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Postlaunch Monitoring of Functional Foods

Methodology development III

N de Jong, HP Fransen, SW van den Berg,

MC Ocké

Contact:

N. de Jong
Centre for Nutrition and Health
Nynke.de.Jong@rivm.nl

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Abstract

Postlaunch Monitoring of Functional Foods

Methodology development (III)

The recognized importance of a detection system of potential health hazards of functional foods consumption has led to the development of methods carrying out the initial phases of such a system. Special focus was placed on feasible methods, key players and the tasks and competences of the players. Although functional food consumption may imply benefits for the user, potential health risks cannot be excluded and should be monitored after launch. A Postlaunch Monitoring system (PLM) provides a means for investigating these health effects. The first phase concerns the passive 'smoke' signaling, i.e. detection of any potential health hazard, based on the registration and evaluation of consumer complaints. Second, active signaling has to be implemented on the basis of the exploration and interpretation of existing and/or emerging data on both exposure and effects. Systematic prioritizing and operating are important in this phase. On the basis of the outcomes of active and passive signaling parts, decisions will have to be taken about whether or not to proceed with further PLM activities.

Key words:

Postlaunch Monitoring, functional foods, risks, signaling, consumer care lines, prioritizing, criteria

Rapport in het kort

Postlaunch Monitoring van functionele voedingsmiddelen

Methodologie ontwikkeling (III)

Door het onderkende belang van een onderzoekssysteem naar gezondheidsrisico's van 'functionele voedingsmiddelen' is het nu mogelijk om de eerste fases van zo'n systeem daadwerkelijk uit te voeren. Hierbij is vooral gekeken naar praktisch uitvoerbare criteria, de betrokken partijen en naar de taken en bevoegdheden van deze partijen.

Functionele voedingsmiddelen zijn voedingsmiddelen waar een positief gezondheidseffect aan wordt toegeschreven. Consumptie van deze voedingsmiddelen kan gezondheidswinst opleveren, maar bepaalde gezondheidsrisico's kunnen niet worden uitgesloten. Een Postlaunch Monitoring systeem (PLM) is een middel om deze gezondheidsaspecten in kaart te brengen. Het eerste deel van PLM is het signaleren van 'rook', oftewel het signaleren van een potentiële bedreiging voor de gezondheid. Dit gebeurt door een passieve signalering van consumentenklachten via consumentenklachtenlijnen. Anderzijds kan actief informatie worden verzameld over gezondheidsrisico's. Daarbij is het belangrijk om te prioriteren en methodisch te signaleren. Hiervoor worden criteria gepresenteerd gebaseerd op blootstellingsdata en gegevens over effecten. Op basis van zowel de passieve als de actieve informatiestromen kan dan de juiste afweging gemaakt worden om bepaalde functionele voedingsmiddelen verder te onderzoeken.

Trefwoorden:

Postlaunch Monitoring, functionele voedingsmiddelen, gezondheidsrisico's, signalering, consumentenklachtenlijnen, prioritering, criteria

Contents

Summary	6
1. Introduction	13
1.1 <i>Background</i>	13
1.2 <i>Demarcation and approach</i>	15
2. Premarket information of different types of functional foods	17
2.1 <i>Novel foods</i>	17
2.2 <i>Enriched foods</i>	18
2.3 <i>Dietary supplements</i>	19
3. Passive signaling of ‘smoke’	21
3.1 <i>Background</i>	21
3.2 <i>LAREB</i>	21
3.2.1 Report channel	22
3.2.2 Information gathering	22
3.2.3 Signal detection	23
3.2.4 PLM experiences on food	24
3.2.5 Possibilities and restrictions regarding PLM on functional foods	24
3.3 <i>VWA</i>	25
3.3.1 Report channels	26
3.3.2 Information gathering	26
3.3.3 Signal detection	27
3.3.4 Possibilities and restrictions regarding PLM on functional foods	27
3.4 <i>Recommendations</i>	28
3.5 <i>Outcomes of the meeting on signal detection</i>	33
4. Active signaling of ‘smoke’	35
4.1 <i>Background</i>	35
4.2 <i>Prioritizing criteria</i>	35
4.3 <i>Literature screening of side effects</i>	37
4.4 <i>Monitoring intake</i>	38
4.5 <i>Further methodological issues</i>	41
Acknowledgements	45
References	47
Appendix 1: Example form of Lareb consumer care line	49
Appendix 2: Example form of VWA consumer care line	55
Appendix 3: Report of a meeting on PLM passive smoke signaling	57

Summary

Introduction

Consumption of functional foods may exert benefits for the particular user, however potential health risks cannot be excluded. The manufacturer is responsible for the safety of the product, but also the government needs to protect public health. A Postlaunch Monitoring system (PLM) will be a vehicle to carry out these tasks. The *objective* of such a system is to systematically monitor (un)expected health effects of functional food consumption after marketing and under customary conditions of use. PLM may consist of the following phases:

- a) passive signaling of consumer complaints ('smoke') through for example consumer care lines;
- b) active signaling of hazardous effects ('smoke') based on active investigation of (pre- and postmarket) 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;
- f) regulation.

The term 'smoke' refers to any 'suspicion to some degree' with respect to potential health hazards due to the consumption of functional foods. *This report will focus on the realization of the first two phases: passive and active signaling.*

Passive signaling

Lareb

Lareb (Netherlands Pharmacovigilance Centre) is the Dutch knowledge centre on side effects of drugs and is instructed by the government to collect, register and analyze possible adverse drug reactions. Despite their lack of expertise on foods, Lareb is an interesting candidate for PLM of functional foods because they have a great general expertise on data management, signal detection and causality assessment. Accurate detection of signals and reliable causality assessment should also be possible for some but not all functional foods. Products that can be monitored by their system are specific foods, for example products that contain one particular ingredient (e.g. the novel food ingredient phytosterol). Examples of foods that cannot be monitored are vitamin and/or mineral enriched foods as detection of signals is not possible

for combinations of foods and their ingredients. Another limitation is that long term adverse events may very difficult to determine. Nevertheless, Lareb is willing to implement the registration of consumer complaints regarding functional foods in their current system.

VWA

VWA (Inspectorate for Health Protection and Veterinary Public Health) is known by the consumers as an authority for product complaints and has the authorization to act if serious complaints about foods are received. Adaptation of the current consumer care line system is complicated but may be possible. The most important limitation is that the emphasis of VWA's mandate has been placed on the detection of legal violations. The problems one expects to find through functional foods consumption may not originate from a legal violation. In addition, as the complaints are judged by VWA-employees from the complaints department, there is a fair chance that these particular functional food complaints will not be registered, as they might appear insignificant and not related to specific food consumption. Nevertheless, VWA may be able to play a scanning role in a future signaling system.

Cooperation Lareb – VWA

A future cooperation of Lareb and VWA for handling consumer complaints as part of the passive signaling phase might be operationalized as follows:

- complaints through the consumer care line will be submitted to VWA → a functional food scanning will take place by VWA;
- in case of a functional food: VWA refers directly to Lareb's website → the registration of a complaint will take place by Lareb;
- information gathering will be done by Lareb;
- evaluation of complaints will be done by Lareb;
- finally, Lareb reports to VWA.

The advantages of the above described set up are:

- VWA is known by consumers as an authority for product complaints;
- the current system of Lareb needs to be adjusted, but Lareb is prepared to do this;
- the current system of VWA needs only a slight adjustment;
- Lareb is experienced in the evaluation and causality assessment of complaints;
- Lareb is experienced in the development and maintenance of a suitable database;
- VWA is authorized to take legal action.

The most important disadvantage is that consumers have to deal with two different complaint handling authorities.

Meeting VWA, Lareb, VWS, RIVM

In order to discuss a future collaboration in the passive signaling of 'smoke' through the consumer care line a meeting with VWA, Lareb, VWS and RIVM (National Institute for Public Health and the Environment) was held in November 2005. At the start it was stressed again that the single result obtained from the analyses on consumer complaints is the relay of a signal, even the faintest, that something might be happening. And again, VWA emphasized the fact that even if something occurs it might not be in the position to act because the observation of side effects of consumption of functional foods may not be a legal violation. Nevertheless, there may be one option to get a registration of consumer complaints adopted through the manufacturer with VWA as a controller. This is via the HACCP (Hazard Analysis Critical Control Point) task of manufacturers. Within this task a consumer care system should be in place. VWA might be able to check the manufacturer's actions with respect to the consumer complaints as part of their inspection's mandate on the HACCP task. In this way pressure is exerted on the manufacturers to register and act upon consumer complaints. Notification to VWA or Lareb should be part of this. Finally, it was stressed that it is highly preferable to have these ideas and protocols implemented in accordance to EU initiatives.

In principle, the outcome of the meeting stroke with the collaboration idea set-up described above, with one main difference: the manufacturers' care lines are more important than VWA's care line in the latter option. If manufacturers have the duty to notify VWA about the registered consumer complaints, VWA's back office may collect the information and call in Lareb's experience to analyze, evaluate and store the datasets on the complaints to find a meaningful signal. In addition to this mainstream of complaints registration through the manufacturers, it may be prudent to have an additional completely independent care line system in place which is also the case in pharmacovigilance.

Active signaling

Similar to the passive signaling of smoke, 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. Active signaling of

