (potential) health enhancing characteristics are used. Below we will give a brief overview of the most important types of products that may play a role in PLM and describe which foods this report is focused on.

In 1997, the EU regulation EG/258/97 came into force in which ‘novel foods’ were described. The Dutch Health Council initially proposed to categorize novel foods into three types: first, the so-called exotic foods, habitually consumed outside the EU, second the genetically modified foods and third the foods containing the so-called bio-active ingredients. This latter group might also be defined as functional foods, but not all functional foods are novel. For example, enriched foods (e.g. vitamin and mineral enriched) may be categorized as functional but are not regarded as novel because vitamins and minerals are known to be traditionally safe substances present in all types of food. For these vitamin and mineral enriched foods a special EU regulation has been proposed in 2003. The rules laid down in this regulation focus among others on the purpose of enrichment, chemical forms allowed,

types of foods allowed, maximum and minimum amounts (to be established), and labeling (2).
Another category of products that may need PLM are the dietary supplements. In the EU dietary supplements are nowadays regarded as foods but appear in pharmaceutical forms like pills, powders, elixirs, capsules etc. Again the EU aims at a harmonization of the existing member state legislation and recently launched regulation 2002/46/EG which focuses especially on supplements containing vitamins and minerals. Other products with potential health enhancing capacities are herbal supplements, and supplements containing substances other than vitamins and minerals (amino acids, essential fatty acids etc.). For the herbal supplements several registry procedures have been proposed and three EU regulations have been proposed (i.e. the Regulation 2002/46/EG, the Regulation with respect to claims (SANCO/1832/02) and the Regulation for traditional herbal medicines (2003/63/EG). For the other supplements the current EU state of affairs is yet unestablished.
For this report we will keep two types of novel foods in mind: those with specific bio-active components, and the exotic foods. In addition we will take the enriched foods and the vitamin and mineral enriched supplements into account, because cumulative effects may especially play a role in case enriched foods and supplements are taken concurrently for a longer timeperiod. We will deliberately not include genetically modified foods as there are special EU regulations for these types of foods and the postmarket policy for these foods and the possible associated risks might involve development of a different monitoring system. As well, herbal products will not be taken into account. Again, a different registration procedure for herbal products is proposed and as a consequence PLM activities might need adaptation from the 'standard'. For the sake of readability, we will however use the term 'functional food' in this report when we refer to the above mentioned products.
Furthermore, in this report we will prioritize integration of existing research activities in the field of *dietary intake assessment* and PLM in the Netherlands. The reason is to have grounded information underpinning the present and urgent debate about the contents of a future food consumption signaling system. Where possible we will, however, take broader research activities into account. Last but not least, we will mainly focus on safety aspects involved and not so much on efficacy and/or effectiveness aspects, because research on these latter aspects is mainly regarded as the manufacturer's responsibility. Therefore, the development of guidelines for the evaluation of efficacy/effectiveness dossiers will be a separate undertaking and will not be a topic of the current report. It should be noted however that this piece of information is nevertheless needed to be able to weigh the pros and cons of functional food consumption quantitatively (task-point 4 of PLM; see paragraph 1.1).

1.3 Approach

To give some background information about the state of the art regarding the existing EU and/or Dutch premarket and postmarket regulations we will start with a brief explanation about the 2003 situation. Second, we will take the set-up of the theoretical PLM model as has

been proposed earlier (3) as a starting point for the description of the necessities to perform adequate monitoring of the newly launched products. Third, we will give an overview of existing research activities with respect to dietary intake assessment in the Netherlands. Fourth, we will describe the possibilities of an integration, stress the opportunities and challenges involved in the set-up of PLM and we will finalize the report with our concluding remarks.

2. State of the art regarding premarket and postmarket safety regulations for functional foods

2.1 Premarket (safety) regulations up till 2003

2.1.1 Novel foods

The European novel food regulation has come into force since 1997 (EU/258/97). In this regulation rules for market admission of those foods that have not yet appeared on the EU market, have been described. In the Netherlands mainly three types of novel foods are recognized by governmental bodies (4). Firstly, exotic foods that are consumed in other parts of world outside the EU are noted, second GMO's (genetically modified foods) and third foods with specific bio-active compounds are mentioned. The foods with specific bio-active compounds might also be called functional foods, however, functional foods are not quite the same as novel foods. For example foods with extra vitamins or minerals are not regarded as novel, as vitamins and minerals are usual ingredients in all sorts of foods. As such, enriched foods are treated as a different category by law. The Dutch government has introduced another term to indicate these special foods namely, 'specific health enhancing foods'. A specific health enhancing food might be a novel food, but could also be a vitamin-enriched food with a proposed beneficial health effect.

Manufacturers who would like to market their novel food have to submit an application according to EU guidelines (Recommendation 97/618/EG, Regulation EG/259/97). This application may be submitted in any of the EU member states. The European Committee and the other member states will be informed about the eventual evaluation of the application by the member state of the manufacturers choice. The novel foods are evaluated on chemical-analytical, nutritional, microbiological, toxicological and epidemiological safety aspects. Until recently, the 'Scientific Committee on Food (SCF) acted as a scientific advisory committee with respect to market admittance of novel foods for the European Committee. Nevertheless, after the formal installation of the European Food Safety Authority (EFSA) in January 2002, a new system came into force with a higher level of transparency, participation and communication. In 2003 eight new scientific panels have been established that differ in the types of food or compounds they focus on. Among others, there is one panel that focuses on the GMO's that have been defined in EU regulation 2001/18/EU. The chairpersons of all panels completed with six independent experts form a so-called umbrella scientific committee. This committee coordinates the activities and focuses on the disclosure of consistent advice to EFSA (http://www.efsa.eu.int). If one or more of the EU member states do not agree with the evaluation results of the first member state, the opinion of the panel will be requested. The original evaluation, the objections and, if necessary, complementary information will be weighed in the final European recommendation. In the Netherlands, the EU novel food regulation has resulted in the installation of the Health Council Committee on the Safety Assessment of Novel foods (Committee VNV) in 1999. This committee consists of

experts with different backgrounds and affiliations and assesses the safety data supplied by the manufacturers based on current scientific knowledge. The committee presents her findings to the Minister of Public Health, Welfare and Sports who in turn represents the Netherlands as a member state. Especially, absence of proven harmful effects and the similarity with 'traditional' well-known safe foods are checked. After several years of experience, the committee is now able to evaluate applications in a consistent and standardized way (4). The committee is of the opinion that a multidisciplinary approach is important. Future focus points will be the finalizing of a) the evaluation protocols, and b) recognized measurement techniques as well as definitions of for example safe novel food use.

2.1.2 Enriched foods

The nutrients most commonly added to foods are vitamins and minerals. Vitamins and minerals can voluntarily or compulsory be added to food. Compulsory addition may be the case for particular foods for nutritional uses, such as dietetic foods, infant foods, flour and salt. This may be dictated by EU law or national law. Voluntary addition of vitamins and minerals is done for three purposes:

- restoration: the level of vitamins and minerals is elevated up to the original level of the particular food before storage, handling and manufacturing;
- substitution: a substitution with a product that resembles the original food with respect to taste, smell, color, appearance and nutritive value;
- fortification: enrichment of foods with extra vitamins and/or minerals irrespective of whether or not the nutrients are originally present in the food.

By the end of 2003 the EU Commission presented a new regulation in which it is attempted to harmonize the rules on the voluntary addition of vitamins and minerals (2). The Commission recognizes that in general the availability and consumption of certain enriched foods can make a significant contribution to adequate nutrient intakes. On the other hand a liberal policy with respect to fortification might result in excessive intakes of certain nutrients and may undermine consumer knowledge of basic nutritional principles and perception of foods. Up till now the latter concern is not supported by any evidence for such adverse effects in countries having experience with a liberal policy regarding addition of nutrients. As well, according to manufacturer data in these countries, fortified foods represent only 1-6% of the total food supply. As a consequence, cumulative effects as such are not very likely. The maximum total amount of the vitamins or minerals in food shall not exceed amounts that have to be set in the near future. With respect to maximum amounts a) the upper safe levels of intake established by scientific risk assessment based on generally acceptable scientific data and b) intakes of vitamin and minerals of other dietary sources will be taken into account. The minimum amounts should at least be at a level that will contribute significantly to any benefit to consumers. Otherwise the presence of extra vitamins and minerals will be unimportant and should not be allowed to be declared in nutrition labeling to avoid misleading of consumers. In this 2003/0262 EU regulation a list of the chemical forms of vitamins and minerals allowed has been annexed.

In the Netherlands, since 1996 the status quo has been that vitamins and minerals may be added to foods at levels at which the most probable daily consumption will be 15% at a minimum and 100% at the maximum of the recommended daily allowance. Addition of vitamin A (retinoids), vitamin D, folic acid, selenium, copper and zinc has only been allowed in the case of substitution and restoration. Only recently, addition of vitamin A to yellow bread spreads has been liberalized and an amendment has been accepted for vitamin D: up to a maximum of 50% of the RDA is allowed in yellow bread spreads with the restriction that the product should be advertised for people over 60 years of age (5) Before launching a fortified product on the Dutch market the manufacturer should give notice to the Dutch government, but any other relay of information is not necessary.

2.1.3 Dietary supplements

The rules for dietary supplements have been adopted in a different EU regulation (2002/46/EC) (6). Dietary supplements are regarded as products which appear in concentrated sources like the pharmaceutical forms as pills, tablets, capsules, sachets of powders, ampoules of liquids and/or drop dispensing bottles. Dietary supplements may contain vitamins and minerals, but could also contain other ingredients like fatty acids, fibers, amino acids, and plants and herbal extracts. The plants and herbal extracts are regarded as a separate category for which a separate regulation has been proposed. For consumers, in general, the difference between food supplements and (OTC (over the counter)) drugs may not always be so clear as their appearance is identical. Nevertheless, a food supplement may not contain any ingredients that are registered as drugs and may not bear any medical claim. In addition, an adequate and varied diet could, under normal circumstances, provide all necessary nutrients for normal development and maintenance of a healthy life, so statements relating to any insufficiency within this context are forbidden. Detailed information about special needs for special riskgroups across the population may be given if the necessity for extra requirements has been proven scientifically. The chemical forms of the vitamins and minerals which may be used in the manufacture of the foods supplements are listed in the regulation. Maximum and minimum amounts of vitamins and minerals per daily portion still have to be set. With respect to nutrients other than vitamins and minerals (e.g. amino acids, essential fatty acids, fiber) EU rules have to be adopted at a later stage. Up till then national rules will apply. In the Netherlands the Food and Commodities Act will be used. With respect to amino acid supplementation a tolerance policy based on a report of the Dutch Health Council (Safety of amino acid supplementation (1999/06)) is applied.

2.2 Postmarket (safety) regulations up till 2003

Postlaunch monitoring (PLM) has been a far less developed activity than the activities encountered in the premarket phase. Several reports investigating ideas about possibilities and requirements for PLM have been published (4, 7, 8). In the recent Health Council report four focal points of PLM have been described: 1) a government supported complaints line for

all consumer complaints associated with health and foods, 2) a continuous monitoring of consumption data for foodstuffs, carried out jointly by government and industry, 3) epidemiological prospective cohort studies into the relationship between chronic diseases and diet, 4) active market monitoring carried out by industries to check the accuracy of the presumed safe intake by the target group. ILSI suggests in her report (8) to focus PLM activities on three aspects: 1) is use of the novel foods as predicted or recommended, 2) are expected effects as predicted, 3) does the use of the food result in unanticipated effects? ILSI proposes to utilize marketplace surveys to establish which consumers are using and in what amounts, market research data to confirm initial safety assessment, and the telephone customer care lines to establish the absence of any (acute) effects. An example of a first PLM activity on novel foods is the study on phytosterol enriched margarine performed by Unilever upon request of the EU Scientific Committee on Food. Unilever was asked to collect data to estimate the extent to which the product is reaching its target group and to estimate exposures to phytosterols from this source in other population groups. Through telephone care lines and market surveys demographic consumer information was obtained in addition to household intake figures which were extrapolated to individual intake figures. Also the consumer comments and complaints obtained through the telephone care lines of the company were evaluated on causal relationships between reported adverse symptoms and consumption of the phytosterol enriched margarine (9). The main conclusion of the Scientific Committee on Food was that the PLM obtained by Unilever obtained valuable information especially with respect to product consumption. However consideration should be given to developing guidance for the future design and conduct of such studies.