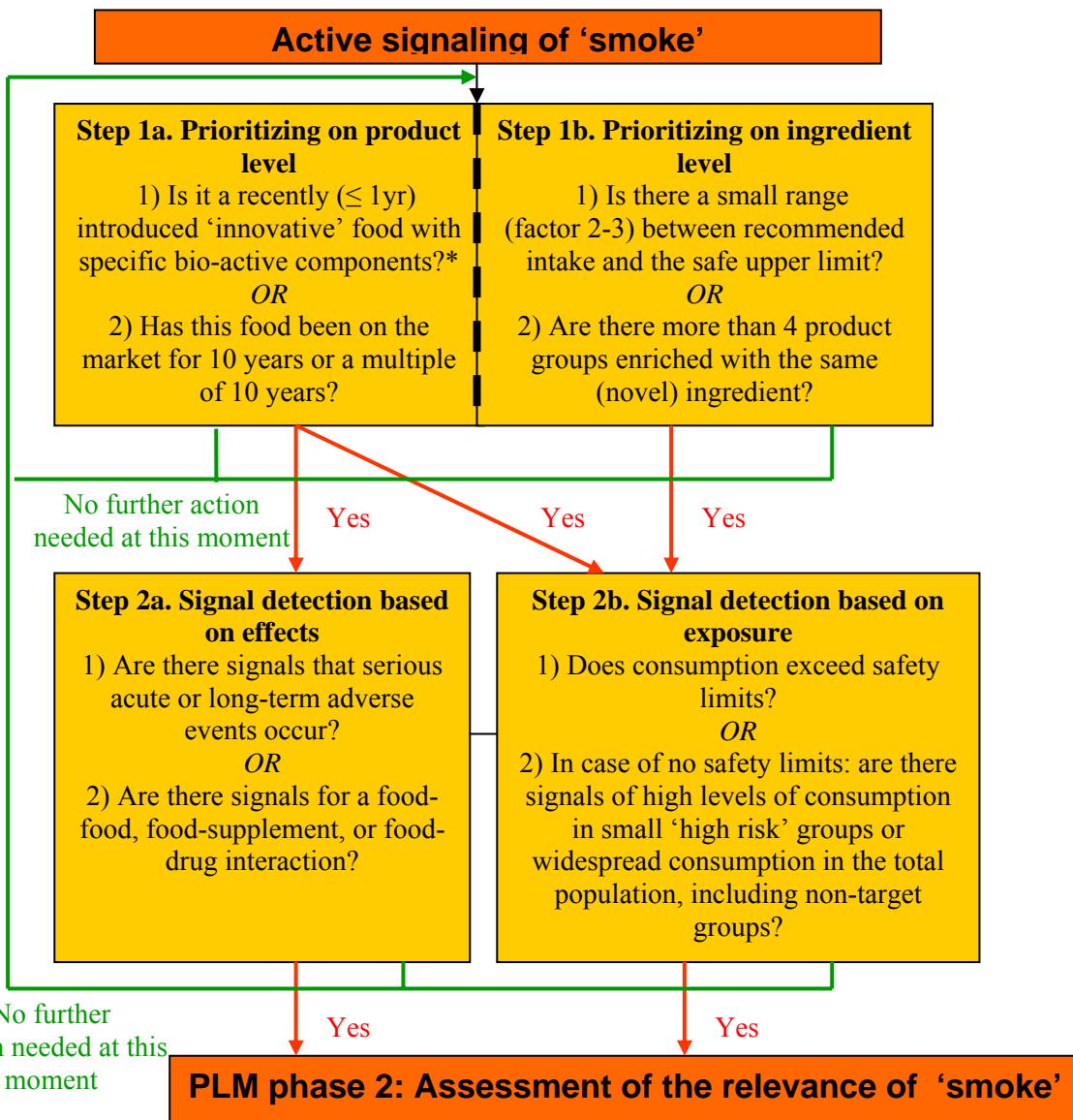
smoke should be operational because it is supposed to pick up other smoke signals than the registration of consumer complaints. It is not feasible to focus on each and every functional food or ingredient immediately. The prioritizing of functional foods or functional ingredients in the active signaling phase means to rank the importance of the topics. If a food or ingredient does not meet the prioritizing criteria in first instance, it does not imply that follow-up is excluded. The *prioritizing process* should be focused on:

- the type of functional food: a more classical food enriched with certain vitamins and/or minerals will get a lower priority than an 'innovative' food enriched with specific bio-active compounds such as phytosterols, but also fibers, bacteria, processed proteins, etcetera.
- moment of market introduction: evaluation moments may be shortly after market introduction (≤ 1 year) and say after 10 years or a multiple of 10 years.
- consumption levels in the population: if the window between the recommended intake and the safe upper limit of intake is rather narrow (factor 2 to 3) the priority will be high.
- the number of available foods: the more foods enriched with similar ingredients, the higher the priority.

The next step will be *signal detection* which is based on the evaluation of exposure and/or effects. Questions that determine the focus are:

- are there signals that serious acute or long term adverse events occur? The seriousness of the potential adverse effect will be a weighing factor.
- are there signals for a food-food, food-supplement, or food-drug interaction?
- does consumption exceed safety limits?
- in case of no safety limits: is there a possibility of a high level in a small group, or is there a moderate consumption pattern but in a large group (the whole population, including non-target groups)?

Schematically, the active 'smoke' signaling phase is presented in a flow chart below.



* The selection process is focused on the distinction between a more classical food enriched with vitamins and/or minerals regarded as safe based on historical use vs. an 'innovative' food enriched with specific bio-active compounds such as phytosterols, fibers, bacteria, processed proteins, etc

Further methodological issues

The work for both the passive and the active 'smoke' signaling should be performed next to each other and for both the passive as well as the active 'smoke' signaling phases, a mandate for investigation should be given by a principle stakeholder in the PLM issue: the (inter)national government. These governments should also prepare to pursue the requested premarket safety information from the manufacturers. They also might need to think about

the gap in food laws with respect to a manufacturer's duty to report any side effects obtained through their consumer care lines.

We propose to try-out our decision scheme on a case-by-case basis. The factual report compiled by the PLM investigators on 'smoke' signaling and their conclusions about whether or not to proceed to a next PLM phase should be evaluated by an ad-hoc expert committee existing of stakeholder members. In the course of time and the experience gained through this case-by-case approach the committee will have to develop a systematic approach to assess the seriousness of the topic.

1. Introduction

1.1 Background

Consumption of functional foods may exert benefits for the particular user, however potential health risks cannot be excluded. The manufacturer is responsible for the safety of the product, but also the government needs to protect public health. The government is responsible for the safety of the overall food supply for the whole population and should also be able to monitor potential safety issues with regard to long term effects, adverse effects in potential risk groups, over consumption of specific ingredients, interaction effects with nutrients and/or drugs in collaboration with the manufacturer. A Postlaunch Monitoring system (PLM) will be a vehicle to carry out these tasks. The *objective* of a PLM system is to systematically monitor (un)expected health effects of functional food consumption after marketing and under customary conditions of use. On commission of the Dutch Ministry of Health, Welfare and Sport, we presented a theoretical proposal for a PLM methodology in an earlier report⁵. Special attention has been paid to the necessities of such a system. In short, PLM may consist of the following phases:

- a) passive signaling of consumer complaints through for example consumer care telephone lines;
- b) active signaling of hazardous effects based on active investigation of (pre- and postmarket) 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;
- f) regulation.

This PLM system is presented in Figure 1.1

In a subsequent report⁴ among others an inventory has been presented about available Dutch cohort and monitoring studies that may constitute suitable (intake) data for PLM purposes. Based on the suitability of these studies two case studies on the intake of functional foods in parts of the Dutch population have been performed. As usage rates of functional foods were sometimes very low, no final conclusions could be drawn. To further build the PLM structure

and realize the six different phases we have to develop classification schemes and decision making models. This report will focus on the first two phases: passive and active signaling.

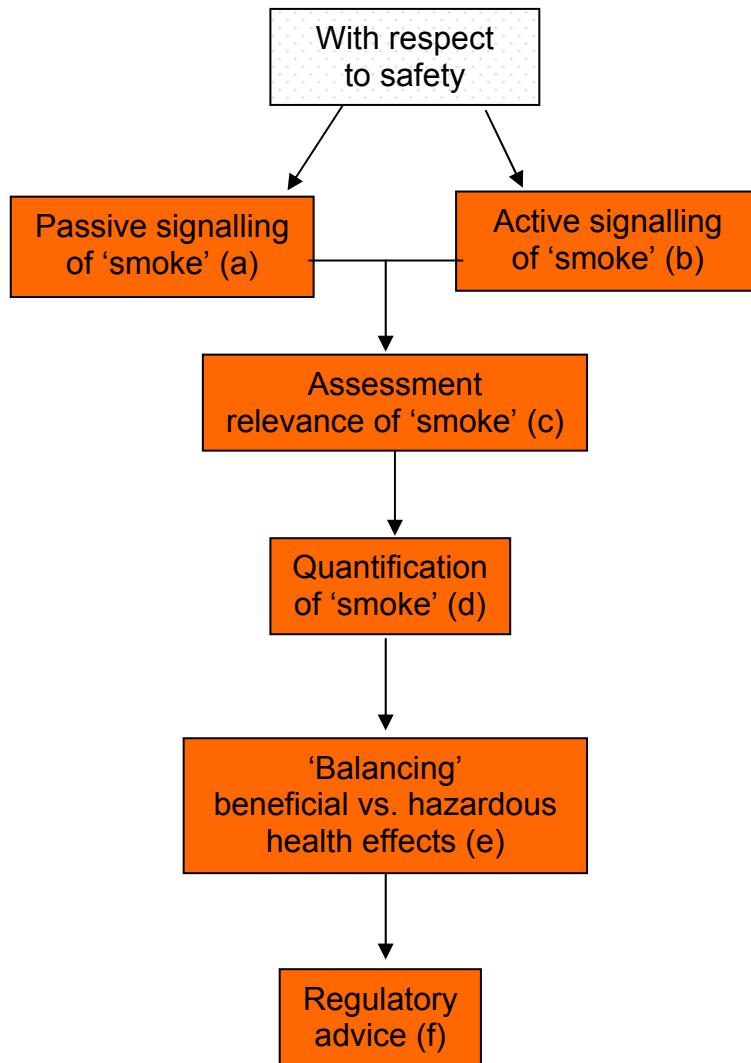


Figure 1.1: Presentation of a theoretical PLM model focused on safety issues. The term ‘smoke’ refers to any ‘suspicion to some degree’ with respect to potential health hazards due to the consumption of functional foods.

In a later stage the other PLM phases will be concretized. Important features to consider in the next phases are among others the further quantification of the expected and unexpected health effects in the population, scenario building techniques, and modeling techniques to balance the risks against the benefits.

1.2 Demarcation and approach

For this report we will keep especially those foods in mind with specific bio-active components. In addition we will take the vitamin and mineral enriched foods into account. Although the added ingredients to these foods are known and historically regarded as safe for consumption, cumulative effects may play a role in case several enriched foods and/or supplements are taken concurrently for a longer time period. Supplements are not dealt with separately. The development of a specific PLM system for supplements may take place in a later stage. 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. For example, we know already that GM food consumption is difficult to trace with the currently available databases. As well, phytotherapeutics with no nutritive value will not be taken into account as there are also different premarket EU regulations for these types of products in force. As already stated in the former paragraph, this report will describe classification schemes of the first two phases only: a) passive signaling of consumer complaints through for example consumer care telephone lines; and b) active signaling of hazardous effects based on active investigation of (pre- and postlaunch) research data. For the sake of readability, we will use the generic term 'functional food' in this report.

2. Premarket information of different types of functional foods

One of the first actions in the PLM system is to define those functional foods that should have priority to include in the monitoring process. Therefore, it is important to know which functional foods are on the market at a certain time point and what information is already available. In this chapter a brief summary of the different types of functional foods and supplements and the premarket information available for these products will be given.

2.1 Novel foods

Under the Novel Foods Regulation (nr 258/97)⁶ a novel food is defined as a food that does not have a significant history of consumption within the EU prior to May 1997. Before a novel food is launched in Europe, the manufacturer has to submit an application according to EU guidelines to a safety assessment committee of one of the EU member states. The European Committee and other member states will be informed about the evaluation and may either accept the outcome or object to it. The submitted application has to contain information about the applicant, description of the food or ingredient, and more specific: specifications of the novel food, description of the production process, source of the product, expected intake, information from previous human exposure, nutritional and microbiological information (physiological research), toxicological assessment, possible allergic reactions, and finally possibilities for Postlaunch Monitoring¹. With respect to information on current and anticipated human exposure from food and other sources, it is obligated to elaborate on calculations, including amount and frequency of consumption as well as on other assumptions made¹². Up till now, a case by case assessment of each novel food is performed. If a novel food is considered substantially equivalent to a food that is already on the market, a simplified procedure (notification) can be submitted. In the Netherlands the Committee on Safety Assessment of Novel Foods (in Dutch: Commissie Veiligheidsbeoordeling Nieuwe Voedingsmiddelen, VNV), which is part of the Medicines Evaluation Board (MEB), performs the evaluation and reports to the Minister of Public Health. Example dossiers and the list of prerequisites can be found on the MEB website (<http://www.cbg-meb.nl/nl/nwvoeding/index.htm>). In the UK the Advisory Committee on Novel Foods and Processes (ACNFP) performs the evaluations. On the internet a reasonably up-to-date list of

the European applications can be found including the result of the evaluations (<http://www.cbg-meb.nl/nl/nwvoeding/index.htm>, or <http://www.acnfp.gov.uk/assess/>). From 1997 until August 2005, 62 full applications have been submitted of which 16 are accepted, 4 are rejected, 12 are withdrawn and 30 are pending. 56 Novel foods have been submitted for a simplified procedure (notification).

2.2 Enriched foods

In 2003, an EU regulation is presented² in which it is attempted to harmonize the rules on the voluntary addition of vitamins and minerals to food between EU countries. At the moment of writing, the regulation is under revision. In expectation of a harmonized regulation several vitamins and minerals may be added to foods with a minimum of 15% and a maximum of 100% of the recommended daily allowance (RDA) per daily consumption in the Netherlands¹⁰. Until September 2004, manufacturers were obliged to give notice of the market introduction of a new enriched food to the Food and Consumer Product Safety Authority (VWA). Notification of removal of enriched foods was not required. As a consequence there was no overview and therefore the obligation of notification has been expired and no other dossiers are required. From July 1996 to December 2001 notice was given of 228 products, fortified with micronutrients⁸. In the Netherlands until 2005, addition of vitamin A (retinoids), vitamin D, folic acid, selenium, copper and zinc was only allowed in the case of substitution and restoration, because the margin between the RDA and the safe upper limit, above which harmful effects might occur, is relatively small. An exception was made for the addition of vitamin A en D to yellow bread spreads as these products were an important substitute for butter, rich in vitamin A and D. 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. Nevertheless, the verdict of the European Court in December 2004⁷ stated that the Dutch government is not allowed to have these exceptions, unless it can be demonstrated that the product is not safe for particular (groups of) consumers. As a result, manufacturers are now able to obtain a release from the Dutch Ministry of Health, Welfare and Sport for the addition of vitamin A, D, folic acid, selenium, copper or zinc to food¹⁰. At the moment of writing, the applications are evaluated on a case-by-case approach. The application has to contain a) the nutritional value of the product b) the target group c) the expected consumption of the product d) if the product

replaces another product that contains the micronutrient concerned. The addition of bio-active substances to food other than vitamins and minerals is regulated by either the EU Novel Foods Regulation, or the general Dutch Food and Commodities Act in case the ingredients have been present in foods already before May 1997. EU regulations for the latter ingredients (e.g. specific amino acids, proteins, fatty acids, fibers, bacteria etc.) are under construction.

2.3 Dietary supplements

On June 10, 2002 the EU Directive on food supplements (2000/46/EU) was adopted by the European Parliament. The directive specifies which ingredients of supplements are allowed to be marketed in Europe. The European Committee has made a positive list of type of ingredients and which chemical forms are allowed in dietary supplements. The minimum and maximum contents of vitamins and minerals allowed per supplement still have to be determined by the European Food Safety Authority (EFSA). There are no pre-market dossiers required. Immediately from the commencement of the directive (August 2005) a transition phase has been defined until January 2010. Member states may provide additions to the positive list for vitamins and minerals and their chemical forms not yet included in the directive. The dossiers had to be submitted to the Commission by mid July 2005 and include information about among others the manufacturing process, stability, proposed use, known exposure, biological and toxicological data¹². In any case, the ingredients had to be used in food supplements marketed in the Community prior to July 12th 2002. The EFSA should have assessed these dossiers before the end of 2009. An overview of the submitted dossiers can be found on www.row.minvws.nl/content.aspx?cid=162. For the Dutch situation the Commodities Decree on Dietary Supplements executes the EU Directive. Unfortunately, there has been no overview of what supplements are currently available on the Dutch market.

Apart from the vitamin and minerals containing dietary supplements there are other supplements such as supplements containing amino acids, essential fatty acids, fiber and various plant and herbal extracts. Again EU regulations for these types of products are under construction. In anticipation of these EU regulations the general Dutch Food and Commodities Act applies also for these products. With respect to the herbal supplements there has been a special Directive in force (Traditional Herbal Medicinal Products (2001/83/EU)) from March 2004 onwards. The aim of this Directive is to register especially those herbal products with (limited) scientific evidence.

In conclusion, the diversity of functional foods and supplements is growing and special (EU) regulations are necessary to fill in the gaps of the national Dutch Food and Commodities Act. For novel foods pre-market dossiers are required by the EU regulations. For the addition of vitamin A (retinoids), vitamin D, folic acid, selenium, copper and zinc special exemption dossiers are required by the Dutch government. Other pre-market information is limited especially with respect to the general vitamin and mineral enriched foods and supplements.

3. Passive signaling of ‘smoke’

3.1 Background

The first phase of our PLM model is signaling of ‘smoke’⁵. The term ‘smoke’ refers to any ‘suspicion to some degree’ with respect to potential health hazards due to the consumption of functional foods. In this chapter we will focus on the registration of the *passive* signaling of ‘smoke’ or in other words the registration of consumer complaints regarding functional foods. In our earlier report we have described the inventory on the different systems that are currently used to register and analyze consumer complaints. Therefore, interviews were performed with representatives of seven institutes (governmental and non-governmental) that probably will receive consumer complaints about foods⁵. Based on these consultations, the Netherlands Pharmacovigilance Centre (Lareb) and the Inspectorate for Health Protection and Veterinary Public Health (VWA) were found to be appropriate candidates for a contribution to the set-up and implementation of such a system. For that reason, a second engagement was arranged with both authorities. The aim of these follow-up consultations was to discuss the opportunities, necessities and willingness to implement the registration of consumer complaints regarding functional foods in their current system. In the next paragraphs we will describe the current daily administration routine, the type of information gathered and how signals are detected by Lareb and VWA. Furthermore, the opportunities for implementing the ‘passive signaling of smoke’ in their current system will be discussed.

3.2 LAREB

Lareb, the Netherlands Pharmacovigilance Centre, is the Dutch knowledge centre on side effects of drugs and is instructed by the government to collect, register and analyze possible adverse drug reactions. The head office in 's-Hertogenbosch is supported by five regional offices mostly embedded in academic hospitals. In each region a doctor or pharmacist is employed. A vital part of their job is to motivate doctors and pharmacists to notify Lareb of their suspicions relating to adverse drug reactions. On behalf of the minister, Lareb is subsidized by the Dutch Medicines Evaluation Board from money paid annually by pharmaceutical companies for registration of their products. Despite their lack of expertise on foods, Lareb will be an interesting candidate for PLM of functional foods as they have a great general expertise on data management, signal detection and causality assessment.

3.2.1 Report channel

Possible adverse drug reactions can be submitted by caregivers, patients and manufacturers. Complaints can be reported by filling out a structured form on the Lareb website (see appendix 1 for this form). This electronic way of reporting works as a filter and results in non-anonymous reports of good quality. The reporting of side effects by patients has been introduced only recently, i.e. since 2003. Lareb is very positive about the reports submitted by this group, which contain sufficient medical information ¹³. In 2004, Lareb received 5000 complaints of which approximately 40% were serious ⁹. In case of supposed serious adverse effects, manufacturers are obliged to pass on reports of these effects to the Dutch Medicines Evaluation Board within 15 days. These reports are compiled by Lareb and added to their Dutch database of reports on side effects (see next paragraph) (www.cbg-meb.nl/nl/reghoudr/index.htm). The main channel of reporting is the electronic channel. In addition, there is a paper version of the forms available in the pharmacotherapeutic compass. Complaints by telephone are redirected to the forms on the internet.

3.2.2 Information gathering

For each complaint, information is gathered about the side effect, the suspected drug, personal patient data, and details from the person who did prescribe and who provided/produced the drug (see Table 3.1). In case, Lareb is in the position to request additional information from the patient for causality assessment (e.g. blood measurements, scan results). Today, Lareb is developing more specific questionnaires depending on the reported complaint. All reports are stored in a database, which by now contains 50,000 reports of side effects ⁹.

Table 3.1: General data gathered by Lareb for each complaint

1) Side effect	<ul style="list-style-type: none"> - Suspected side effect - Starting date - Duration of use before side effect occurred - Outcome (e.g. recovered, died) - Other side effects - Treatment of side effect, which medication? - Did side effect already occur with previous use of the same drug? - Other possible explanations for occurring or worsening of side effect?
2) Drugs	<ul style="list-style-type: none"> - Name - Starting date and end date - Dose - Way of administration - Indication - Adjustment after occurrence side effect (e.g. quitted, lower doses) - Co medication
3) Personal/patient details	
4) Details from person who did prescribe	
5) Details from provider	

3.2.3 Signal detection

In general, detection of signals by Lareb can be divided into three steps. First, each individual report is evaluated by a single expert and is also assessed by a multidisciplinary scientific staff during regular meetings. Second, statistical calculations are carried out weekly on the existing database to examine if a certain combination of reported side effect and drug occurs more often than can be ascribed to a random statistical likelihood. This serves as an extra surveillance so that no signals will be undetected. Third, a comparison with data from the WHO database is made. This database is managed by the Uppsala Monitoring Centre (UMC) in Sweden commissioned by the WHO and contains reports of possible adverse effects of drugs from all over the world. The causality assessment between the reported side effect and the suspected drug is an important, but difficult task. This evaluation is based on an assessment of all available (predominantly clinical) data of the individual patient, in most cases, additional clinical data will be retrieved through general practitioners or medical specialists. Important factors that play a role in causality assessment are; time span/period of

time, plausibility of the side effect, literature data, biological working mechanisms of the drug and exclusion of other explanations that may cause the complaint (e.g. influenza virus, sun exposure, cosmetic products). The assessment procedure is established in a handbook.

Complaints reported to Lareb can be forwarded to the Dutch government, the European register of adverse drug reactions (Eudravigilance) and WHO. Quarterly, Lareb reports the most important signals to the Dutch Medicines Evaluation Board (MEB). This board may then decide to carry out additional investigations. Furthermore, it has the authority to take further measures, such as adaptation of the accompanying instruction or removal of the drug from the market. Serious reports are directly forwarded to the relevant authorities.

3.2.4 PLM experiences on food

Lareb has been approached by a multinational food company for assistance in setting up a safety monitoring system for functional foods. Lareb has supported the set up of a database for the registration of complaints and has offered medical expertise for five foods with a health claim. So far, a few complaints have been reported (10 – 100 per year). Most complaints have been referred to confounding variables. Unfortunately, it is difficult to determine the true cause of a complaint, because information gathering is poor till now. The assignment, however is a good opportunity to increase the knowledge in this area.