3. Theoretical PLM model

The general opinion among the Dutch experts is that PLM for functional foods should focus mainly on the safety aspects involved in the consumption of these products. Based on the outcome of an earlier undertaking to define PLM tasks (3) a PLM system assessing safety aspects might look as follows:

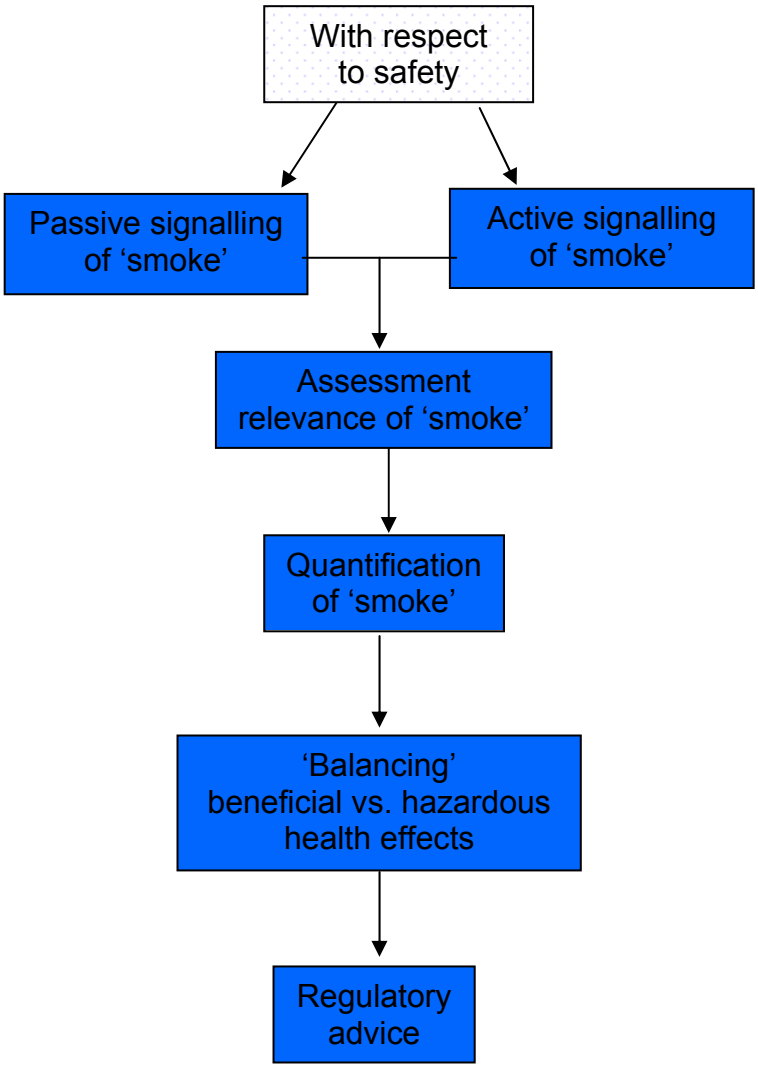

Figure 3.1: Presentation of a theoretical PLM model focused on safety issues

The term 'smoke' refers to any 'suspicion to some degree' with respect to potential health hazards due to consumption of functional foods. Below the different phases of the PLM system are discussed separately. In each paragraph the meaning and the purpose of each phase is described and the specific actions that have to be executed to get the proposed PLM system operational are defined.

3.1 Passive signaling of ‘smoke’

3.1.1 Background

The main objective of a system that registers the passive signaling of ‘smoke’ or in other words the consumer concerns regarding particular functional foods, is hypothesis generation. If it is decided to develop a PLM system for functional foods, the passive signaling should therefore always be operational. One of the pitfalls of a passive signaling system is the ‘tip of the iceberg’ problem, i.e. it is difficult to get the overall picture of the problem. Furthermore, it requires the input of specialists to be able to assess causality between the reported problem and the consumption of a particular food.

3.1.2 Interviews with experts

In order to get more insight in the background and operationalization of (existing) registrations of consumer complaints as well as to hear expert views on the development of a signaling system for functional foods, interviews were performed with representatives of several parties concerned, i.e.:

- Dutch Health Council
- Inspectorate for Health Protection and Veterinary Public Health
- Netherlands Nutrition Centre
- Netherlands Pharmacovigilance Foundation
- National Poisons Information Centre
- Dutch Consumer Association
- producers of functional foods (i.e. Unilever, Yakult, Campina).

In short, experts do not expect many complaints being ventilated by consumers. Products most likely to induce complaints are thought to be supplements and enriched foods. The existing premarket safety regulations for novel foods are supposed to prevent difficulties and as a consequence only few complaints are anticipated for these type of foods. The nature of the potential complaints might predominantly be unspecific like headache, skin rashes, gastro-intestinal problems, total malaise, and asymptomatic allergy.

3.1.3 PLM actions to be undertaken

The experts were moderately optimistic about the relevance of a complaints registration system. Outcomes of the interviews revealed two channels of complaint registration: i.e. an independent registry directly accessible for consumers next to an indirect registry in which complaints are filtered through intermediate persons, for example GP’s. In addition, manufacturers should have the duty to report all complaints received. Formalization of the manufacturers duty to report according to strict guidelines may need to be undertaken. According to most experts, complaints received from the different sources should be registered, checked for duplicates, and assessed for causality by an experienced panel. It

might be necessary to educate different assessment panels depending on the different types of food groups and their functionality. Along with the formalization aspects, procedures with respect to confidentiality may need to be established as well as the contents and lay-out of report forms, and last but not least the data-analyses. The panel members should have access to a decision making model about when and how to act. For this decision making model several issues need to be clarified, for example when do we have a serious complaint, how many complaints are necessary before follow-up is needed etcetera. Experiences obtained in the pharmaceutical area could be helpful to tackle this issue. It was advised by most experts to locate the set-up of this registration at the Inspectorate for Health Protection and Veterinary Public Health as this organization is independent, well-known, experienced in the registration field and has the opportunity to take legal steps. Collaboration with the Netherlands Pharmacovigilance Foundation was preferred as this organization is very experienced in assessing causal relationships. Especially, manufacturers and the Dutch Consumer Association would like to have a system that also focuses on effectiveness of functional foods (consumers might have questions about the effectiveness) in addition to safety. Finally, the system should be made widely known to consumers, manufacturers, and intermediate persons like GP's, pharmacists, dietitians etcetera. Thorough education is warranted in order to overcome unnecessarily negative publicity for manufacturers and not to make consumers unnecessarily worried.

3.2 Active signaling of smoke

3.2.1. Background

Again, active signaling of smoke should always be operational because it is also supposed to function as a hypothesis generating action, next to passive smoke (consumer complaints) registration. The topic of active research on smoke, is to evaluate whether there is evidence of any potential health hazards that can be related to functional food exposure that might need further research and follow-up. It is not feasible to focus on each and every functional food or ingredient immediately. Criteria should therefore be developed to prioritize the focus of the active signaling (see 3.2.2). The smoke signals about health hazard evidence will come from two different levels:

a) From in vitro and in vivo premarket studies that have focused on toxicological, microbiological, and/or chemical-analytical safety aspects. Data may be available from the literature and/or from the safety dossiers compiled by the manufacturers according to the EU regulatory guidelines, and/or upon request from ad hoc focused research performed by (independent) research institutes.
b) From in vitro and in vivo postmarket studies. Mostly, the postmarket data will be human data, but new in vitro data and animal data may also provide new insights in risks and benefits related to intake of certain foods or food constituents. Again, (human) data could be collected from the literature available in the public domain and/or from the safety

dossiers compiled by the manufacturers, and/or from focused (clinical) trials performed by (independent) research institutes.

3.2.2 PLM actions to be undertaken

As stated before it is not possible to focus on potential health hazards for each functional food or ingredient that is launched on the market immediately. Therefore a prioritizing phase needs to be incorporated. An independent committee should have criteria available for prioritizing specific topics for active research. The process of prioritizing might be fed by health hazard indications from available premarket safety dossiers and/or readily available information from the public domain. For this, the possibility of a collaboration with the Committee on Safety Assessment of Novel Foods of the Dutch Health Council may need to be explored as they have access to the premarket dossiers. Along with the priority-criteria, elucidation should be given about whom should be assigned to gather these smoke signals (manufacturer, universities, research institutes). As has also been suggested by the US Committee on the Framework for Evaluating the Safety of Dietary Supplements in their report (10) about a proposed framework for evaluating the safety of dietary supplements a scoring system may need to be developed to structure and evaluate the seriousness of the smoke signals. Smoke signals originating from human data have more weight, but evidence may also originate from animal data or in vitro studies. Based on the outcome of these scores it should be decided whether to proceed to the next PLM phase.

3.3 Assessment of the relevance of 'smoke'

3.3.1. Background

In case it has been decided that a further safety evaluation might be necessary, it is important to assess the relevance of the smoke, i.e. to assess the potential health hazards for the population or specific subpopulation caused by the consumption of the functional food. For this assessment specific data need to be gathered:

1. the identification and description of users and their lifestyle;
2. the prevalence and type of functional food and drug usage (intake);
3. data about the clinical effects in humans, such as (long-term) health and nutritional status characteristics and/or biomarkers per individual.

In this phase, a 'quick and dirty' method has to be applied in order to maintain a speedy process. There are two tracks that can provide data on the above mentioned topics:

a) The specific manufacturer has to be informed and has to hand over any data gathered before on the specific problem (if available). In case of an unknown problem to the manufacturer, he/she will have a duty to study the complaint in depth either by performing new trials or by re-analyzing the existent (worldwide) data as is also the case in the pharmaceutical world.

b) An independent research institute will be assigned to follow the topic either by analyzing existing (epidemiological) databases, by defining relevant scenarios followed by modeling exercises, or by performing new focused research.

A potential problem with track a might occur if the ingredient under study is present in many types of functional foods like vitamins and minerals. In that case one specific manufacturer cannot be appointed, which leaves track b as the preferred option. Collaboration between the manufacturer (track a) and research institutes (track b) might be necessary in all cases. In the occasion of a potentially very urgent problem the possibility of buying commercially available datasets in order to have a quick and focused database should be appropriate.

3.3.1.1 Description of available databases

For track b several databases are available in the Netherlands and might be suitable to provide the requested information. In Table 1 we have systematically formulated potential necessities of PLM activities and have described the suitability of the different datasets. Details of all studies incorporated in the inventory are presented in Appendix 1. As stated in the introduction we have mainly focused on those datasets that contain at least dietary intake data, either on individual level or on household level. The summary descriptions in Appendix 1 have been checked with the study contact persons.

Dietary intake

With respect to the intake data, the ideal situation would be to have recent and historical information about individual food consumption figures on food level as well as nutrient/ingredient level. Recent data are necessary in order to reliably estimate the magnitude of a potential problem. The functional food market is a fastly moving market and figures might change rapidly. Questions to be answered are for example: which and how many people do consume product x and in what quantity? Or how many people do consume product x in combination with product y? Historical (long-term) intake data are needed to study long-term effects. At this moment data on household level are easier and cheaper to obtain. Under some assumptions household figures can be extrapolated to individual figures. This has for example been investigated in a preliminary PLM study performed by Unilever (9), in which the mean one-person household consumption levels of phytosterol-enriched margarines appeared to be almost equal to the mean consumption level of the larger (two to four) households. In addition, a UK-FSA (Foods Standards Agency) funded report described the feasibility of nutrition surveillance and postmarket monitoring of potential health effects of novel foods using commercially available datasets on household food consumption and on sales through major supermarkets (11). The study only involved the evaluation of the food product data, as no other health related data could be included. The key questions were whether it was possible to use such data as a means of quantifying possible ‘exposure’ to certain foods and nutrients at a population level and to establish whether there is any socio-economic, geographical or temporal variation in ‘exposures’. In short, several difficulties were encountered with the supermarket sales data, whereas problems with the household

purchase data could be solved satisfactorily. Based on the experience with four different marker products to trace consumption of specific food items, it appeared that the penetration rate of the selected marker foods was low (up to a maximum of 4%). The household purchase data approximately underestimated 30% of total daily energy intake but estimated mean macronutrient intakes (expressed as % of total energy intake) and variances were comparable to those reported in other nutritional studies. Several temporal, geographical and socio-economic differences were detected. As such, the authors conclude that these household purchase data could be used to provide information on population 'exposure' to novel food products. Surveillance of ingredients is not possible based on the currently available coding information. Electronic data about lists of ingredients for each product linked to barcode data would enable this type surveillance. Nevertheless, any appropriate surveillance system needs to correlate (individual) food purchase data to health data. It was concluded that based on household purchase figures ecological analyses (on group level) could be carried out; e.g. to study temporal clusters of health events that might be related to the introduction of certain novel foods. However, to enlarge the surveillance opportunities fine tuning should among others focus on a) the inclusion of both nutrient and product ingredient information, b) linkage between barcodes and brand names, product names and nutrient data, and c) liaison with manufacturers to ensure up-to-date information in the right (electronic) up-to-date format. Last but not least, the authors advised to investigate the possibility to link health events (e.g. hospital admissions, cancer diagnosis etc.) of the household panel to the household purchase data. In that case, obtaining appropriate consents and very likely other questionnaire data would be an important undertaking.
In line with this, in the Netherlands the TNO institute has been investigating the possibilities of using EAN barcodes (European Article Numbering) in a general signaling system (12). The main conclusion was that with the EAN codes intake of some but not all product groups could be estimated accurately on a household level. For the beginning, TNO investigated three types of product groups. From these three groups especially two groups were difficult to estimate: i.e. fresh fruits and vegetables (partly purchased without EAN codes) and chocolate and candybars (part of the consumption not at home). The estimates of the product group containing bread spreads and cooking fats and oils (well-coded with EAN codes) approached the true consumption.
In the Netherlands, there are several large, commercially available datasets containing information about household purchases. At this moment, linking this piece of information to other health related factors of an individual seems to be a bridge too far, but opportunities might be investigated in the near future. Methodological experiences obtained in the DAFNE initiative (Data Food Networking, a databank for monitoring trends in food habits in Europe: www.nut.uoa.gr) may be useful.