3.2.5 Possibilities and restrictions regarding PLM on functional foods

Lareb is of the opinion that accurate detection of signals and reliable causality assessment should also be possible for some but not all functional foods. A non-anonymous report of high quality that contains sufficient information is a prerequisite. According to Lareb it is not possible to focus on all functional foods, therefore it is necessary to have a demarcation of foods that should be monitored. Products that can be monitored by their system are specific foods, for example products that contain one particular ingredient (e.g. the novel food ingredient phytosterol). Examples of foods that cannot be monitored are vitamin and/or mineral enriched foods as accurate detection of smoke signals is not possible for combinations of foods and their ingredients (e.g. all foods enriched with vitamin E). Another limitation is that Lareb's system only detects acute adverse effects caused by specific functional foods and/or food ingredients. Long term adverse events may very difficult to

determine with the current system because a) causality assessment over a long time is almost impossible because of a lot of potential confounding variables and b) the quality of the complaints reported is questionable as people may not be able to suspect a relationship between their functional food consumption say 10 years ago and their currently experienced adverse effects.

Lareb is willing to implement the registration of consumer complaints regarding functional foods in their current system. Therefore adaptation of their current reporting system is required, for example questionnaires which focus on specific functional food consumption should be developed and uploaded.

3.3 VWA

The VWA (the Inspectorate for Health Protection and Veterinary Public Health) is an independent agency of the Ministry of Agriculture, Nature and Food Quality (LNV). The VWA aims to achieve the visible reduction of food and consumer product risks and thus promote public health, animal health and animal welfare. The VWA includes a Bureau of Risk Assessment alongside the Directorate Inspection, Strategy and Communication and the Directorate Implementation, Enforcement and Surveillance. Activities are evaluated in terms of the strategic triangle: Risk Assessment, Supervision and Risk Communication. The VWA is mainly financed by the Ministry of Health, Welfare and Sports (VWS), and also partly by the Ministry of Agriculture, Nature and Food Quality. The specific tasks of the Inspectorate are a) the enforcing of compliance with regulations for foodstuffs, consumer items and veterinary matters, b) the investigation of health hazard situations and consumer complaints, c) advise to policy-making authorities (both asked-for and unasked-for), and d) development and publication of research methods¹⁴. In addition to the General Inspectorate in The Hague, there are 5 Regional Offices: North, East, South, North-West and South-West. Each Regional Inspectorate carries out a special task with regard to a selected product area and has its own laboratories. These areas of special interest support the national surveillance and enforcement policy. In the Region South office the interest focuses among others on 'composite food products', which includes functional foods and supplements.

3.3.1 Report channels

Complaints about food and consumer products can be reported by the consumer through a questionnaire on the VWA website or by phone. On the website there are three options: 1) a complaint about food poisoning, 2) a complaint about a product (food or non-food) and 3) other complaints, e.g. about a dangerous playground. If the complaint is about a food poisoning, the consumer is advised to phone the complaints department (in Dutch: Warenklachtenlijn) instead of emailing the complaint. Food poisoning is an acute situation and therefore it is preferred to handle the complaint by telephone. Other complaints can be dealt with through the internet (see Appendix 2 for an example of a report form). Complaints can be reported anonymously if desirable. Personal information is only used for feedback to the consumer. Most complaints received by VWA are about inferior products. Manufacturers are not obliged to report complaints received through their own consumer care lines to VWA. Only if a product is withdrawn from the market a report to VWA is obliged. In 2004, the VWA received 42,213 complaints and questions by phone and 4,362 complaints and questions by e-mail. Of these contacts, 6,432 were registered as a complaint and 2,394 resulted in legal action. Food poisoning was reported 749 times and misleading 228 times.

3.3.2 Information gathering

In Table 3.2 the data is presented which is gathered by VWA in case a food-related complaint is received. Not all food-related complaints are registered. The employee at the complaints department who receives the complaint or question decides whether a complaint or question needs follow-up. If this is the case, the complaint is registered. In general, the detection of legal violation is the main focus in order to protect the consumer.

Table 3.2: General data gathered by VWA for each complaint

1) Personal data of the consumer	
2) Complaint	- Anamnesis
3) Sale information	- Where was the product bought? - When was the product bought?
4) Details of the manufacturer	- Name, address - brand - name of the product
5) Details of the product	- 'best before' date - production code - content - package material
6) Consumption information	- When did you eat the product? - Did you keep the remainder? - Where did you keep the remainder?

3.3.3 Signal detection

The complaint system is computer-based, but complaints about functional foods are not registered separately. If several complaints about one type of food product are received, a systematic investigation can be started. Usually, this investigation is initiated if five or more complaints about one type of food product are received. The investigation consists of the following parts: a) food product sampling, both at the consumer site and at the restaurant or the manufacturer site, b) blood and faeces examination, if appropriate and if the consumer consents, if appropriate information might also be collected at the local community health service. A report on the findings and the conclusions are send to the consumer, if desired. If a legal violation is found (e.g. pathogenic bacteria in a food product), VWA can take legal action (written warning or fine).

3.3.4 Possibilities and restrictions regarding PLM on functional foods

Adaptation of the current system in force may be possible but is dependent on the amount of information on functional foods that needs to be collected. It may be possible to flag complaints about functional foods and include for example one or two questions about

specific functional foods and redirect the consumer to another specific website. VWA is known by the consumers as an authority for product complaints. Consumers are familiar with the telephone care lines and the consumer website. The most suitable option would be to make use of this gateway, because it is very difficult to make consumers aware of a new website or telephone care line for complaints about functional foods without introducing apprehension about this particular food group. Nevertheless, it is important to be able to act if serious complaints about functional foods are received. VWA has this authorization.

There are also a few limitations to note. Indeed, the emphasis of VWA's mandate has been placed on the detection of legal violations. The complaints one expects to find through functional foods consumption probably do not originate from a legal violation. In addition, as the complaints are judged by VWA-employees from the complaints department, there is a fair chance that these particular functional food complaints will not be registered, as they might appear insignificant and not related to specific food consumption.

3.4 Recommendations

After consulting Lareb and VWA about the necessities, opportunities and limitations to implement a PLM system regarding functional foods, four different options may be considered. The pros and cons of the different options are described below.

1) Cooperation Lareb - VWA:

- Complaints submitted to VWA → registration of complaint by VWA;
- VWA forwards the complaint to Lareb (website): if necessary, more information will be gathered;
- Evaluation of the complaints by Lareb;
- Lareb reports to VWA.

PRO: VWA is known by consumers as an authority for product complaints;
Lareb is experienced in the evaluation and causality assessment of complaints;
Lareb is experienced in the development and maintenance of a suitable database;
VWA is authorized to take legal action.

CON: Current system of VWA needs to be adjusted: the amount of information that has to be gathered will increase. As well, all complaints need to be registered, which is not the case at the moment.

2) Cooperation Lareb - VWA:

- Complaints submitted to VWA → Functional food scanning by VWA;
- In case of a functional food: VWA refers directly to Lareb (website) → registration of complaint by Lareb;
- Information gathering by Lareb;
- Evaluation of complaints by Lareb;
- Lareb reports to VWA.

PRO: VWA is known by consumers as an authority for product complaints;
Current system of Lareb needs to be adjusted, but Lareb is prepared to do this;
Current system of VWA needs only a slight adjustment;
Lareb is experienced in the evaluation and causality assessment of complaints;
Lareb is experienced in the development and maintenance of a suitable database;
VWA is authorized to take legal action.

CON: Consumers have to deal with two different complaint handling authorities.

3) Cooperation Lareb - VWA:

- Complaints submitted to Lareb → registration of complaints by Lareb;
- Information gathering by Lareb;
- Evaluation of complaints by Lareb;
- Lareb reports to VWA.

PRO: Current system of Lareb needs to be adjusted, but Lareb is prepared to do this;
Current system of VWA does not need any adjustment;
Lareb is experienced in the evaluation and causality assessment of complaints;
Lareb is experienced in the development and maintenance of a suitable database;
VWA is authorized to take legal action.

CON: Lareb is not known to the consumers as an authority for complaints about food.

4) VWA:

- Complaints are submitted to and registered by VWA;
- Information gathering by VWA;
- Evaluation of complaints by VWA;
- If necessary, VWA can take action.

PRO: VWA is known by consumers as an authority for complaints about food;

VWA is authorized to take legal action.

CON: Current system of VWA needs to be adjusted: the amount of information that has to be gathered will increase. As well, all complaints need to be registered, which is not the case at the moment.

Looking at the pros and cons of each option, preference might be given to the second option.

VWA already receives complaints about foods and the authority is known to the consumer.

However, the telephone operators of VWA function as a first sieve. Registration of complaints is subject to a personal assessment of the telephone operator and this might be a future pitfall. As it is not known what kind of complaints will be received through functional foods consumption, it is important to register all incoming complaints. For medicines, Lareb uses this approach: all complaints are registered and evaluated on a case by case basis. For the second option the complaints are submitted to VWA. The complaint department has to be instructed to redirect the consumer to the Lareb website, if the complaint involves a functional food. In this way adaptation of the current system of VWA is minimal. No special consumer campaigns are necessary to inform them about where to submit a complaint.

The system of Lareb needs to be adapted in order to include complaints about functional foods, but Lareb is willing to make this adjustment. Lareb has experience with the follow-up of complaints and the set up and maintenance of a suitable database of reports.

In Figure 3.1 the performance of passive 'smoke' signaling is visualised.

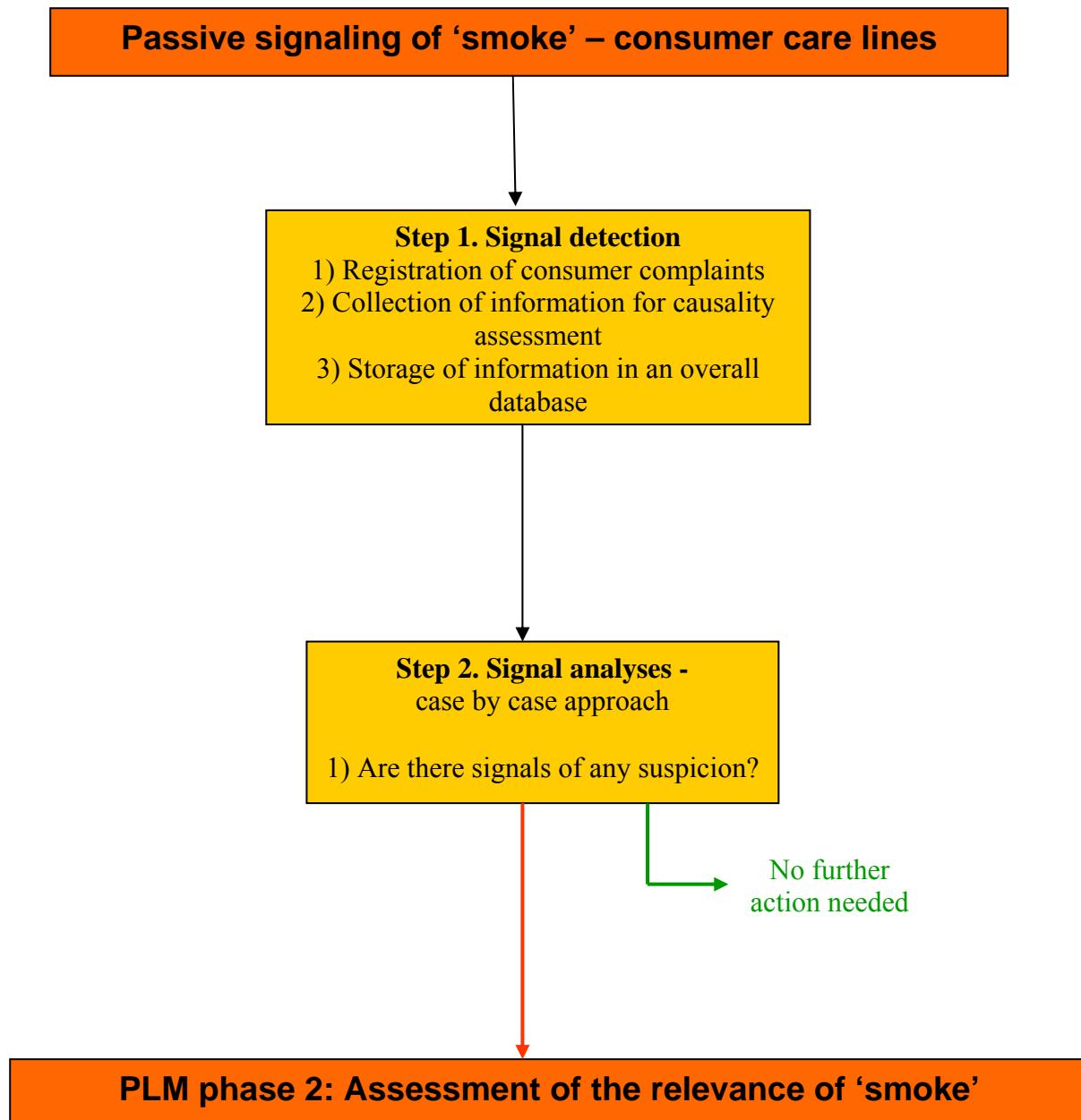


Figure 3.1: Graphical presentation of the passive signaling of 'smoke' within PLM