Health related data
As stated earlier, the possibility of linkage of dietary intake data to nutritional or health status data including data on complaints, diseases, and medication use is a necessity in order to reach a higher level of safety monitoring compared to what has been done so far. Apart from

the ‘smaller’ scale studies in Table 1 which already have this information for specific subgroups a larger scale set-up may be of interest for the future. A data linkage approach in which individuals are flagged every time they appear in health datasets (hospital admissions, GP-records, disease and mortality registrations etcetera, but also linkage with datasets such as PHARMO) has been suggested earlier by others. Health effects, either short- or long-term, could be monitored and linked to dietary figures obtained in other studies. To have blood samples at disposal would be very helpful to investigate specific suspicions in specific populations. Privacy rules should of course be fully recognized.

Other prerequisites
Other factors of importance to determine the appropriateness of the database is the size of the dataset, as to whether any specific riskgroups can be extracted. Health effects in small groups are difficult to detect, thus effects would have to be large with large variations among groups in order to have meaningful results. Therefore, to have different datasets on different populations at disposal in which specific safety issues can be investigated will be practical. Also, the design of the study is of significance. Linkage of temporal trends in health outcomes to surveillance data related to the time of introduction or withdrawal of a functional food on the market should be possible

*Table 1, part 1: Indicative systematic overview of potential databases that might be of use for PLM purposes**

STUDY	Study description		Sample			Dietary intake	
	type of study	period	n baseline (n follow-up)	composition	age at baseline	method	type of information
DNFCS / VCP	monitoring	1987/88, 1992, 1997/98, 2003 (partly), ongoing	± 6000	F + M / general population	>1y	2-day dietary record and additional FFQ	product level + nutrient level
Zutphen Elderly Study	cohort	1960, 1985, 1990, 2000, finished	878 (171)	F+M / Zutphen	40-59 y	dietary history	product level + nutrient level
PPHV (peilstation)	monitoring	1987 – 1991	± 36000	F + M / general population	20-59 y	global FFQ	product level
MORGEN	monitoring	PPHV, 1993-1997 partly ongoing	± 23000	F + M / general population	20-59 y	extensive FFQ	product level + nutrient level
Doetinchem cohort	cohort	PPHV, MORGEN, 1998-2002, 2003-present, ongoing	6400 (4650)	F + M / general population	20-59 y	extensive FFQ	product level + nutrient level
Maastricht cohort	cohort	PPHV, MORGEN, 1998, 2000, 2003	13000 (2300)	F + M / general population	20-59 y	extensive FFQ	product level + nutrient level
Hartslag Limburg	monitoring / intervention	1998, 2000, 2003	3000 (2300)	F + M / general population	20-59 y	extensive FFQ	product level + nutrient level
Amsterdam cohort	cohort	PPHV, MORGEN, 1998-2002 (EPIC)	± 4500 (± 2300)	F + M / general population	20-59 y	extensive FFQ	product level + nutrient level
EPIC	cohort	1992-2000 ongoing	520000	F + M / general population	35-70 y	extensive FFQ	product level + nutrient level
Prospect-EPIC	cohort	1993-1997 ongoing	17500	F / Utrecht	50-70 y	extensive FFQ	product level + nutrient level
Utrecht health monitoring study (Leidsche Rijn)	cohort	2000 – present, ongoing	5500 + annual increase	F + M / Leidsche Rijn (Utrecht)	all	few indicator questions	very global
PIAMA	cohort / intervention	1996/1997 – present, ongoing	4000	F + M / children	0 till 8 y	specific FFQ	product level
SENECA	cohort	1988/89, 1995, 2000	2590 (1221, 715)	F+ M / elderly population	70-75y	dietary history, dietary habits	product level + nutrient level
NLCS	cohort	1986 – present (subcohort of 5000), ongoing	121000	F + M / general population	55-69y	FFQ: 150 food items	product level + nutrient level
ERGO – R'dam	cohort	1990/1993 – present, ongoing	8000	F + M / Ommoord, R'dam	>55y	FFQ: 170 food items	product level + nutrient level

part 1 continued:

Hoorn study	cohort	1989, 1996-98, 2000-01 (partly newly sampled), 2006, ongoing	2500 (1513)	F + M / Hoorn	50-75 y	FFQ	product level + nutrient level
CoDAM	cohort	1999-2000 (partly from PPHV and MORGEN)	574	F + M / specific inclusion criteria	40-70 y	FFQ	product level + nutrient level
LASA	cohort	1992-93, 1995-96, 1998-99, 2001-02 2002-03 (new cohort), present, ongoing	3,107 (1,691)	F + M / elderly population	>55y	10 item questionnaire	global
AGAHLS	cohort	1977-81, 1985, 1991, 1996, 2000, 2004, ongoing?	600 (450)	F + M / adolescents from Amsterdam and Purmerend	13 y	dietary history method with cross-check	product level + nutrient level
MONICA (NL did not participate)	monitoring	1982-1992	10 million	F + M / general population	25-64 y	3 day unweighed dietary record only in subsample	product level + nutrient level
GLOBE	cohort	1991, follow-up: annually or bi-annually, ongoing	19000 (5700)	F + M / Eindhoven	15-74 y	FFQ: 58 items in subsample remaining sample: few indicator questions	subsample: product level + energy and fatty acids remaining sample: global
Generation R	cohort	2002, ongoing	10000	F + M / newborns in Rotterdam	newborns	FFQ	product level + nutrient level
ABCD study	cohort	2003/2004, ongoing	7600	F + M / newborns in Amsterdam	newborns	fish and supplemental intake	only fish rather detailed
Netherlands Twin Register	cohort	1986, ongoing	32000	F + M	0-15 y, 15-30 y, > 30 y	2-diet records (subgroup)	product level + nutrient level
Monitor VGZ	monitoring	data collection every 4-5 years, national data available from 2004, ongoing	2000-3000 each year (expected)	F + M / general population	18-65 y	few indicator questions	vegetables, fruit, and fruit juices, bread, bread spreads, cooking fats, breakfast habits
PGO-peilingen	monitoring	1991- present, ongoing	6000	F + M / children from the general population	0-21 y	20 item recall (1993-1994)	product level
POLS	monitoring	from 1997 – present ongoing	20000	F + M / general population	all	no	-
REGENBOOG	monitoring	1999-2001 (sample from POLS)	5500	F + M / general population	>12y	FFQ focused on WHO guidelines	vegetables, fruits, red meat, fats and oils
Dutch national survey of general practice	monitoring	1987-1988, 2000-2002	195 GP's 390000 patients	patients: general Dutch population	all	few indicator questions	fruit and vegetables, potatoes, fats and oils, bread, dairy foods, sandwich filllings

*Table 1, part 2: Indicative systematic overview of potential databases that might be of use for PLM purposes**

STUDY	Nutritional status		Health status			morbidity / mortality registration	Blood samples available
	body composition #	blood parameters	collection of disease data	determinants	questions on drug use		
DNFCS	self-reported	no	no	global	no	no	no
Zutphen Elderly Study	measured	yes	illness and disorders	detailed	yes	yes	yes
PPHV (peilstation)	measured	yes	CVD	detailed	yes	yes	yes
MORGEN	measured	yes	chronic disorders	detailed	yes	yes	yes
Doetinchem cohort	measured	yes	CVD and other chronic disorders	detailed	yes	yes	yes
Maastricht cohort	measured	yes	CVD and other chronic disorders	detailed	yes	yes	yes
Hartslag Limburg	measured	yes	CVD and other chronic disorders	detailed	yes	yes	yes
Amsterdam cohort	measured	yes	CVD and other chronic disorders	detailed	yes	yes	yes
EPIC	measured	yes	cancer and other chronic disorders	detailed	yes	yes	yes
Prospect-EPIC	measured	yes	cancer and other chronic disorders	detailed	yes	yes	yes
Utrecht health monitoring study (Leidsche Rijn)	measured	yes	extensive registry of diseases and use of medical care	detailed	yes	yes	yes
PIAMA	measured	yes	respiratory disorders and allergies	detailed	yes	yes	yes
SENECA	measured	yes	chronic diseases	detailed	yes	yes	yes
NLCS	self-reported	yes	cancer	detailed	yes	yes	yes (subcohort)
ERGO – R'dam	measured	yes	CVD and other chronic diseases, use of medical care	detailed	yes	yes	yes
Hoorn study	measured	yes	CVD and diabetes, and diabetes complications	detailed	yes	yes	yes

part 2 continued:

LASA	measured	yes	lung disease, CVD, CVA, diabetes, cancer arthritis	detailed	yes	yes	yes
AGAHLS	measured	yes	a.o: CVD, lung function, skeletal disorders, diabetes	detailed	yes	no	yes
MONICA (NL did not participate)	measured	yes	CVD, stroke, registration of medical care	detailed	yes	yes (some research centres)	yes (some research centres)
GLOBE	self-reported	no	hospital admissions, cance registry	detailed	yes	yes	no
Generation R	measured	yes (maternal and child)	CVD, diabetes, obesity, infectious diseases	detailed	yes	yes	yes (maternal and children)
ABCD study	parents: self reported child: measured	yes (maternal), neonatal screening samples	general diseases (partly to be determined)	detailed	yes	only child mortality	yes (maternal)
Netherlands Twin Register	measured in subgroups	yes in subgroups	chronic diseases	detailed	yes	yes	yes (subgroups)
Monitor VGZ	self-reported	no	chronic diseases	facultative indicators (differs per municipal health service)	different per municipal health service	no	no
PGO-peilingen	measured	no	general diseases	global	yes	yes until 1995	no
POLS	self-reported	no	general diseases	global	yes	no	no
REGENBOOG	measured	yes	chronic and infectious diseases	detailed	yes	no	yes
Dutch national survey of general practice	self-reported	potentially available from GP records but otherwise: no	GP records on chronic and acute diseases	detailed	yes	GP records during the study period, no follow-up	no

***** indicative list: other studies not referred to in this table might potentially be suitable too

in case of self-reported data, body composition mainly constitutes height and weight.

3.3.1.2 evaluation of the databases

As stated before, in order to be able to assess the magnitude of the problem in this fastly moving functional food area, recent intake figures are needed. A regular National Food Consumption Survey (NFCS) will be a suitable vehicle for this, but perhaps a commercially available dataset on household level might also be appropriate. Based on recent intake details, one is better able to evaluate whether there might a serious safety problem that needs to be followed up. By illustration: we are unable to estimate the intake of products enriched with phytosterols based on the former NFCS data (1998) as these products have been marketed from 1999 onwards. Of course, the more details like socio-demographics or data on nutritional and health status or endogenous factors are being gathered with, for example the NFCS, the more questions can already be
answered based on this single dataset. Remaining issues after analyzing the initial dataset need to be investigated in specific cohort or monitoring databases (described in Table 1) depending on the type of problem investigated (e.g. depending on the (size of) risk groups, target groups (children, the elderly, middle-aged people, people with specific diseases), type of functional food, type of possible interaction, time and onset of adverse effects etcetera). These specific databases will function as so-called backing databases. As a consequence, it would be helpful to describe users from the NFCS database as detailed as possible in order to select the most suitable backing database. Through this two-step fragmented approach it might not be necessary to evolve a complete new and expensive inventory just for PLM purposes.

3.3.2. PLM actions to be undertaken

In order to decide on which ‘quick and dirty track’ (a or b or a combination) should be followed, again a decision making structure should be developed. To have the future NFCS also suitable for part of the PLM purposes, attention is in place during the designing phase of the new NFCS. It will also be necessary to formalize and point out any collaboration activities with respect to the use of the datasets described as these systems are at disposal at different institutes. Scenario building and modeling techniques are to be developed as an aid to estimate the relevance of the smoke or in other words the risk on a population or population group level. And again a scoring system for a committee should be developed as to determine whether the population health risk, seems to be serious enough to follow on to the next step, the quantification of risk.