Lareb is not authorized to take legal action. Therefore, the evaluation and interpretation of the complaints has to be reported to among others VWA as they are authorized to take the appropriate legal steps. The decision about whether or not to proceed to a next PLM phase should be based on the factual report obtained through the passive 'smoke' signalling phase and should be made by an independent expert committee (see further Paragraph 4.5). In Figure 3.2 an overview of the potential players in the PLM field is presented. Lareb reports back to VWA, but also has to report to the expert committee deciding on whether or not to proceed to a next PLM phase in addition to VWS and/or MEB. There is still one question

mark in the Figure. At the moment manufacturers are not legally obliged to report any side effects of their products to a governmental institute only in case of a severe situation. This might imply that minor complaints are neglected or that the product is silently removed from the market keeping a pitfall open for the next manufacturer and consumer.

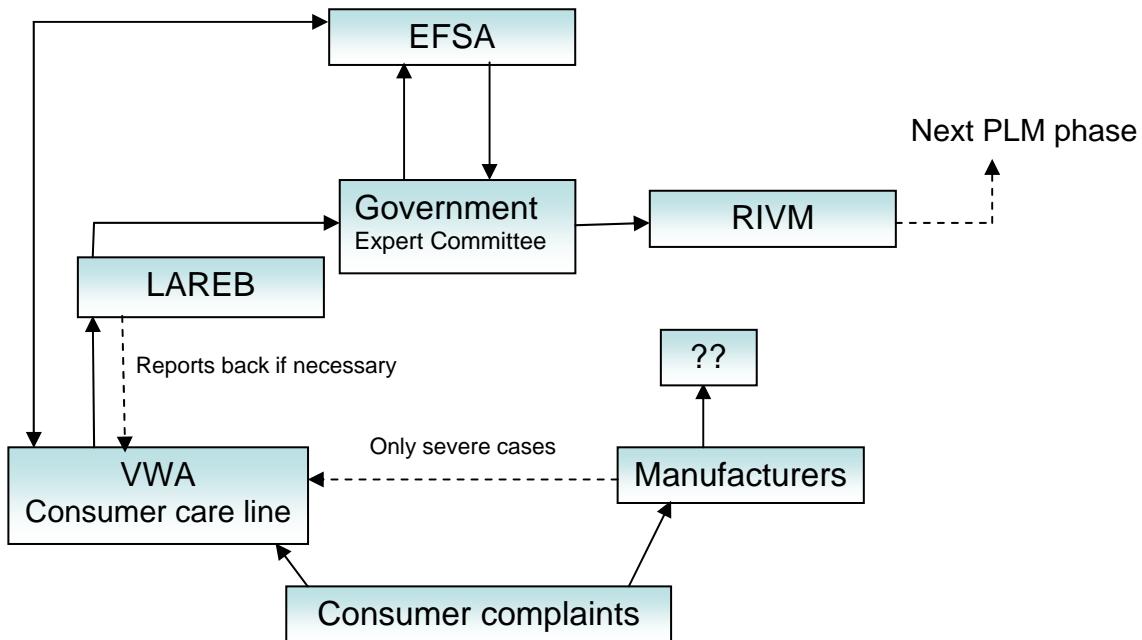


Figure 3.2: Presentation of the players in the PLM field

For the moment, the system described above is only effective in case of acute adverse events or perhaps events that frequently occur through cumulative effects after a long term steady consumption of one particular functional food. It is impossible to link a certain health problem to a food consumed some years ago. Also effects from a combined use of several functional foods cannot be investigated. Last but not least, financial issues should be arranged. It might be prudent to ask the functional food and supplement manufacturers for financial support of the described PLM actions as is also the case in post marketing surveillance of medicines. Another possibility that might be worth to examine is whether insurance companies could benefit from such a system and therefore be interested in financing parts of PLM in addition to governmental (national and EU) money.

3.5 Outcomes of the meeting on signal detection

‘there is no effect without a side effect’

Discussion partners were Hugo de Sitter (VWA), Eugène van Puijenbroek (Lareb), Heidi Fransen, Saskia van den Berg, Nynke de Jong (RIVM), and Wieke Tas (VWS). In Appendix 3 a description of the meeting is given. In short, it was questioned by Lareb whether there is any reason not to perform PLM? The answer to that would be ‘no’ apart from financial constraints. It is therefore that VWS is hesitant to invest in the development of systems that might not be imbedded in future EU-regulations or structures. The single result obtained from the analyses on consumer complaints is the relay of a signal, even the faintest, that something might be happening. VWA emphasised the fact that even if something is happening it might not be in the position to act because the observations of side effects of consumption of functional foods do not seem to be legal violations. Nevertheless, there may be one option to get a registration of consumer complaints adopted through the manufacturer with VWA as a controller. This is via the HACCP (Hazard Analysis Critical Control Point) task of manufacturers. Within this task a consumer care system should be in place. VWA might be able to check the manufacturer’s actions with respect to the consumer complaints as part of their inspection’s mandate on the HACCP task. In this way pressure is exerted on the manufacturers to register and act upon consumer complaints. Notification to VWA or Lareb should be part of this. In case a manufacturer wants to provide a specific claim then he/she should also pay for consumer safety, even if the complaint is based on overdosing via many different foods. The first task that needs to be performed is to develop a uniform and structured protocol for the manufacturers about how to operate their consumer care line for among others PLM purposes. The implementation of these structured protocols can only be successful if the government exerts pressure on this. It is highly preferable to have these ideas and protocols implemented in accordance to EU initiatives. The second task would be to organise the VWA back office that may come into action if a manufacturer notifies a complaint. Lareb may come into action in case causality needs to be assessed. One might consider a flow from VWA to Lareb, but one might also consider a flow from the manufacturer to Lareb.

How does the outcome of this meeting stroke with second option described above? In fact it does not completely match, but the main elements and principles do. If manufacturers have

the duty to notify VWA about the registered consumer complaints, VWA's back office may collect the information and call in Lareb's experience to analyze, evaluate and store the datasets on the complaints to find a meaningful signal. In addition to this mainstream of complaints registration through the manufacturers, it may be prudent to have an additional completely independent system in place like the second option described above. This is also the case in pharmacovigilance but it is upon the (inter)national policy makers to decide.

4. Active signaling of ‘smoke’

4.1 Background

Similar to the passive signaling of smoke, 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. Active signaling of smoke should be operational because it is supposed to pick up other smoke signals than the registration of consumer complaints (i.e. passive signaling of ‘smoke’). 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. Furthermore, the methodology for the active signaling of smoke should be outlined, both for the active signaling of potential negative effects of functional foods as well for the active signaling of too high exposure levels. Moreover, decision criteria should be developed that indicate which smoke signals are relevant to follow-up in a next PLM phase.

4.2 Prioritizing criteria

The prioritizing of functional foods or functional ingredients in the active signaling phase means to rank the importance of the topics. If a food or ingredient does not meet the prioritizing criteria in first instance, it does not imply that follow-up is excluded. The prioritizing can be assigned on different grounds. The selection process may be focused on the type of functional food, for example a more classical food enriched with certain vitamins and/or minerals vs. an ‘innovative’ food enriched with specific bio-active compounds such as phytosterols, but also fibers, bacteria, processed proteins, etcetera. This distinction is less clear than the traditional distinction made by the EU Novel Food Regulation⁶ between novel foods vs. non-novel foods. Consumption of most classical vitamin/mineral enriched foods is generally and historically regarded as safe and as such may get a lower priority. Exceptions are foods enriched with those vitamins and minerals for which exemption is needed by Dutch law (vitamin A, D, folic acid, selenium, copper, and zinc). Consumption levels in the population will be of importance too: e.g. is there a possibility of a high level in a small group, or is there a moderate consumption pattern but in a large group (the whole population, including non-target groups). The window between the recommended intake and the safe upper limit of intake may be a decision factor in this: e.g. when the range between recommended dietary intake and the safe upper limit is rather narrow (factor 2 to 3) the

priority may be high. This accounts among others for the exemption vitamins and minerals mentioned above. Also, the seriousness of the potential adverse effect may be a weighing factor. The number of available foods, supplements and/or medicines with a similar active ingredient may count as a weighing factor as well as the number of years passed after market introduction. It might be prudent to incorporate an evaluation moment at 10 years after market introduction to check the consumption patterns and associated effects and to keep checking this after every multiple of 10 years. In their extensive report ³, the FDA has among others proposed a framework for evaluating the safety of dietary supplement ingredients. Within this framework a first action is the screening of the large list of supplements and their ingredients currently available on the market. As a starting point the number of serious adverse events reported could function as a prioritizing criterion. Also, a priority list prepared by experts or by sales volume could function as such. One of the last options would be a random selection. To this end, answers to 'yes or no' questions were suggested to flag substances that warrant some level of attention. Questions focused on: the novelty of the ingredients (market introduction after 1994), evidence of serious adverse events observed in humans (does the number of serious adverse events reported appear high compared to the prevalence of use of the ingredient? does it seem plausible that particular subpopulations are particularly susceptible to serious adverse events reported for this ingredient?), evidence of other concerns (safety concerns from other groups or organizations, strong evidence of serious interactions with prescription drugs, evidence of hormonal mimicking) ³.

In Figure 4.1 we present the flow chart of the active signaling of 'smoke': the prioritizing criteria and the signal detection for the first PLM phase. In order to find the answers to the questions formulated in this Figure several databases are needed. In addition to basic information on RDA's (recommended daily allowances), UL's (safe upper level), NOAEL's, LOAEL's (no and lowest adverse effects level), sales data, and safety review data (public or manufacturer's private) on adverse events, also food consumption data are a primary source of information to base the follow-up of 'smoke' signals on. In Paragraph 4.4 we elaborate on the availability and implications of intake data.