3.4 Quantification of risk

3.4.1. Background

This is again another delicate step because for a *valid* estimate of the risk for the population large datasets are necessary. The penetration rates of newly launched products are most of the time not very high, and only slowly increase on an annual basis. In order to have enough power to classify consumers into certain population risk groups, either a combined (EU/global) study-force approach or a realistic scenario building and modeling approach will be necessary in order to estimate and quantify risk on a population or population group level. If risk quantification should

be done with the help of real data it is preferred to include several (prospective) studies. Meta-analyses in order to synthesize the evidence from several studies should be utilized. A second supporting approach yet to be developed will be again realistic scenario building and modeling of the various options in order to not only estimate but also quantify risk on a population or population group level. This scenario building should be fed by realistic figures extracted from the existing datasets as described in paragraph 3.4.1. Requirements for this approach will especially focus on exposure assessment (market penetration of the new products, user characteristics, dietary intake and intake of the functional foods, drug use etc.) as well as general population statistics like the composition of the population (definition of risk groups), prevalence of morbidity or mortality etcetera.

3.4.2 PLM actions to be undertaken

If the outcomes of the 'quick and dirty' method point towards a serious health hazard in the population or subpopulation, the independent committee should come into force and decide on whether it is necessary to have more quantitative data through performance of further meta-analyses or modeling activities. These further activities will be time-consuming so the major question in this phase is whether it is appropriate to perform this step. This depends on the health hazard in case and should be carefully weighed according to the to be developed standards. Perhaps intermediate regulatory actions are necessary while the work load is assigned to research institutes. One of the first investments to be done is to solve the methodological problems involved in the meta-analysis technique. It is therefore proposed to start with an investigation of the prerequisites for meaningful meta-analyses regarding the functional food topic. Also requirements for realistic scenario building should be mapped. The engagement to model the various scenarios in order to estimate and quantify risk on a population or population group level might need an extra impulse through specific investments as the modeling approach is still in a developmental phase. Interpretation of the outcomes needs to be standardized and formalized and should be done in the light of the next step: the weighing of pros and cons of consumption of the functional food under investigation.

3.5 Balancing hazardous vs. beneficial health effects

3.5.1 Background

For many years risk assessment and the assessment of beneficial health effects have followed different tracks. Methodologies for a quantitative *risk* assessment of food compounds have been developed during recent years (13). Also, as a separate track modeling methodologies have been developed to estimate public health benefits in terms of prevented morbidity or mortality in a population due to changes in for example food or nutrient intake in that population (14). Up till now, the outcome measures of both tracks have been quite different and as a consequence difficult to compare or to balance to each other. Therefore, so far, a risk/benefit assessment has been performed on a qualitative (subjective) basis. Quantitative methods (and thus more objective methods) to simultaneously assess both risks and benefits of a given food or compound are under

construction and have been spuriously applied. Fish (15) and drinking water (16) are known examples from the literature. The key objective of the simultaneous approach is to express the net effect of use of the functional product through the application of a uniform outcome measure such as a composite public health measure. Examples of overall composite measures are: HLE (healthy life expectancy), QALY's (Quality Adjusted Life Years) or DALY's (Disability Adjusted Life Years), or even a monetary unit (cost-effectiveness). At the RIVM Centre for Public Health Forecasting a method based on the calculation of DALY's has been developed. The burden of disease is expressed in DALY's which are the sum of years lived with disease and years of life lost. The amount of years lived with disease is calculated by multiplying the prevalence with previously assessed disability weights. DALY's may be calculated for diseases, but also for risk factors based on the proportion of disease caused by the particular riskfactor. Important information needed to calculate DALY's for a particular risk factor is the Population Attributive Risk (PAR). This is a measure that describes which part of the disease in the population is caused by the particular risk factor exposure. In turn PAR is determined by the prevalence of the risk factor in the population and the degree of association between the risk factor and the disease.
In order to calculate the net effect of functional food consumption it is important to establish how important the health risks are and how important the beneficial effect(s) are. Indications for the importance of the different effects might be revealed from data analyses performed in the previous PLM phases or from established importance-weights published in the literature.

3.5.2 PLM actions to be undertaken

The outcomes of the risk-benefit analyses should form the ultimate basis for the policy decisions regarding the functional food(s) under study. A policy decision tool should be developed in order to end with the functional outcome of the whole process: advice on the particular functional food. This advice may vary from changing the label up to complete market withdrawal. The outcomes of the PLM process might also be helpful to advice on new or more of the same type of functional foods. Again an independent committee should be in charge to prepare the advice and share their thoughts with the policy makers.

4. The PLM decision making process

Along the PLM route several evaluation and decision steps have to be taken. In Table 2 we present schematically which decisions have to be made and for which decisions an independent committee is requested. In case serious health hazards are indicated, it should be possible to take quick ‘in between’ regulatory actions, instead of completing the whole PLM structure up to the last action.

Table 2: Overview of the PLM system, the specific actions involved and the specific necessities. In bold the feasible short-term actions

PLM phase	PLM actions involved	PLM needs
passive signaling of 'smoke'	- evaluation of spontaneous reports	- **development and formalization of procedures** - **construction of decision-making model about when to act** - installation of independent supervising (interpreting) committee
active signaling of 'smoke'	- prioritizing topics of interest - job assignment to study topics of interest - evaluation of reports	- **construction of prioritizing criteria** - arrangement of collaboration structure with the bodies assessing premarket safety dossiers - **development of a scoring system to assess seriousness of the topic** - installation of independent supervising (interpreting) committee
assessment relevance of 'smoke'	- 'quick and dirty' track assignment - gathering of 'quick and dirty' data - evaluation of reports	- **development of structured analyzing techniques** - **investigation of scenario building and modeling techniques** - arrangement of collaboration structure with the institutes having the datasets at disposal - **development of a scoring system to assess seriousness of the topic** - installation of independent supervising (interpreting) committee
quantification of 'smoke'	- job assignment - gathering of data - evaluation of reports	- **mapping of meta-analyses requirements** - putting meta-analyses into operation - **investigation of scenario building and modeling techniques** - putting modeling activities into operation - installation of independent supervising (interpreting) committee
risk / benefit analyses	- job assignment - gathering of data - evaluation of reports (weighing of pro's and cons)	- development of a decision support tool - installation of independent supervising (interpreting) committee
regulatory action	- construction of summarizing overall report	- organization of meeting structure with policy makers - organization of formal/statutory actions

5. Necessary investments?

This report is one of the first structural attempts to body out a PLM system for functional foods. We therefore would like to invite those involved to react on this report and discuss new or other ideas. In the end we should have a feasible system that is manageable at reasonable costs. There is much work to do at different levels. In the first place proposed organizational structures have to be concretized. Second, decision structures have to be developed, and third, methods and frameworks for data-analyses, scenario building and modeling techniques have to be formulated. Once a theoretical PLM framework has been established a case-by-case approach (one product at the time out of the wide range of functional foods) is advised in order to learn and evaluate the suitability of the whole system. It is foreseen that especially the data-analyses and modeling procedures will be a time consuming process. It is proposed to start with the development of the bold-faced items out of Table 2. In summary, special actions for the future are:
- Formalization of several procedures and defining decision criteria. This could for example be the mandate of a task force representing the institutes involved in PLM activities;
- Installation of a broadly oriented but independent PLM committee: a fair chance for research institutes to collaborate with each other on this topic;
- Investments in optimizing meta-analyses techniques, scenario building techniques, the modeling process, and the development of a risk/benefit equation to reliably complete the evaluative phases of the PLM model;
- Close association with the development of a new National Food Consumption Survey in order to have also data suitable for PLM purposes (intake figures plus at least detailed demographics);
- Pay attention to the accessibility of the different backing datasets for PLM purposes;
- Association with the development of modern linking techniques and investments in order to link intake data with registries of morbidity and mortality through different channels.

The question whether the above described investments are necessary given the requested input and the anticipated population risks is difficult to answer at this moment and might be the topic of future work. There is a continuous change in, and enlargement of the functional foods range. Also, new EU legislations is underway which will influence the functional food area and might change the functional food supply. In a future assignment RIVM might document risks and benefits of key functional foods. Also collection of recent intake figures should take place as input for scenario building exercises. Basic modeling applications of the available risk/benefit data might then give more insight in any anticipated population risks.

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Appendix 1 Description of cohort and monitoring studies

Contents

Dutch National Food Consumption Survey (DNCFS/VCP)

TNO Nutrition and Food Research

Objective
Providing information on average food and nutrient intake of the Dutch population.
Type of study
Monitoring study
Period and sampling
Periodically from 1987 to 1998, data were collected once every 4-5 years.
DNFCS-1 in 1987-1988.
DNFCS-2 in 1992.
DNFCS-3 in 1997/1998.
DNFCS-2003
Population
3 DNCFS have been held with different samples of individuals from the Dutch population. Households were selected from an existing representative panel of Dutch household (market research bureau GFK). Institutionalised individuals and households with persons with inadequate fluency in the Dutch language were not eligible. For DNCFS1 and –2, households with a housekeeper (defined as men or women responsible for housekeeping) aged 75 years or over were not eligible either.
The sample in DNFCS-1 (1987-1988) comprised 5898 subjects aged 1-85 y.
The sample in DNFCS-2 (1992) comprised 6218 subjects aged 1-92y.
The sample in DNFCS-3 (1997-1998) comprised 6250 subjects aged 1-97y.
DNFCS-2003 comprised 780 subjects aged 19-30. The sample was not household based: individuals were selected from a representative panel.
Methods
DNFCS 1-3
Dietary intake was measured using a 2-day dietary record method and a limited food frequency questionnaire.
Some lifestyle factors, weight, and height were collected by questionnaire.
Information about sociodemographic variables was already known by the research bureau.
DNFCS-2003
Dietary intake was measured using 2 repeated 24-h recalls and a limited questionnaire on smoking, physical activity, alcohol use, sociodemographic factors, height and weight.
Determinants
Lifestyle: nutrition (nutrients), use of nutritional supplements, special dietary practices.
Socio-demographics: gender, age, smoking, education, occupation, ethnicity.
Medical status: none.
Endogenous: weight, height (self-reported).

Future plans
At this moment a new DNFCS is being designed. More attention will be paid to food safety and risk groups (teenagers, the elderly, individuals with lower SES, ethnic minorities).

Contact person(s)
K.F.A.M. Hulshof (TNO Nutrition and Food Research)
M.C. Ocké (RIVM)

Zutphen Elderly Study

National Institute for Public Health and the Environment (RIVM)

Objective
To study risk factors for chronic diseases
Type of study
Prospective study
Period an sampling
Baseline: 1985
Follow-up: 1990, 1995, 2000 (quite probably final follow-up), mortality registration ongoing.
Population
In 1985, 555 survivors of the original cohort of 876 (Zutphen study which started in 1960) and a random sample of 711 men of the same age (65-84) also living in Zutphen were approached. Of those invited 74% (939/1266) entered the study. Complete information on nutrition and risk factors was available for 876 men.
1990: 560 out of 718 survivors participated (78%)
1995: 351 out of 462 survivors participated (76%)
2000: 171 out of 260 survivors participated (66%)
Methods
Baseline
Dietary intake was measured using a cross-check dietary history method adapted to the Dutch population.
Questionnaire on lifestyle, cardiovascular diseases, respiratory disorders, cancer, health (subjective), life events, loneliness, emotions, future orientation. medication (cholesterol, blood pressure, diabetes, aspirin and anticoagulants)
Body composition measurement, physical examination, blood and urine samples
Follow-up
Baseline measurements + glucose tolerance, questionnaires on Mini-Mental State (MMSE), physical functioning (EPESE).
Information on vital status was obtained from the municipal registries.
Information on cause of death was obtained from Statistics Netherlands until 1990 and thereafter from hospital discharge data and/or general practitioners (ICD codes).
Determinants
Lifestyle: nutrition (foods and nutrients), physical activity, alcohol, smoking.
Socio-demographics: age, gender, civil state, education, profession, social environment.
Medical status: illness and disorders (extended), quality of life, medication, physical and mental functioning, depression (CSD).
Endogenous: blood sample (small, still available), ECG, glucose tolerance, blood cholesterol (total, HDL), blood chemistry, blood pressure, height, weight, skin fold thickness, arm circumference.

Note
The Zutphen Study is the Dutch contribution to the Seven Countries Study and the Zutphen Elderly study is also the Dutch contribution to the FINE study (Finland, Italy, the Netherlands)

Contact person(s)
D. Kromhout (RIVM)

Monitoring Project on Cardiovascular disease Risk Factors ‘Peilstationsproject Hart- en Vaatziekten’ (PPHV)

National Institute for Public Health and the Environment (RIVM)

Objective
To monitor the major risk factors for cardiovascular disease.
Type of study
Monitoring study
Period and sampling
1987-1991
Population
Information was collected from more than 36,000 men and women aged 20-59. The project was carried out through the municipal health services in Amsterdam, Doetinchem and Maastricht. Each year a new random sample of men and women was selected in each town. The overall response rate was 50% in men and 57% in women.
Methods
Dietary intake was questioned globally: dieting behaviour, supplement use, use of dairy products, bread consumption, use of fats, frequency of consumption of: cabbage, sprouts, chicory, spinach, beans, carrots, beets, tomatoes, raw vegetables, oranges, mandarins, apples, beef meat, pork meat, fish, chicken, egg, bread, sandwich filling (meat, cheese, sweet), use of fats, coffee, alcohol, and snacks.
Questionnaire on sociodemographic factors, risk factors of cardiovascular diseases, medication, lifestyle, reproductive history, social experience checklist (SEC).
Blood samples were taken and body composition and blood pressure were measured.
Determinants
Lifestyle: nutrition (frequency), alcohol intake, smoking, physical activity.
Socio-demographics: gender, age, education, occupation, ethnicity.
Medical status: presence of and risk factors for cardiovascular diseases, self-rated health, psychosocial conditions, medication.
Endogenous: weight, height, blood pressure, cholesterol (total and HDL), blood samples still available.

Contact person(s)
A. Blokstra (RIVM)

MORGEN study: Monitoring Project on Risk Factors and Health in the Netherlands

National Institute for Public Health and the Environment (RIVM)
(MORGEN is part of the **EPIC** study)

Objective
To gain insight in the prevalence of chronic disease and its risk factors
Type of study
Monitoring study, multi-centre
Period and sampling
Baseline: 1993-1997
Follow up: ongoing in specific other studies
Population
Representative samples of individuals (from the birth registry) in the age of 20-59 in three towns in the Netherlands: Amsterdam (response rate 45%), Maastricht and suburbs (response rate 58%) and Doetinchem (response rate 62%). Samples were generated periodically during the research period. In Doetinchem most subjects had formerly taken part in the PPHV project (see previous page), only a new sample of 20-25 year olds was generated. Non-respondents differed slightly from respondents in among others social economic status, smoking habits, alcohol use and physical activity. Data on 23,100 individuals became available.
Methods
Extensive semi-quantitative food frequency questionnaire (EPIC)
Questionnaire on sociodemographic factors, risk factors of chronic diseases, chronic diseases, medication (blood pressure, cholesterol, diabetes, migraine), reproductive history, use of hormones, family history of chronic diseases, lifestyle, health-related quality of life (RAND36)
Blood samples were taken and body composition and blood pressure were measured.
Assessment of vital status of all cohort members is ongoing and the newly diagnosed cancer cases are determined through linkage with the National Cancer Registry.
Determinants
Lifestyle: nutrition (nutrients), alcohol intake, smoking, physical activity.
Socio-demographics: gender, age, education, occupation ethnicity, household, social class.
Medical status: presence of chronic disease (detailed), risk factors for chronic diseases, self-rated health, psycho-social conditions, medication.
Endogenous: weight, height, waist and hip circumference, blood pressure, cholesterol, blood samples still available.

Note
In each of the three ‘MORGEN cities’ study participants were approached to participate in follow-up studies. Therefore each of the individual cohorts is described hereafter in more detail

Contact person(s)
W.M.M. Verschuren (RIVM)
A. Blokstra (RIVM)

Doetinchem cohort

National Institute for Public Health and the Environment (RIVM)

Objective

To gain insight in the prevalence of chronic disease and its risk factors and the influence of changes in risk factors on chronic disease risk

Type of study

Prospective follow-up

Period and sampling

1987-1991 PPHV, 1993-1997 (MORGEN), 1998-2002, 2003-today

Population

Representative sample of individuals (birth registry Doetinchem, response rate 62%) in the age of 20-59 at baseline (1987-1991). Samples were generated periodically during the first research period.

Data on 6400 individuals are available. For 4650 individuals there are data for all three measurement periods.

Methods

1987-1992 PPHV (See description PPHV)

1993-1997 MORGEN (See description MORGEN study)

1998, 2002, 2003-present

For the last measurement period the general questionnaire was adapted slightly to prevent repeating questions and to have some questions on problems specific for the elderly.

Questionnaire on health and life experience: 3.5 years after baseline measurements (response rate approximately 50%).

Determinants

Lifestyle: nutrition (nutrients), alcohol intake, smoking, physical activity

Socio-demographics: gender, age, education, occupation ethnicity.

Medical status: presence of chronic disease (detailed), risk factors for chronic diseases, self-rated health, psycho-social conditions, medication.

Endogenous: weight, height, waist and hip circumference, blood pressure, cholesterol (total and HDL), blood samples still available, lung capacity, cognitive tests for 45+ (from 1995).

Contact person(s)

W.M.M. Verschuren (RIVM)

A. Blokstra (RIVM)

Maastricht cohort

National Institute for Public Health and the Environment (RIVM)

Objective
To gain insight in the prevalence of chronic disease and its risk factors
Type of study
Monitoring study
Period and sampling
Baseline samples: 1987-1992 (Peilstation) and 1993-1997 (MORGEN)
Follow up: 1998 (Herbenadering) and 1998-2002 EPIC, ongoing
Population
Baseline sample (Peilstation and MORGEN): representative sample of individuals in the age of 20-59 at baseline extracted from the birth registry Maastricht and suburbs
19,587 subjects are invited and 13,184 agreed to participate (response rate 66%)
Methods
1987-1992 PPHV (See description of PPHV)
1993-1997 MORGEN (See description of MORGEN)
1998 Follow-up Maastricht
Dietary intake was questioned only globally: dieting behaviour, use of fats, consumption of bread, sandwich filling (meat, cheese, sweet), milk, yoghurt, potatoes, gravy, French fries alcohol and use of (raw) vegetables in summer- and wintertime,
Questionnaires on history of several diseases, medication (blood pressure, cholesterol, diabetes), smoking, nutrition behaviour and physical activity.
No physical examination was carried out.
1998-2002 EPIC follow-up
An extensive questionnaire on weight, smoking, alcohol, physical activity, use of medication and supplements, reproduction history, use of exogenous hormones, cancer, heart and vascular diseases, cholesterol, diabetes
Questionnaire on health and life experience: 3.5 years after baseline measurements (respons rate approximately 50%).
2004 EPIC follow-up
Questionnaire with roller tape to measure waist and hip circumference.
Determinants
Lifestyle: nutrition (products and/or some nutrients), vitamin supplement use, alcohol intake, smoking, physical activity.
Socio-demographics: gender, age, civil state, education, occupation, ethnicity.
Medical status: body weight, height, waist and hip circumference, blood pressure, cholesterol chronic diseases (detailed), family history of chronic diseases, reproductive history, use of hormones, medication, health-related quality of life.
Endogenous: weight, height, blood pressure, waist and hip circumference, blood pressure, cholesterol, blood samples still available.

Contact person(s):
E.J.M. Feskens (RIVM)

Hartslag Limburg

National Institute for Public Health and the Environment (RIVM)

Objective

To evaluate the effect of the community intervention project Hartslag Limburg on risk factors for cardiovascular disease and health-related quality of life.

Type of study

Monitoring and intervention study

Period and sampling

	Area	
	Intervention (Maastricht)	*Control (Doetinchem)*
Baseline sample	1998	1998
Follow-up	2000 and 2003	2003

Population

Intervention area (Maastricht):
A selective sample of 3,000 subjects (response rate 74%) extracted from participants of the 'Herbenadering 1998 Maastricht' (see previous page). 2300 Subjects completed all three measurements.
Control area (Doetinchem):
The control group existed of 800 subjects of the Doetinchem cohort.

Methods

Food frequency questionnaire (EPIC) (not carried out in 2000)
Questionnaire on (history of) disease, complaints and disorders, smoking, alcohol, physical activity and health-related quality of life (RAND36).
Blood samples were taken and body composition and blood pressure were measured.

Determinants

Lifestyle: nutrition (nutrients), alcohol intake, smoking, physical activity
Socio-demographics: gender, age, education, occupation ethnicity, household, social class
Medical status: presence of chronic disease (detailed), risk factors for chronic diseases, self-rated health, psycho-social conditions
Endogenous: weight, height, blood pressure, waist and hip circumference, cholesterol, blood samples still available.

Contact person(s)

G.C.W. Wendel- Vos (RIVM)

Amsterdam cohort

National Institute for Public Health and the Environment (RIVM)

Objective
To gain insight in the prevalence of chronic disease and its risk factors
Type of study
Monitoring study
Period and sampling
Baseline samples: 1987-1991 PPHV, 1993-1997 (MORGEN)
Population
Representative sample of individuals (birth registry Amsterdam) in the age of 20-59 at baseline (Peilstation or MORGEN)
Methods (all measurements)
1987-1992 PPHV (See description of PPHV)
1993-1997 MORGEN (See description of MORGEN)
1998-2002 EPIC follow-up
An extensive questionnaire on weight, smoking, alcohol, physical activity, use of medication and supplements, reproduction history, use of exogenous hormones, cancer, heart and vascular diseases, cholesterol, diabetes
Questionnaire on health and life experience: 3.5 years after baseline measurements (response rate approximately 50%).
2004 EPIC follow-up
Questionnaire with roller tape to measure waist and hip circumference.
Determinants
Lifestyle: nutrition (nutrients), alcohol intake, smoking, physical activity
Socio-demographics: gender, age, education, occupation ethnicity,
Medical status: presence of chronic disease (detailed), risk factors for chronic diseases, self-rated health, psycho-social conditions, medication.
Endogenous: weight, height, waist and hip circumference, blood pressure, cholesterol, blood samples still available.

Contact person(s)
see MORGEN study

European Prospective Investigation into Cancer and Nutrition (EPIC)

IARC-WHO (Lyon) and participating centres

Objective
To investigate the relationship between nutrition and cancer, with the potential for studying other diseases as well
Type of study
Ongoing multi-centre prospective cohort study
Period and sampling
Baseline: 1992-2000
Follow-up: 2000-today
Population
519,978 participants in 23 centres in 10 European countries. General age range: 35-70 years. Participant eligibility within each cohort was based essentially on geographic or administrative boundaries. The source populations were identified according to age, gender and, optionally, other criteria. The actual study populations are convenience samples of volunteers who agreed to participate. Random samples of defined populations were not required. In general, individuals who were eligible for the study were selected from the general population of a specific geographical area, a town or a province. Exceptions include the French cohort, which was based on members of the health insurance system for state-school employees, the Utrecht and Florence cohorts, which invited women undergoing breast cancer screening, the Italian and Spanish cohorts which included members of local blood donor associations, the Oxford cohort, which consists for 50% of subjects who do not eat meat.
After their initial enrolment, cohort members are contacted at regular intervals every 3-4 years to obtain information on various aspects of lifestyle that might have changed.
The cohorts of Doetinchem, Amsterdam, Maastricht and Utrecht (see the description of the PROSPECT study) are the Dutch contributions to the EPIC study.
Methods
Participants were invited to participate by mail or in person.
Baseline 1992-2000
Dietary intake was measured using an extensive self or interviewer-administered EPIC food frequency questionnaire (Italy, the Netherlands, Germany, Greece, Spain, France, Ragusa (Italy)) or a semi-quantitative food frequency questionnaire (Denmark, Norway, Naples (Italy), Umea (Sweden)) or combined dietary methods (UK, Malmo (Sweden)). For comparability additional dietary intake data by a computer-assisted 24-hour dietary recall (EPIC-SOFT) in representative sub-samples of each of the subcohorts (for 36,900 participants) where used as a reference method to correct for systematic between-centre over- or underestimations in the baseline dietary assessments.
Questionnaire on lifestyle, health and disease, Socio-demographics, sexual maturation, contraception and reproduction,
Blood samples are taken and body composition and blood pressure were measured
Follow-up 2000-todate
Questionnaire on lifestyle, health status and reproduction,
Registry of occurrence of cancer and other diseases, and overall mortality
Determinants
Lifestyle: nutrition (nutrients), alcohol, smoking, physical activity
Socio-demographics: age, gender, education, occupation

Health status: history of previous illness, disorders or surgical operations, menstrual and reproductive history, use of exogenous hormones, menstruation, pregnancies, menopause
Endogenous: body weight, height, waist and hip circumference, blood samples are still available (plasma, serum and buffy coats)

Contact person(s)
H.B. Bueno de Mesquita (RIVM)

The Prospect-EPIC study

Julius Centre of the University Medical Centre Utrecht (UMCU)
(Prospect-EPIC study participates in the EPIC study)

Objective
To investigate the relationship between nutrition and cancer, with the potential for studying other diseases as well
Type of study
Prospective cohort study
Period and sampling
Recruitment: 1993-1997
Follow-up: within an interval of 3-5 years
Population
17,500 healthy women living in Utrecht and surroundings are recruited from an existing region population-based program of breast cancer screening. The women were aged 50-70 years at enrollment. The response rate was approximately 35%.
Methods and Determinants
Corresponds with the method and determinant description of EPIC.