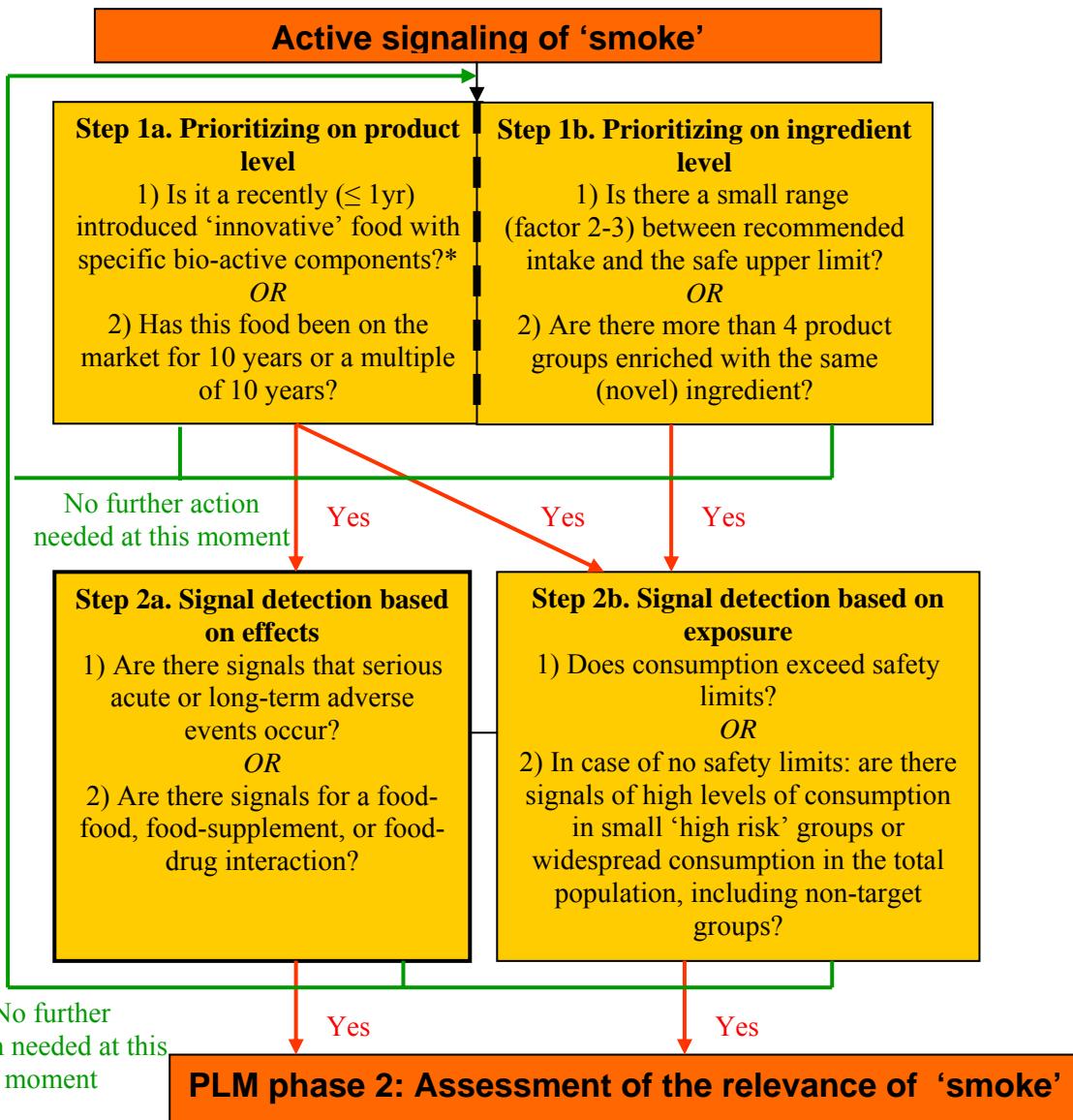


Figure 4.1: Graphical presentation of the active signaling of 'smoke' within PLM

* The selection process is focused on the distinction between a more classical food enriched with vitamins and/or minerals regarded as safe based on historical use vs. an 'innovative' food enriched with specific bio-active compounds such as phytosterols, fibers, bacteria, processed proteins, etc.

4.3 Literature screening of side effects

The literature screening on side effects should focus on a) gathering information on serious acute or long term side effects, and b) gathering information on the potential for a food-food, food-supplement or food-drug interaction. The information on side effects might be obtained by scanning the literature databases available in the public domain, but might also be

obtained by retrieving information known to the manufacturer. For novel foods this information should be presented in the toxicological reports accompanying the EU-Novel Food approval applications. As such this information should be made available to the PLM performing investigators. For other foods and supplements not seeking EU approval any information on side effects known to the manufacturer should also be made available to the active investigators in the PLM field. This should also be the case for new insights on side effects of novel foods after approval has been obtained.

The basic information on potential interactions should also be retrieved from the literature databases available in the public domain. Additional specific information, among others with respect to size of the problem, might also be retrieved from specific knowledge or focused investigations or trials in collaboration with for example pharmacies, physicians, drugstores, supermarkets or market research agencies.

The methodologies and results of the literature screening should be systematically stored in a database. Information on the date, and source of the information, specifications of the compound or food involved, a description of the side effect, the strength of evidence, and the population groups involved, how the side effect was discovered by the source, as well as follow-up actions should be stored systematically in a central database.

4.4 Monitoring intake

As described above, part of the active signaling can involve monitoring of adoption and consumption patterns of the new product, and its components in specific samples or even representative samples of the population. Post-launch monitoring provides among others a means to confirm or refute that the actual intake levels are within the anticipated range and that usage patterns in the target population are or are not consistent with predictions.

Monitoring of exposure/consumption of a (group of) functional food(s) may be possible in the new Dutch National Food Consumption Surveys. An advise regarding the outline of future dietary monitoring in the Netherlands has been published recently ¹¹. In brief, the main elements are:

1. Continuous food consumption data collection in the general population (living in household) aged 7 and above; 2 independent 24-h recalls + additional questionnaire

including food frequency questions; 3 year cycles for analysis and reporting (n about 4000 for each cycle); (=core survey)

2. Additional food consumption data for groups that require other dietary assessment methods/design/approaches, like children aged ½ - 6 years, ethnic groups, institutionalized elderly, pregnant and lactating women. Similarly to the core survey information on actual food intake on 2 independent days + additional information on habitual intake of specific foods are collected in a limited number of people. (=specific groups surveys)
3. Follow-up studies, e.g. nutritional status or studies on determinants of food consumption (=follow up surveys)
4. Consumption data on specific foods (supplements, specific functional foods, foods known to be polluted) that are consumed by a relatively small part of the population, sometimes on an irregular basis. Data should be collected in very large samples (n 50.000 and above) by internet questionnaires (=specific products survey).

Figure 4.2 shows the elements in relation to each other.

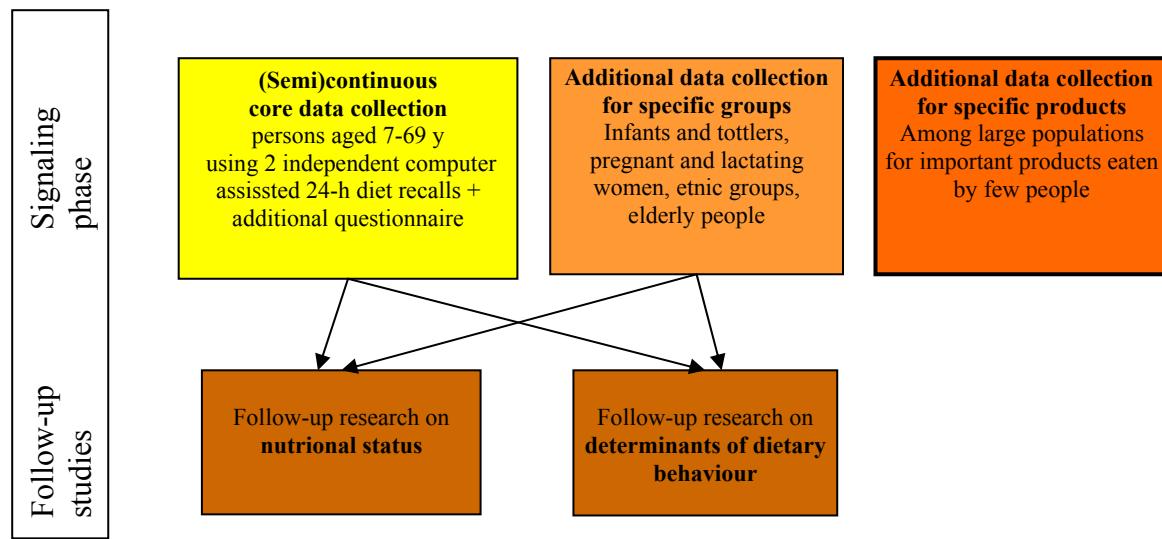


Figure 4.2: Schematic overview of the proposed new system of dietary monitoring in the Netherlands including a semi(continuous) collection of data pertaining to the general population aged 7 to 69 years (yellow module), and additional surveys for the specific target groups (orange module) and specific foods (red module), and nutritional status and determinants of behavior (brown modules).

Depending on the type of functional foods and the (sub)population of interest, consumption may either be monitored in the core survey, the survey on specific groups or the survey on specific products. In the next section we will discuss the possibilities within these elements and give some advice to adapt the elements for Postlaunch Monitoring purposes.

In the *core survey*, two types of dietary assessment methods are employed in the general population, i.e. 2 independent dietary recalls and a concise food frequency questionnaire. Experience with this type of survey has been gained in 2003, and is planned to be extended for children aged 7 and above in the coming years. When the outcome is successful the continuous data collection could start afterwards, if sufficient funding is available. The 24-h recall data in the core survey are suitable to estimate the usual distribution of intake of foods that are frequently consumed by a large proportion of the population, or for nutrients/compounds that have various food sources that are together frequently consumed by a large proportion of the population. The food frequency questionnaire has the advantage that it provides valuable information for foods that are consumed infrequently by a considerable proportion of the population. The usual intake distribution of micronutrients that are used abundantly for enrichment, like vitamins C and B6 can be estimated from the core survey data. For other enriched foods like those with folic acid or for specific novel foods like products with phytosterols or -stanols, which are consumed by fewer people, the data give some insight but insufficient to estimate the percentage of subjects above a safe upper level. For PLM of functional foods, we advise that those (types of) functional foods that are estimated to be consumed by say 1-10 % of the population but not on a daily basis is incorporated in the food frequency questionnaire. In the anticipated study population of 4000 subjects in the three year period, this would give information on consumption frequency (and amounts if relevant) in 40-400 subjects. The usefulness of the final data is depended on type of product, type of consumer and for example the associated within-person and between-person variations in intake.

Similarly, the *specific groups surveys* are valuable for PLM for the same types of functional foods but in specific groups. Since the study size of these surveys will probably be smaller than that of the core survey, functional foods that are consumed by a higher percentage of subjects can be included. In 2005/2006 experience will be gained for the group of children aged 2-6 years (intended study size 1280), and the food frequency questionnaire will provide information on margarine and dairy foods enriched with phytosterols/-stanols, probiotics,

vitamin and/or mineral enriched juices, deserts, dairy foods or biscuits and dietary supplements.