Contact person(s)
H.B. Bueno de Mesquita (RIVM)

Utrecht Health Monitoring Study Leidsche Rijn (LRGP)

Julius Center of the University Medical Center Utrecht

Objective
To generate data on etiologic and diagnostic determinants of health and disease prevalence, and information on the efficacy and side effects of healthcare interventions
Type of study
Prospective cohort study
Period and sampling
Start in 2000
Population
Residents (all ages) of Leidsche Rijn (Utrecht) are invited to join the study as soon as they register with their new GP. In 2003 the sample consisted of 5.500 subjects and will increase with 2-5.000 subjects per year until an approximate participation rate of 65% of Leidsche Rijn residents has been achieved.
Methods
Individual Health Profile (IHP) based on biometrical data (blood samples, anthropometry, ECG, lung capacity), previous medical registration (checked in extended first GP consultation) and self-administered questionnaires on health status (physical and mental), medication, socio-economic status, lifestyle and use of medical care .
Follow up data are gathered by extraction of information from the GP's patient database every three months. Prescriptions, diagnoses, additional examinations and referral to other primary care staff or to secondary care are coded using internationally accepted methods (ICPC, ICD).
Determinants
Lifestyle: alcohol, smoking, nutrition (few global questions)
Socio-demographics: age, sex, education, profession, housing
Medical status: self-reported health status and extensive registry of diseases, medication, accidents, and use of medical care.
Endogenous: body composition, blood pressure, cholesterol (LDL), fasting glucose, lung capacity, EKG, blood samples still available.

Future plans
Depending on the funding a more extensive focus on nutritional intake might be possible

Contact person(s)
M. Numans (Julius Centrum)

Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study

National Institute for Public Health and the Environment (RIVM); Institute for Risk Assessment Sciences, Utrecht University (UU); Sophia's Children Hospital, Erasmus University Rotterdam (Erasmus MC); University of Groningen (RUG); University Hospital Groningen; Sanquin, Amsterdam.

Objective

Intervention Study

To evaluate the effectiveness of allergen reduction measures for prevention of asthma and mite allergy in high risk children

Natural History Study

To investigate the natural history of childhood asthma in high and low risk children, incidence and risk factors.

Type of study

Prospective/Birth Cohort study (intervention/natural history study)

Period and sampling

1996/1997: baseline (2-3 months before birth).

Follow-up: 3 months and 1, 2, 3, 4, 5, 6, 7 and 8 years of age.

Population

The birth cohort consists of about 4000 children who were born between July 1996 and October 1997. Mothers who were about 3 months pregnant were recruited with the help of 52 midwife practices in three different regions in the Netherlands. Pregnant women were categorised into 'allergic' mothers and 'nonallergic' mothers and their children respectively into 'high risk' and 'low risk' children.

Intervention Study

Two-thirds of the high risk children (n=855, response 53%) were allocated to the Intervention Study: either allergen reduction strategies or placebo.

Natural history Study

The remaining one-third of the high risk children (n=472, response 62%) was allocated to the Natural History study as well as the random sample of the low risk children (n=2819, response 55%)

Methods

Baseline:

Self-administered questionnaire on pets and lifestyle: smoking and maternal diet (vegetables, fruit, fish, egg, milk (products), nuts(products), supplements

Home visit: collection of dust from floors and mattresses for determination of allergen exposure (only intervention study).

Follow-up:

Intervention study: home visit at 3 months of age (dust and questionnaires), age 1, 4 and 8 years (physical examination, blood sample and questionnaire).

Natural History Study: approximately 600 low risk children and approximately 450 high risk children receive home visits at 3 months of age (dust and questionnaire) and at age 4 and 8 years (physical examination, blood sample and questionnaire). 2,200 Low risk children receive only questionnaires.

Entire study population at all follow-up points: self-administered questionnaire on respiratory symptoms, weight and height (self-measured or through GP visit), environmental and lifestyle factors.

Questionnaire on nutrition: dairy products, yoghurt or supplements with lactic acid bacteria, bread, fats, cheese, meats, peanut butter, eggs, beverages, biscuits, bars, sweets, vegetables, fruit, meat, fish, snacks, vitamin supplements.
Information about medication use was obtained from pharmacies until 4 years of age. Possibly this will also occur for the period 4 – 8 years.

Determinants

Lifestyle: maternal diet and supplement use (also during breastfeeding), smoking, passive smoking, child's diet (e.g. formula feed, breast feed, time of introduction of several foods or beverages, food frequencies).
Socio-demographics: age, gender, housing, environment, maternal and paternal education.
Medical status: (family history of) allergies, asthma, respiratory complaints, maternal and child medication use and allergen exposure.
Endogenous: weight, height, blood samples still available.

Contact person(s)

H.A.. Smit (RIVM)
A.H. Wijga (RIVM)

SENECA study (Survey in Europe on Nutrition and the Elderly: A Concerted Action)

Department of Human Nutrition of Wageningen University (WUR) and participating centres

Objective

To explore cross-cultural differences in dietary patterns and lifestyle affecting health, and performance of elderly European people, and to test specific hypotheses of healthy ageing.
To assess the predictive value of diet and lifestyle for health maintenance and survival (mortality and cause-specific mortality)

Type of study

Prospective cohort study

Period and sampling

Baseline: 1988/1989
Follow-up: 1995, 2000

Population

Baseline

2590 elderly subjects of 12 European countries, born between 1913-1918 in 19 traditional towns with a stable population of 10,000 to 20,000 inhabitants and a socio-economic structure comparable to that of the country or the region as a whole were selected from a random age-and sex-stratified sample (average participation rate of 51%). Persons living in psycho-geriatric nursing homes who were not able to answer questions independently were excluded.

Follow-up 1995

Examination of 1221 (58%) re-invited subjects and 210 (33%) newly-invited subjects.

Follow-up 2000

Nine longitudinal towns completed all the three studies. Data from 715 subjects who were still alive are available. For all subjects: a survival follow-up and a recording of cause of death for those who died is carried out.

Methods

Food consumption data are obtained through personal interviews using a modified version of the dietary history method consisting of two parts: firstly an estimated 3-day record and secondly a check-list of foods.
General questionnaire: socio-demographics situation, lifestyle, social network, health, self-perceived health, medication, activities of daily living, physical activities.
Performance: mental (MMSE, GDS) and physical (PPT)
Body composition was measured and blood samples were taken
Non-responders questionnaire
Morbidity and mortality registration, coding of cause of death

Determinants

Lifestyle: nutrition (nutrient), alcohol, smoking, physical activity
Socio-demographics: age, gender, civil state, education, occupation, social networks, housing
Health status: self-perceived health, medication, morbidity and mortality registration
Endogenous: weight, height, skinfold thickness, circumferences, haemoglobin, hematocrit, albumin, cholesterol (total and HDL), triglycerides, retinol, carotene, alpha-tocopherol, folic acid, vitamin B12, pyridoxal-5P, vitamin D, blood samples still available.

Contact person(s)

L.C.P.G.M. de Groot (WUR)

The Netherlands Cohort Study on Diet and Cancer (NLCS)

Maastricht University (UM) and TNO Nutrition and Food Research

Objective
To study the association between dietary factors and the development of cancer.
Type of study
Prospective cohort study
Period and sampling
Baseline: 1986
Follow-up: up to 1998 available for cancer and up to1996 for mortality, both extended at regular intervals
Population
The cohort consisted of 120,852 subjects (48% men and 52% women) aged 55–69 years selected from 204 computerised municipal population registries. Immediately after baseline measurements, a subcohort of 5000 subjects was randomly sampled from the entire cohort and is being followed up biennially.
Methods
Baseline
Self-administered semi-quantitative validated food-frequency questionnaire, which consists of 150 items selected according to their contribution to the interindividual variance in intake of energy, macronutrients and several micronutrients. Use of vitamin and mineral supplements.
Extended questionnaire on potential confounding variables such as smoking, physical activity, anthropometry, occupational history, medical history and history of drug use, family history of cancer, reproductive history (women only), and socio-demographic variables.
Provision of toenail clippings (about 67% of the participants).
Follow-up
Cancer follow-up by record linkage with the Cancer Registry, a pathology registry (PALGA) and mortality registry. Possibility to link with causes of death.
Questionnaire on a variety of topics, changing from year to year in the subcohort only: e.g., current use of vitamin & mineral supplements.
DNA samples from part of the subcohort (sampled in 2000)
Determinants
Lifestyle: nutrition (nutrients e.g. plant sterols), physical activity, smoking, alcohol.
Socio-demographics: gender, age, education, residence, occupation.
Medical status: family history of cancer, incidence of specific cancers, menstrual and reproductive history, use of exogenous hormones.
Endogenous: height, weight, weight at age 20 (self reported).

Contact person(s)
S. Bausch-Goldbohm (TNO Nutrition and Food Research)
P. van den Brandt (UM)

The Rotterdam study (ERGO: Erasmus Rotterdam Health and the Elderly)

Erasmus Medical Centre Rotterdam (Erasmus MC)

Objective
To investigate the prevalence and incidence of and risk factors for chronic diseases in the elderly (especially cardiovascular, neurological, locomotor and ophthalmologic diseases).
Type of study
Prospective cohort study
Period and sampling
Baseline: 1990-1993
Follow up: every 2-3 years, the 3rd follow-up measurement is still going-on, in the end of 2005 the 4th follow-up will start.
Population
All inhabitants over 55 years of age (n=10,275) living in the suburb of Ommoord in Rotterdam were invited. In total 7,983 subjects (4,878 women and 3,105 men) participated, including 897 subjects living in one of the six elderly homes.
In 2002 another 3,011 participants (55 years of age since 1990) were added to the cohort which now comprises a total of 10,994 subjects.
Methods
Baseline
Questionnaire on lifestyle, socio-demographic factors and health status.
Dietary interview by trained dietician who used a 170-item (13 food groups) semi-quantitative validated food frequency questionnaire (SFFQ) adapted for use in the elderly.
Physical examination and blood samples.
Follow-up
Physical examination and blood samples.
Registration of incidence of several diseases (cancers, cardiovascular diseases, neurological diseases, ophthalmologic, thyroid and anxiety disorders, depression, fractures).
Registration of mortality and cause of death.
Information on morbidity and mortality (ICPC and ICD coding) is obtained from the general practitioner (weekly), hospital discharge records and controlling the GP's patient database every 2-3 years.
Determinants
Lifestyle: nutrition (nutrients only at baseline), smoking, physical activity, alcohol.
Socio-demographics: gender, age, education, occupation.
Medical status: current health status, medical history, use of medical facilities, current medication use (ATC-classification), morbidity and mortality registration.
Endogenous: cognitive function, indicators for Parkinson's disease, DEXA (bone mineral density), X-rays of hands, thoraco-lumbar spine, hips and knees, extensive ophthalmologic examination, ultrasound assessment of cardiac dimensions, diameter of the abdominal aorta, carotid arterial wall thickness and plaques thickness, a computerised ECG, blood pressure, height, weight, cholesterol (total, HDL), height, weight, hip circumference, blood pressure, blood samples are still available, glucose tolerance test.

Contact person(s):
J. Heeringa (Erasmus MC)

The Hoorn study

EMGO institute, VU University Medical Center Amsterdam

Objective
Initially: to determine the prevalence of type 2 diabetes and associated risk factors
Later: to study risk factors for diabetes and cardiovascular disease and other diabetes complications
Type of study
Prospective cohort study
Period and sampling
Baseline: 1989-1990
Follow-up: 1996-1998, 2000, 2006 (planned)
Population
Random sample was extracted from the municipal register of Hoorn, 2484 of 3553 invited subjects aged 50-75 agreed to participate (71.5%). 700 subjects of the original cohort were invited to undergo more extensive measurements.
1996-1998: 1513 of 2086 subjects who were invited participated (72.5%)
2000: 878 subjects which included newly-diagnosed diabetic subjects recently identified through a screening study in the region.
Methods
Baseline
Semi-quantitative food frequency questionnaire (validated).
Questionnaires on health status, lifestyle (e.g. physical activity), socio-demographic factors, medical history and familial history.
Physical examination and oral glucose tolerance test.
Extensive measurements: vascular and autonomic function test, test for the presence of atherosclerosis, neuropathy, nephropathy and retinopathy.
Follow-up
Semi-quantitative food frequency questionnaire (validated).
Questionnaires on health, status, lifestyle (e.g. physical activity), sociodemographic factors, cardiovascular disease (ROSE), medical history and familial history.
Questionnaires on quality of life (SF36), depression (CES-D) only in 2000.
Information on vital status was obtained from the population register of the city of Hoorn.
Causes of death and information about morbidity are extracted from medical record in the general practices and local hospital (ICD codes are used).
Determination of glucose tolerance and physical examination.
Determinants
Lifestyle: diet (nutrients), smoking, physical activity.
Socio-demographics: gender, age, education, profession.
Medical status: current health status, medical history (including prior cardiovascular disease), current medication use, quality of life, depression.
Endogenous: weight, height, waist and hip circumference, DEXA, blood pressure, ECG, arterial properties, glucose, glycated hemoglobin (HBA,1C), serum total cholesterol, HDL, LDL, triglyceride levels, sICAM-1, s-vcam, vWf, CRP, leptin, adiponectin, ADMA, details of lipid metabolism, ankle-arm blood pressure ratio, intima media thickness, microalbuminuria (only subsample), blood samples still available.