The *specific products surveys* are specifically aimed at those products of interest that are consumed by too few people in the core survey or the specific groups survey. Until now, this type of survey has not been conducted within the national food consumption survey system. The specific products that may be included are specific dietary supplements, specific functional foods, and foods high in potential hazardous chemicals (e.g. fatty fish). For Postlaunch Monitoring, we advise that the questionnaires are flexible in nature and will be targeted on those functional foods and dietary supplements for which the decision tree indicates that consumption should be monitored but that are consumed by less than e.g. 5% of the general population. Depending on the groups at risk or the target group, the questionnaire could be set out to specific subgroups. In order to reach a sufficient number of consumers of the specific foods, screening questions in very large population samples should be applied preferably through internet. The targeted food frequency follow-up questions can then be shown to those subjects that indicate in the screening questions they are users of the products. Details of the procedures and the types of questions will be developed on commission of VWA and will be published in a separate RIVM report.

The third element '*follow-up studies*' may also be of interest for Postlaunch Monitoring of functional foods, but more with respect to follow-up of 'smoke signals', rather than for smoke detection. This will be part of the next phase of PLM and therefore out of the scope of the current report.

4.5 Further methodological issues

The work for both the passive and the active 'smoke' signaling should be performed next to each other (see Figure 4.3), and for both the passive as well as the active 'smoke' signaling phases, a mandate for investigation should be given by the principle stakeholder in the PLM issue: the government. The national and/or international governments should also prepare to be able to pursue the requested premarket safety information from the manufacturers. Among others liaison with novel food committees to obtain this private information may be necessary. These same governments might need to think about the gap in food laws with

respect to a manufacturer's duty to report any side effects obtained through their consumer care lines.

We propose to try-out our decision scheme on a case-by-case basis. The factual report compiled by the PLM investigators with their answers on the questions formulated in the schemes in the Figures 3.1 and 4.1 and their conclusions about whether or not to proceed to a next PLM phase should be evaluated by an ad-hoc expert committee existing of stakeholder members (e.g. scientists of different disciplines, government, consumer representatives). A manufacturer representative will be invited too to present and possibly defend the case, but will not have a 'voting right'. In the course of time and the experience gained through this case-by-case approach the committee will have to develop a systematic approach to assess the seriousness of the topic. Based on the compiled information the ad-hoc committee will have to make a 'go – or no go' decision. In case of a 'no-go', it should be decided whether a renewed valuation is deemed to be appropriate in a later stage, for example if additional data have become available.

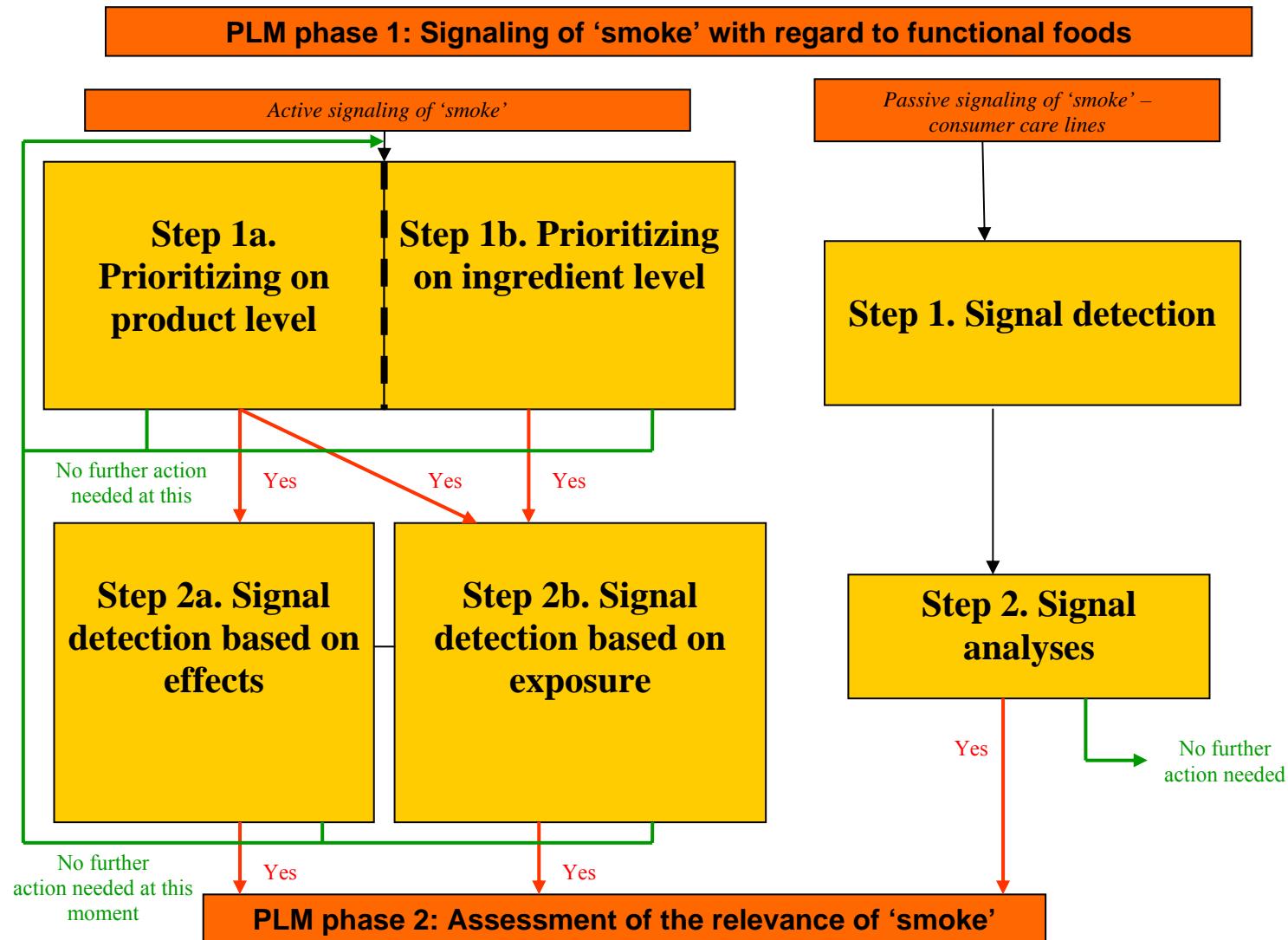


Figure 4.3: Passive and active monitoring should be performed concurrently

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References

1. Bureau Nieuwe Voedingsmiddelen (CBG). Toelichting bij aanvraag Europese markttoelating van nieuw voedingsmiddel, voedselingrediënt of proces. 2005; Available at www.cbg-meb.nl/nl/docs/nwvoeding/Toelichting%20aanvraag%20nieuw%20voedingsmiddel.pdf.
2. Commissie van de Europese Gemeenschappen. Voorstel voor een Verordening van het Europees Parlement en de Raad betreffende de toevoeging van vitamines en mineralen en bepaalde andere stoffen aan levensmiddelen. Brussel, 2003; COM (2003) ; vol 671 (definitief).
3. Committee on the Framework for Evaluating the Safety of Dietary Supplements. Proposed Framework for Evaluating the Safety of Dietary Supplements. Washington, DC: National Academy Press, 2003.
4. de Jong N, Buurma-Rethans EJM, Fransen HP, Ocké MC. Postlaunch monitoring of functional foods. Methodology development (II). Bilthoven: RIVM, 2005; reportnr. 350030005.
5. de Jong N, Ocké MC. Postlaunch Monitoring of Functional Foods - Methodology Development (I). Bilthoven: RIVM, 2004; reportnr. 350030001.
6. European Commission. Regulation (EC) No 258/97 of the European Parliament and of the Council of 27 January 1997 concerning novel foods and novel food ingredients Official Journal, 1997; vol L043.
7. Hof van Justitie. Arrest Commissie/Nederland, Zaak C-41/02. 2004.
8. Kreijl CF, Knaap AGAC, Busch MCM *et al.* Ons eten gemeten. Houten: Bohn Stafleu Van Loghum, Bilthoven; RIVM, 2004; reportnr 270555007.
9. Lareb (Netherlands Farmacovigilance Centre). Annual report 2004. 's-Hertogenbosch, the Netherlands: Lareb, 2004. Available at www.lareb.nl.
10. Ministerie van VWS. Toevoeging microvoedingsstoffen aan levensmiddelen. 2005; Staatscourant; vol nr. 48.
11. Ocké M, Hulshof K, Bakker M, Stafleu A, Streppel M. RIVM report: towards a new system of dietary monitoring in the Netherlands . Bilthoven, RIVM and TNO, 2005; reportnr 350050001. Update available at http://cms2preview/vcp/Images/briefrapport%20toekomst_tcm68-25896.doc.
12. Scientific Committee on Food. Guidance on submissions for safety evaluations of sources of nutrients or of other ingredients proposed for use in the manufacture of foods. Brussel, 2001; SCF/CS/ADD/NUT/21 Final.
13. van Grootenhuis AC, Passier JL, van Puijenbroek EP. Direct reporting of side effects by the patient: favourable experience in the first year. Ned Tijdschr Geneesk 2005; 149(10):529-33.
14. VWA (The Food and Consumer Product Safety Authority) . Annual report VWA 2004. The Hague, the Netherlands: VWA, 2004. Available at www.vwa.nl.

Appendix 1: Example form of Lareb consumer care line

Lareb
Nederlands Bijwerkingen Centrum
Netherlands Pharmacovigilance Centre

MELDFORMULIER
PATIENT

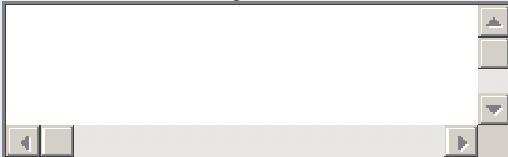
A BIJWERKINGEN

	Bijwerking [1]	
⌚	Vermoedelijke bijwerking*	<input type="text"/>
⌚	Begindatum bijwerking* (dd-mm-jjjj bijvoorbeeld 03-03-1996, dag en maand zijn niet verplicht, maar graag zo precies mogelijk invullen)	<input type="text"/> <input type="text"/> <input type="text"/>
⌚	Hoe lang gebruikte u het geneesmiddel voordat de klachten optraden?	<input type="text"/> <input type="text"/> selecteer eenheid <input type="button"/>
⌚	Afloop*	<input type="text"/> selecteer afloop... <input type="button"/>
Waren er nog andere bijwerkingen?		Andere bijwerking +
⌚	Is/zijn de bijwerking(en) behandeld en zo ja waarmee?*	<input type="checkbox"/> Nee <input type="checkbox"/> Onbekend <input type="checkbox"/> Ja. Behandeld met: <input type="text"/>

 Zijn de klachten bij een eerder gebruik van het verdachte geneesmiddel ook al eens opgetreden?*

Nee
 Onbekend
 Niet van toepassing
 Ja. Klachten die opgetreden waren:


 Zijn er mogelijk andere omstandigheden of oorzaken die de klachten kunnen hebben veroorzaakt of verergerd?*