Contact person(s)
J. Dekker (VUMC)

Cohort study Diabetes and Atherosclerosis Maastricht (CoDAM)

Maastricht University (UM)

Objective

To study the effects of glucose tolerance (NGT, IGT, DM), lipids, lifestyle and genetics on cardiovascular diseases.

Type of study

Population based cohort study.

Period and sampling

1999-2000

Population

Subjects were recruited from existing cohorts (PPHV and MORGEN, see description earlier). Inclusion criteria were age between 40 and 70 years, Caucasian ethnicity, absence of use of medication that affects glucose metabolism, and one of the following: a BMI >25 kg/m², a positively family history for type 2 diabetes mellitus, a history of gestational diabetes, use of anti-hypertensive medication, a postprandial blood glucose larger than > 6.0 mmol/l, glucosuria. The study population consists of 574 subjects, response 46%.

Methods (all measurements)

Extensive semi-quantitative food frequency questionnaire (EPIC).
Questionnaire containing questions on socio-demographic factors, lifestyle, reproductive history, use of hormones, quality of life (SF 36), medical history, cardiovascular disease (ROSE), depression (CES-D), diabetes symptoms (DSC-2), medication, family history of chronic diseases.
Blood samples were taken and body composition was measured as well as measures of cardiovascular diseases.

Determinants

Lifestyle: diet (nutrients), alcohol intake, smoking, physical activity.
Socio-demographics: gender, age, education, occupation.
Medical status: presence and history of (chronic) disease (detailed), risk factors for chronic diseases, self-rated health, psychosocial conditions, medication.
Endogenous: weight, height, waist and hip circumference, sagital and transversal diameter, glucose tolerance, ECG, blood pressure, ankle-arm blood pressure rate, intima-media thickness of the a. carotis, compliance, microalbuminuria, cholesterol (total, HDL), distensibility, Young's elastic module, insulin, triglycerides, free fatty acids, several antioxidants, blood samples still available.

Note

The CoDAM study and a part of the Hoorn Study (see description) are included in the DIALOG study (Prospective cohort study for DIAbetes, Lifestyle, Obestiy and Genetics).

Contact person(s)

E.J.M. Feskens (RIVM)
C. van der Kallen (UM)
E. Blaak (UM)

Longitudinal Aging Study Amsterdam (LASA)

VU University Amsterdam

Objectives

To get insight in the predictors and consequences of changes in physical, cognitive, emotional and social functioning in older persons and to provide a basis for developing and evaluating (central and local government) policy in the fields of aging.

Type of study

Prospective study

Period and sampling

Baseline 1992-1993
Follow-up: 1995-1996, 1998-1999, and 2001-2002
New cohort: 2002-2003 (age range 55-65 years)

Population

The initial sample was weighed according to expected mortality after 5 years within each sex and age group, so that after five years equal numbers of men and women were expected to be alive in the ages 55-59, 60-64, 65-69, 70-74, 75-79, and 80-85 years. Subjects were extracted from municipal registries. The sample was constructed so as to reflect the national distribution of urbanisation and population density. The municipalities included in the sample are: Amsterdam, Wormer, Waterland (three municipalities in the West), Zwolle, Ommen, Genemuiden, Zwartsluis, Hasselt (Northeast), and Oss, Uden, Boekel (South). During follow-up observations, subjects who moved out of the municipality were traced and re-interviewed. To be able to distinguish age, cohort and period effects, in 2002 a new cohort (in the age range 55-65) has been sampled from the same sampling frame as the original cohort.
Number of subjects: baseline: 3107; 1995-96: 2545; 1998-99: 2076; 2001-02: 1691; new cohort 02-03: 1002

Methods

Home visits by trained interviewers for personal interview and tests.
Self-administered questionnaire on health status and personality
Blood and saliva samples and body composition measurement.

Main outcomes

Physical functioning (functional limitations, mobility, co-ordination, balance, strength, vision, hearing),
Cognitive functioning (screening test for cognitive impairment, test for intelligence, learning capacity, memory and psychomotor speed),
Emotional functioning (depression and anxiety screening scales, diagnostic interviews),
Social functioning (composition of social network, frequency of contacts, exchange of support, various forms of social participation).
Information on mortality and causes of death were obtained from municipalities and Statistics Netherlands (CBS) respectively.

Determinants

Lifestyle: nutrition (10 items questionnaire), smoking, physical activity, use of calcium, vitamin, iron, alcohol.
Socio-demographics: gender, age, housing, household composition, work, pets, education, income.
Medical status: habitual physical activity level, present and future health perception (RAND), chronic conditions (chronic lung disease, CVD, CVA, diabetes, cancer, arthritis, incontinence), self-perceived health, pain, menopause, prescription medication use.

Endogenous: height, weight, waist and hip circumference, fat distribution (bioelectrical impedance, DXA) blood pressure, heart rate, lung function (peak flow), weight history, blood samples still available.

Contact person(s)
D. Deeg (VUMC)

Amsterdam Growth and Health Longitudinal Study (AGAHLS)

VU Medical Center Amsterdam (VUMC)

Objective

To describe the natural growth, health and lifestyle of a group of healthy adolescent boys and girls and to study the longitudinal relationships between lifestyles (daily physical activity and nutrition, smoking and alcohol drinking habits on health. The focus is multidisciplinary and involves both physical and psychological determinants in relation to a wide range of health outcomes.

Type of study

Prospective cohort study.

Period and sampling

Baseline: 1977-1981 four annual measurements.
Follow up: 1985, 1991, 1993, 1996, 2000, 2004.

Population

A sample of over 600 healthy boys and girls, 13 years of age were selected from two secondary schools in Amsterdam and Purmerend. In 2000, almost 450 (36 year-old) participants attended the 9^{th} repeated measurement, so now 23-year follow-up data are available.

Methods:

Structured interviews and questionnaires.
Nutrition: 1977-1996: face to face dietary history method, 2000: cross-check dietary history computer-assisted method.
Physical activity: 1977-1981: cross check interview, heart rate monitoring and stepcounters.
Physical examination: body composition, cardiovascular disease risk factors, bone mineral density (by DEXA and ultra sound), atherosclerosis and arterial stiffness (by ultra sound) skeletal age (by x-ray), lung function, personality, attitudes, sociometric status, stress, direct measurement of maximal oxygen uptake on treadmill, isokinetic leg muscle force, battery of physical fitness tests (force, speed, co-ordination and flexibility).

Determinants

Lifestyle: nutrition (nutrients), alcohol, smoking, physical activity (metabolic and peak strain activities).
Socio-demographics: gender, age, education, profession.
Medical status: medical consumption, physical fitness, stress, copings, subjectively experienced health.
Endogenous: height, weight, body fatness, 4 skinfold thickness, cholesterol (total, HDL), blood pressure, HBA1C, VO2-max, carotid-intima media thickness, carotid and femoral arterial distensibility, markers of chronic inflammation and endothelial dysfunction, DEXA, bone density of the lumbar region hip and wrist, blood samples still available, pedometers, heart rate monitors.

Note

The AGAHLS data are available for secondary analyses (after permission) from the NIWI /Steinmetz Archive in Amsterdam)

Contact person(s)

HCG Kemper (VUMC)
LLJ Koppes (VUMC)
W van Mechelen (VUMC)
JWR Twisk (VUMC)

MONICA study (Multinational Monitoring of Trends and Determinants in Cardiovascular Disease)

World Health Organization (WHO)

Objective
The objectives of the MONICA Project were to measure the trends in cardiovascular mortality and coronary heart disease and cerebrovascular disease morbidity and to assess the extent to which these trends were related to changes in known risk factors.
Type of study
Multi-centre monitoring study
Period and sampling
10 year study, started in 1982,
Population
Ten million subjects aged 25- to 64-years (at baseline) in 38 centres from 21 countries participated.
Methods
Registry of all acute myocardial infarction and stroke events by medical records and community health services
Registry of medical care of patients before, during and after attack through information provided by local health system
Inventory of medical services
Census data on demographics
Questionnaires (self-administered or personal interview depending on study centre) on smoking, high cholesterol awareness, drug use, socio-demographics.
Physical examination: blood pressure, cholesterol measurements, weight, height, waist and hip circumference.
Dietary intake was measured in a sub-sample of men aged 45-64 years- 3-day un-weighed record method. Centres where free to adapt their dietary assessment methodology. After an inventory of the comparability of collected dietary data it was concluded that the dietary data need to be standardised before the datasets of the different study centres can be compared. Up today, no funding is available for these additional activities.
Determinants (especially focused on cardiovascular risk factors)
Lifestyle: nutrition (nutrients in subsample), smoking
Socio-demographics: age, gender, education, marital status
Medical status: drug use, menopause, awareness and treatment of high cholesterol, treatment of hypertension, cardiovascular events.
Endogenous: height, weight, waist, hip, blood pressure, total and HDL cholesterol.

Note
The Netherlands did not participate in this study. Several centres of the MONICA project are collaborating in the follow-up project MORGAM (not further described here).

Contact person(s)
M.C. Ocké (RIVM)
K. Kuulasmaa (KTL-Finland)

GLOBE (Health and living conditions of the population of Eindhoven and surroundings)

Erasmus Medical Centre Rotterdam (Erasmus MC)

Objective
To explain health differences between socio-economic groups in the Netherlands.
Type of study
Prospective cohort study
Period and sampling
Baseline: 1991
Follow-up: still ongoing; annually of bi-annually (differs per sub-sample)
Population
An a-select sample (stratified by age, degree of urbanisation and socio-economic position) of 27,070 non-instutionalised Dutch persons (aged 15-74 years) was drawn form 18 municipal population registers in the south-eastern part of the Netherlands (Eindhoven and its surroundings). 18,973 subjects participated (response rate 70%) and responded to a postal survey. Additionally, two subsamples (a healthy sample and a sample with a lot of chronic diseases) were interviewed in 1991 (response 79% and 72% respectively, n=5667).
Methods
Baseline
Postal questionnaires on food habits, socio-economic position, health indicators, health related behaviour, material circumstances, psychosocial factors, health care utilisation, childhood circumstances.
Additional interview (both subsamples) which existed of a more detailed questionnaire on the above mentioned main points of the postal questionnaire. Nutrition was asked through a 58-item FFQ focused on energy, total fat and fatty acids and fruit intake.
Follow-up
Interview (one subsample annually and one sub-sample biennially)
Both sub-samples received a postal questionnaire.
Linkage with national databases: hospital admissions, regional Eindhoven cancer registry and national register of cause of death (1998/99 and 2004 PRISMANT)
Determinants
Lifestyle: nutrition (energy and fatty acids in subsample), smoking, alcohol, physical activity.
Socio-demographics: education, occupation, income, housing.
Medical status: perceived general health, chronic conditions, long-term disabilities, prescription medication, subjective health.
Endogenous: height, weight (self-reported).

Contact person(s)
F. van Lenthe (Erasmus MC)

Generation R: Growth and development study Rotterdam

Erasmus Medical Centre Rotterdam (Erasmus MC)

Objective

To study growth, development and health in a contemporary population-based multi-ethnic cohort of urban children from foetal life until young adulthood. There are four primary areas of research: growth and physical development, behaviour and cognition, diseases, health and health care for pregnant women and their offspring.

Type of study

Prospective cohort study

Period and sampling

Start of the data collection: 2002.

Follow-up of the children until the age of 20 years (1, 2, 6, 14, 24, 36, 48 months of age and each year thereafter).

Population

10,000 new-borns of different ethnicities in the city of Rotterdam

Methods

Assessments are carried out in pregnant women (at 12, 20 and 30 weeks of gestation), their partners (one assessment) and children.

Data from the women will be collected through physical examinations, questionnaires, ultrasounds, and biological samples (blood, cord blood). Maternal diet will be assessed with a FFQ.

Partners will get a physical examination, questionnaires and a blood samples will be taken.

Until the age of 4 years, 6 assessments (questionnaires (among others a FFQ) and physical examinations) will take place in the children. In between anthropometrics, development and medical history will be recorded through the routine child health centres. In 1000 children a special focus study will be carried out to obtain information on among others determinants of CVD, diabetes, obesity, infectious diseases and the immune system. For this study ultrasounds and biological samples (blood, urine and saliva) will be collected.

Determinants

Lifestyle: nutrition (nutrients), behaviour (children), child-rearing.

Socio-demographics: gender, age, education, profession, housing, ethnicity, living conditions.

Medical status: medical consumption, drug use, medical history, family history, motor development, depression, cognition (children).