Nee
 Onbekend
 Ja. Andere omstandigheden waren:


 Heeft de bijwerking geleid tot een van de hieronder genoemde situaties?*

Nee
 Ja, namelijk:
 Overlijden
 Levensbedreigend
 Ziekenhuisopname
 Blijvende arbeidsongeschiktheid
 Afwijkingen bij pasgeboren kind
 Overige ernstige afwijkingen

Gegevens van de moeder	
 Geboortedatum (dd-mm-jjjj bijvoorbeeld 03-03-1996, volledig invullen)	<input type="text"/> <input type="text"/> <input type="text"/>
 Wanneer in de zwangerschap (gerekend vanaf het begin) werd het verdachte geneesmiddel voor het eerst gebruikt?	<input type="text"/> <input type="button" value="selecteer eenheid..."/> 

B GENEESMIDDEL

	Geneesmiddel [1]	
--	------------------	--

<p>7 Verdacht geneesmiddel* <input type="text"/></p> <p>7 Startdatum* (dd-mm-jjjj bijvoorbeeld 03-03-1996, dag en maand zijn niet verplicht, maar graag zo precies mogelijk invullen)</p> <p>7 Dosering <input type="text"/></p> <p>7 Indicatie <input type="text"/></p> <p>7 Aanpassing gebruik na optreden bijwerking <input type="text"/> selecteer... <input type="button" value="▼"/></p> <p>indien gestopt: <input type="text"/></p> <p>7 Stopdatum (dd-mm-jjjj bijvoorbeeld 03-03-1996, dag en maand zijn niet verplicht, maar graag zo precies mogelijk invullen)</p>	<p>Gebruikt andere geneesmiddelen die volgens u ook verdacht zijn? Geneesmiddelen die niet verdacht zijn of waarvan u niet weet of ze een rol hebben gespeeld bij de klachten (comedicatie) kunt u hieronder invullen</p> <p>Ander verdacht geneesmiddel +</p>
--	--

		Comedicatie
⑦	Gebruikt u nog andere - niet verdachte - geneesmiddelen?*	<input type="radio"/> Nee <input type="radio"/> Onbekend <input type="radio"/> Ja (hieronder specificeren)

C UW GEGEVENS		
⑦	Geslacht*	<input type="radio"/> Man <input type="radio"/> Vrouw
⑦	Voornaam/letter*	<input type="text"/>
⑦	Achternaam*	<input type="text"/>
⑦	Geboortedatum* <i>(dd-mm-jjjj bijvoorbeeld 03-03-1996, volledig invullen)</i>	<input type="text"/> <input type="text"/> <input type="text"/>
⑦	Gewicht	<input type="text"/> kilogram
⑦	Lengte	<input type="text"/> centimeters
⑦	Email*	<input type="text"/>
⑦	Adres	<input type="text"/>
⑦	Postcode	<input type="text"/>
⑦	Plaats	<input type="text"/>
⑦	Telefoon	<input type="text"/>

D GEGEVENS VAN DE VOORSCHRIJVER

Door wie is dit geneesmiddel
voorgeschreven?*



huisarts



specialist



niemand (middel zonder
recept)



Naam



Adres



Plaats

E GEGEVENS VAN DE VERSTREKKER

Waar heeft u het geneesmiddel
opgehaald?



apotheek



drogist



Naam



Adres



Plaats

F VERWERKING VAN DE GEGEVENS

Wilt u een inhoudelijke
schriftelijke terugkoppeling op



Nee

uw melding ontvangen?*

Ja

 Ruimte voor eventueel overig commentaar:

 Wilt u een bevestigingsmail van deze melding met een overzicht?*

Nee

Ja, emailadres:

Vul svp alle velden zo precies mogelijk in! Dit is in het belang van de kwaliteit van de melding.

Klik de knop hieronder om de melding gereed te maken voor verzending.

[GA NAAR HET OVERZICHT VOOR VERZENDING >](#)

Appendix 2: Example form of VWA consumer care line



Warenklachtenlijn

Meer informatie

Omschrijf uw klacht zo volledig mogelijk. Noem bijvoorbeeld omschrijving van het product, samenstelling van het product, omschrijving van de verontreiniging of het vreemde voorwerp (b.v. centimeters), hoeveelheden, gevolgen, omstandigheden, etc.

Uw gegevens

voornaam	<input type="text"/>	achternaam	<input type="text"/>
straatnaam	<input type="text"/>	huisnummer	<input type="text"/>
postcode	<input type="text"/>	plaatsnaam	<input type="text"/>
telefoonnummer	<input type="text"/> 1	telefoonnummer	<input type="text"/> 2
(S.v.p. het telefoonnummer noteren waarop u overdag bereikbaar bent. Het tweede telefoonnummer kunt u desgewenst leeg laten.)			
email-adres	<input type="text"/>		

Wat is uw klacht?

Waar heeft u het product gekocht?

naam	<input type="text"/>
adres	<input type="text"/>
postcode	<input type="text"/> Plaatsnaam <input type="text"/>

Wie is de fabrikant?

naam	<input type="text"/>
adres	<input type="text"/>
postcode	<input type="text"/> Plaatsnaam <input type="text"/>
Merk	<input type="text"/> Productsoort/ Productnaam <input type="text"/>

Wij verzoeken u het artikel waarop uw klacht betrekking heeft te bewaren.

Onderstaande vragen alleen invullen wanneer uw klacht betrekking heeft op etenswaren

Ten-minste-houdbaar-tot- datum	<input type="text"/>
Productiecode	<input type="text"/>

Inhoud

Soort verpakking

karton papier metaal glas
 plastic overig

Op welke datum heeft u het product gekocht / genuttigd het probleem
geconstateerd? / /

Heeft u het restant bewaard? ja / nee

Als u het restant bewaard heeft, heeft u dit dan gedaan in de koelkast in de
diepvries elders

Verzenden

Appendix 3: Report of a meeting on PLM passive smoke signaling

Report of a meeting on PLM passive smoke signaling



LAREB / VWA / VWS / RIVM

Bilthoven, 28 November 2005

Participants:

LAREB

Eugène van Puijenbroek

VWA

Hugo de Sitter

VWS

Wieke Tas

RIVM

Nynke de Jong, Saskia van den Berg, Heidi Fransen

Objective of the meeting:

- To determine in what way existing consumer care systems can be applied to passive 'smoke signaling' for functional foods
- To determine how this signaling system should be organised in the near future

Beforehand, five questions were formulated:

- 1) Is the PLM part of passive 'smoke signaling' useful enough to be carried out?
- 2) If yes, how?
- 3) How can we contribute to each others activities?
- 4) Is there any possibility to include manufacturers in this PLM activity?
- 5) How are we going to proceed?

Welcome

A word of welcome was expressed. We agreed to have a written report from this meeting. This report will also be published in the future RIVM report on PLM smoke signaling.

Key words with respect to the starting points

Lareb: carefully optimistic, actual ideas, willingness, experience

VWA: hesitant, practical limitations, mandate (legal offence?)

VWS: make use of current systems, financial constraints

RIVM: design PLM, future executor?

LAREB:

The starting point in the pharmaceutical field is 'there is no effect without a side effect'. This may also apply to functional foods. The effect of novel ingredients or altered concentrations of ingredients in foods may also induce side effects which we are not aware of at this moment. Lareb is currently in contact with Unilever to investigate the possibilities of their consumer care lines. Lareb has a lot of experience in the pharmaceutical field and is reasonably optimistic about the opportunities for complaints registration about functional foods. The most important thing is to have a clear description of the reported consumer problem. One of the prerequisites of passive smoke signaling is to structurally ask about the details of the complaint. There are two issues that are difficult to analyze (also in the pharmacovigilance): *long term effects* due to confounding issues and deteriorating quality of consumer reports, and *general problems* that cannot be assigned to specific foods. The single result obtained from the analyses on consumer complaints is the relay of a signal, even the faintest, that something might be happening. Of course one should be cautious about the negative publicity that might occur after the relay of a signal. The question LAREB poses is whether there is any reason not to perform PLM?

VWS:

At the moment there are more important public health issues to solve than a potential side effect of functional foods consumption. Also, VWS is hesitant to invest in the development of systems that might not be imbedded in future EU-regulations or structures. It has been decided to await new EU/EFSA regulations on this topic. For example, the novel food regulation will be revised soon. As a consequence, VWS has chosen not to finance PLM developmental activities for 2006. VWS prefers cooperation with other Union Member States.

RIVM:

RIVM has been working on the development of a PLM system on commission of VWS. Key issues have been the investigation of the possibilities of utilisation of existing data systems for PLM purposes. Two reports have already emerged about the topic, and the third report about the signaling phases of PLM, for which this meeting was organised, will appear in the next coming months. In the future RIVM might be one of the executors of special parts of the PLM system.

VWA:

The adaptation of the VWA consumer care lines is not very feasible. Also the education level of the care line operators should not be overestimated. VWA mainly acts in case of legal violations. The question is whether the observations of side effects of consumption of functional foods are legal violations. There is one other option to get a registration of consumer complaints adopted through the manufacturer with VWA as a controller. This is via the HACCP (Hazard Analysis Critical Control Point) task of manufacturers. Within this task the product safety is regulated, and one of the prerequisites is to have a consumer care system

in place. VWA might be able to check the manufacturer's actions with respect to the consumer complaints as part of their inspection's mandate on the HACCP task. In this way pressure is exerted on the manufacturers to keep a check on their system. VWA proposes to pass the registration of consumer complaints back to the manufacturers. Key issue will be the notification duty of the manufacturers.

Future issues:

The notification duty can be dealt with as part of the claim regulations. In case a manufacturer wants to provide a specific claim then he/she should also pay for consumer safety. The notification to e.g. VWA or LAREB may be part of this. In case generic issues that originate from for example overdosing of many different types of products form the basis of the complaint, no specific manufacturer may feel responsible. The manufacturer might push the problem back to the government. Nevertheless, it was mentioned again that if a manufacturer wants to provide a specific claim then he/she should also pay for consumer safety of which a care line and the follow-up of any type of complaint about any type of product are components. The first task that needs to be performed is to develop a uniform and structured protocol for the manufacturers about how to operate their consumer care line for among others PLM purposes. The information that should be retrieved should fulfill a set of minimal demands in order to further investigate complaints. VWA's mandate allows inspection on the actions performed by the manufacturer after a consumer complaint has been registered. The implementation of these structured protocols can only be successful if the government exerts pressure on this. It is highly preferable to have these ideas and protocols implemented in accordance to EU initiatives. The second task would be to organise the VWA back office that may come into action if a manufacturer notifies a complaint. Up till now judgement of these complaints through VWA's own consumer care line has been prone to bias due to a subjective assessment. Lareb may come into action in case causality needs to be assessed. To gain experience with this the complaints need to be structurally registered and filed in order to retrieve the information when necessary. Lareb's surplus value will among others surface in case it is known what the PLM investigator is looking for. One might consider a flow from VWA to Lareb, but one might also consider a flow from the manufacturer to Lareb.

Last but not least, it was mentioned that education about pro's and cons of functional foods would be in place. Not only the consumers should be educated but also physicians, dietitians and other care takers as they might report complaints as well. Awareness of the role of specific foods and nutrition on health is a basic feature of a passive signaling branch of PLM.