Endogenous: height, weight, blood pressure, head circumference (children). Women: ultrasounds for gestational age, foetal growth and placental function. Focus study women: foetal brain, heart, aorta, kidney development. Focus study children: body composition (skinfold thickness, DXA), neurological development, ultrasounds from brain, heart, aorta, kidney development, glucose tolerance, blood lipids, genetics, vaccine response, infection serology, maturation immune system. Blood samples from women, partners and children available.

Contact person(s)

R. Snijders (Erasmus MC)

ABCD Study: Amsterdam Born Children and their Development

Municipal Health Service (GG&GD) Amsterdam, VU Medical Centre (VUMC) and the Amsterdam Medical Centre (AMC)

Objective
To survey to what extent childrens' health (at birth and later in life) is influenced by the mother's lifestyle during pregnancy.
Type of study
Prospective cohort study
Period and sampling
Pregnant women of different ethnicities were recruited from January 2003 until March 2004. Data collection started at 12-weeks pregnancy, and continued 3 months after delivery. Thereafter every 5 years data on the child's health will be collected.
Population
Pregnant women and their offspring residing in Amsterdam (questionnaires from 7,600 women, response rate 64%, blood samples from approximately 4.000 women).
Methods
Blood samples and some socio-demographic information obtained during the standard 12-weeks prenatal screening will be gathered by the Central Municipal Health Services lab.
Subsequently a written questionnaire (in Dutch and mother tongue) will be sent. Questionnaire on: age, education, ethnicity profession, height, weight, pregnancy details, expectancies and worries, diseases, drug use, intention to breastfeed, folic acid use, alcohol use, caffeine use, fish intake, smoking, mood and subjective health.
Upon birth of the child information from the neonatal screening tests will be obtained together with birth outcome information retrieved by the midwives.
When the child is 3 months of age, a second written questionnaire for mother and child will be sent. Every 5 years another follow-up questionnaire will be sent. Questionnaire on: pregnancy details, delivery details, smoking, alcohol, drug abuse, drug use, supplement use, diseases, feeding details, child's crying pattern, child's sleeping pattern, health status of the child, fatigue, mood.
Blood samples will be analysed on several (nutritional) parameters: to be determined in the near future.
Determinants
Lifestyle: nutrition (fish intake, folic acid, vitamin and mineral supplements, caffeine), smoking, alcohol.
Socio-demographics: age, ethnicity, education, profession.
Medical status: maternal and child's diseases and/or complaints, maternal drug use, mood, subjective health, child's behaviour (crying, eating, sleeping)
Endogenous: maternal height, weight (self reported), blood nutrients. Maternal blood samples still available. Child's (birth) weight and height (measured)

Future plans
Every 5 years the child's health status will be assessed.

Contact person(s)
M. v.d. Wal (GG&GD Amsterdam)

The Netherlands Twin Register (NTR)

VU Medical Centre Amsterdam (VUMC)

Objective

To examine the contribution of genetic and environmental factors and their interaction, to variation in growth, development, personality, mood disorders, disease and risk factors for disease.

Type of study

Cohort study

Period and sampling

From 1986 onwards, data are collected from registered monozygotic and dizygotic twins soon after birth, and at the age of 2, 3, 5, 7, 10 and 12 years. In addition in 1990 data have been collected from adolescent and adult twins (born between 1970 and 1986). They are also followed-up longitudinally (surveys in 1991, 93, 95, 97, 2000, 2002). Older twins (born between 1909 and 1971) were invited to participate in order to investigate the successful ageing aspect.

Population

Dutch twin population. Approximately 25.000 twin pairs (0-15 years), 7300 twin pairs (15-30 years) and 700 twin pairs (30 years and older) have been registered. Of the newly born twins in the Netherlands almost half is being registered as participant.

Methods

Young twins: parents receive questionnaires soon after birth, and at the above mentioned time points, including questions about pregnancy and delivery details, birth weight, height, breastfeeding details, daycare, behaviour, medical status, motor development, and socio-demographics.

Dietary intake has been measured in a subgroup by 2-day dietary records.

Adult twins (15 years and older): receive a survey every 2 or 3 years about health behaviour, lifestyle, personality, health status, and demographic characteristics. Their parents, siblings and spouses are also invited to participated.

In subgroups of young and adult twins reaction time, cognitive abilities, attention, brain activity (EEG/ERP), ability to concentrate, brain volume, heart rate, blood pressure, risk factors for cardiovascular disease, diet, is measured.

Determinants

Lifestyle: physical activity, smoking, alcohol, other drugs (nutrition in subgroups) .

Socio-demographics parameters: information from twins and their parents.

Medical status: chronic diseases, behaviour, physical and mental development.

Endogenous: height, weight, hormones, ECG, ICG, blood pressure (subgroups), blood samples still available

Contact person(s)

D. Boomsma (VUMC)

Monitor VGZ: Local and national monitor public health

The Netherlands association of community health services (GGD Nederland), National Institute for Public Health and the Environment (RIVM) and all participating Municipal Health Services

Objective
To monitor health and health determinants of health on local and national level. Harmonising indicators and construction of a (national) database.

Type of study
Monitoring study

Period and sampling
Local data collection every 4-5 years, till 2004 no uniformity in questionnaires, no general database with data available. From 2004 onwards standardised data will be collected at local level and brought together in a national database

Population
Dutch adult population (18-65 years)
Until 2004: no data available in the national database
From 2004: 2000-3000 subjects per year expected

Methods
All Municipal Health Services will choose individually which indicator(s) they want to study, but they are obliged to use a standardised questionnaire
Until 2004: written health questionnaire, only for a few indicators comparable information on a national level is available
From 2004: for about 20 indicators standardised questionnaires are available. One of the 20 indicators is a 'nutrition indicator'.
Available questionnaires on:
Accidents, smoking, education, geographic indicator, occupation, sex, age, ethnicity, BMI, alcohol use, physical active, chronic disorders, nutrition (intake of vegetables, fruit, and fruit juices (only quantity), breakfast habits, bread consumption (quantity and type of bread), fat on bread, fats for cooking).
From Sept 2004 questionnaires on:
Psychological well-being, social environment and social security, use of health care facilities, depression, loneliness, quality of live, indicator psychological disorders, family
From Nov 2004 questionnaires on:
Drug abuse, income, physical environment, living situation, living environment, inside environment (moisture, noise, dust, radiation, etc.), environmental disturbance (noise, stench, etc.), religion, participation in breast cancer screening, participation in cervical screening, influenza vaccination, use of narcotics and tranquillisers

Determinants
Lifestyle: nutrition (frequencies of a few items), physical activity, smoking, alcohol.
Socio-demographics: age, gender, education, profession, social environment.
Medical status: chronic diseases, quality of life.
Endogenous: height, weight.

Future plans
Development and use of more standardised indicators from 2004 (see above) and in the future possibly incorporation of physical examinations (such as Amsterdam Health Monitor 2004).

Contact person(s)
A.J.M. van Loon (RIVM)

Periodical Medical Survey ('PGO-peilingen')

TNO-PG and all participating Home Care organisations and Municipal Health Services

Objective

To gain insight in the health status of the Dutch youth and in the acting of the Youth Health Care in case of experienced health problems.

Type of study

Monitoring study

Period and sampling

1991 - today

Population

Samples contain ca. 6,000 children (aged 0-21 years) from 20 participating municipal health services. Sample sizes do vary each sampling period. Response rates are high and the samples are representative for the Dutch population.

Methods

Questionnaires on socio-demographics factors, biometry and until 1995 morbidity, medication, health judgement.

Questionnaires vary each survey period and focused among others on nutrition (24 h recall with special emphasis on 20 food items) in 1993/94: dairy products, cheese, eggs, flesh foods, bread, cereals, potatoes, rice, pasta, pulses, vegetables, fruit, fruit juices, lemonade/soda, sweet or harty snacks.

Physical examination

Determinants

Lifestyle: among others food habits (1993/1994), exercise (1992/1993), leisure activities (2002/2003), milk nutrition for infants (1996-1998)

Socio-demographics: gender, age, education level, ethnicity

Medical status: until 1995 morbidity, medication, subjective health

Endogenous: biometry (1991/92, 1996/97)

Contact person(s)

L. Hinne-Pluimgraaff (TNO-PG)

Integrated system of surveys on living conditions (POLS: permanent onderzoek leefsituatie)

CBS (Statistics Netherlands)

Objective

POLS-basis:
To gain insight in different items of the living situation as health, lifestyle, working conditions, political and social involvement, environment, safety, leisure activities, and victim of criminality.
Module health and work:
To gain insight in lifestyle, health status and use of medical service of the Dutch population and also in the development over time of these three items. Furthermore, to gain insight in trends in working conditions of persons belonging to the labour force.

Type of study

Monitoring study

Period and sampling

Started in 1997 and several previous studies as the Continuing Health Survey and Continuing Living Situation Study are integrated.
Continuous data collection: every month a proportionally random subgroup of the selected year sample is approached.

Population

The yearly random extracted two-stage sample (first towns and second residents of these towns) consists of individuals from the general population, except those who live in institutions and those who belong to the driving and sailing population. Sample size is differing yearly, but mostly consist of minimal 20,000 participants. Because of the rather low response rate (approximately 60%) the data may have been affected by selection bias. Computed weighing coefficients were applied to correct for such bias.

Methods

Questionnaire on demographic and social-economic characteristics and core- indicators of the different living situation items via computer assisted personal interviewing (CAPI)
Questionnaire on several subject specific modules: health and work, law, environment, involvement, youngsters, leisure activities, day care via CAPI or self-administered.

Determinants

Lifestyle: smoking, alcohol, use of drugs, physical activity, safe sex and participation in preventive screening programmes
Socio-demographics: gender, age, civil state, residence, household composition, income, ethnicity, education and socio-economic group
Medical status: health status, perceived health, disability, medical consumption
Endogenous: weight, height (self-reported)

Contact person(s)

F. Otten (CBS)

REGENBOOG study: Risk factors and health survey in the Netherlands: a survey on municipal health services

Dutch Municipal Public Health Services, CBS (Statistics Netherlands), National Institute for Public Health and the Environment (RIVM)

Objective
To monitor risk factors or determinants of chronic and infectious disease in the general population.
Type of study
Monitoring study
Period and sampling
1998-2001
Multistage probability sample
Population
Individuals participating in the POLS study (see description POLS), older than 12 years and living in a region of one of the 42 municipal health services are asked to undergo a physical examination. 5441 subjects are examined from 1998 tot 2001 and participate in the REGENBOOG study. Dietary information was collected from 2001 of 1284 persons, participation rate 53%.
Methods
POLS questionnaires: basis and module health and work (see method description POLS)
Questionnaires on infectious diseases
Physical examination at participating municipal health service: body composition, medical information, blood samples
Food frequency questionnaire to compare the Dutch diet with the World Cancer Research Fund nutrition guidelines (vegetables, fruit, vegetable foods, alcohol, red meat, fats, oil, preparation temperature of meat and fish).
Determinants
Lifestyle: smoking, alcohol, vaccination, physical activity (only 2001), nutrition (2001).
Socio-demographics: gender, age, civil state, residence, household composition, income, ethnicity, education.
Medical status: health status and use of medicines/medical devices, perceived health, medical consumption.
Endogenous: height, weight, waist and hip circumference, ‘joint-function test’, blood pressure, glucose, cholesterol (total, HDL), blood samples still available.

Contact person(s)
A.L. Viet (RIVM)

Dutch National Survey of General Practice

National Institute of Health Services Research (NIVEL), National Institute for Public Health and the Environment (RIVM)

Objective
To gain actual and national representative information on the role and position of GP's in the Dutch health care system
Type of study
Monitoring study
Period and sampling
1987-1988 (first survey) and 2000-2002 (second survey)
Population
General Practitioners who were members from the National GP Information Network were recruited. In the second survey 104 practices with 195 GP's participated, which was representative for among others age, gender, region, urbanisation degree. In total 390,000 patients were registered at these practices. The registered patients were also representative for the Dutch population with respect to age, gender, and insurance arrangements.
Methods
To investigate the patient population:
Questionnaire on socio-demographics (all patients, response rate 76%)
Personal interview (4% of the study sample): subjective health, health status, lifestyle (among others nutrition), social context, illnesses, use of care. Questions on nutrition constituted food frequency questions for fruit and vegetables, potatoes, fat (spreads, gravy and cooking), bread (type and amount), sandwich fillings, dairy products and questions on meal patterns and dieting behaviour.
GP records on patient visits, drug use, ICPC coded diagnoses.
Determinants
Lifestyle: nutrition, physical activity, alcohol, drug use, smoking.
Socio-demographics: gender, age, civil state, housing, household composition, education, country of origin.
Medical status: drug use, chronic and acute diseases, psychological and social problems, disabilities, quality of life, personality characteristics, use of care, social network and interaction.
Endogenous: height, weight (self reported), information from GP records.

Contact person(s)
F. Schellevis (NIVEL)
G.P. Westert (RIVM)